NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Alectinib for adjuvant treatment of ALK-positive non-small-cell lung cancer [ID6368]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Alectinib for adjuvant treatment of ALK-positive non-small-cell lung cancer [ID6368]

Contents:

The following documents are made available to stakeholders:

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

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

2. **Clarification questions and company responses**
   a. Initial clarification response
   b. Further clarification response

3. **Patient group, professional group, and NHS organisation submission** from:
   a. Roy Castle Lung Cancer Foundation
   b. British Thoracic Oncology Group

4. **External Assessment Report** prepared by BMJ Technology Assessment Group (BMJ-TAG)

5. **External Assessment Group response to factual accuracy check of EAR**

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Alectinib for adjuvant treatment of ALK-positive non-small-cell lung cancer [ID6368]

Document B

Company evidence submission

June 2024

File name	Version	Contains confidential information	Date
ID6368_Alectinib for ALK+ NSCLC_Doc B_v2.0 [Redacted]	2.0	Yes	20th June 2024

Contents

Tables and figures

Abbreviations

Acronym	Definition
AIC	Akaike information criteria
AIDS	Acquired immunodeficiency syndrome
AJCC	American Joint Committee on Cancer
AKT	Protein kinase B
ALE	Alectinib
ALK	Anaplastic lymphoma kinase
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate aminotransferase
BCRP	Breast cancer resistance protein
BIC	Bayesian information criteria
BID	Twice daily
BNF	British National Formulary
BSA	Body surface area
BTOG	British Thoracic Oncology Group
CCOD	Clinical cut-off date
CDF	Cancer Drugs Fund
CEA	Cost effectiveness analysis
CEM	Cost effectiveness model
CHMP	Committee for Medicinal Products for Human Use
CHT	Chemotherapy
CNS	Central nervous system
COVID	Coronavirus disease
CPK	Blood creatine phosphokinase
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DFS	Disease-free survival
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EAG	External Assessment Group

EBUS	Endobronchial ultrasound
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EORTC	European Organisation for the Research and Treatment of Cancer
ESMO	European Society for Medical Oncology
EUR	The euro
EUS	Endoscopic ultrasound
FDA	Food and Drug Administration
FISH	Fluorescence in situ hybridisation
GBP	Great British Pound
HIV	Human immunodeficiency virus
HRG	Healthcare Resource Groups
HTA	Health Technology Assessment
ICER	Incremental cost effectiveness ratio
ICI	Immune checkpoint inhibitors
IHC	Immunohistochemistry
INV	Investigator-assessed
IQR	Interquartile range
ITT	Intent-to-treat
LDH	Lactate dehydrogenase
LOS	Length of stay
LRR	Local/regional recurrence
LYG	Life years gained
MAA	Marketing authorisation application
MCS	Mental Component Summary
MHRA	Medicines and Healthcare products Regulatory Agency
MID	Minimal important difference
MLND	Mediastinal lymph node dissection
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NDRS	National Disease Registration Service
NED	No evidence of disease

NGS	Next-generation sequencing
NHB	Net health benefit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMB	Net monetary benefit
NOS	Not otherwise specified
NSCLC	Non-small cell lung cancer
PAS	Patient Access Scheme
PBC	Platinum-based chemotherapy
PCS	Physical Component Summary
PET	Positron emission tomography
PFS	Progression-free survival
PORT	Post-operative radiation therapy
PRO	Patient-reported outcomes
PSA	Partitioned survival analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QLQ	Quality of life questionnaire
RATS	Robotic-assisted thoracoscopic surgery
RET	Rearranged during transfection
ROS1	ROS proto-oncogene 1
SAE	Serious adverse advent
SEER	Surveillance, epidemiology, and end results
SLR	Systematic literature review
STAT 3	Signal transducer and activator of transcription 3
TNM	Tumour, node, metastasis
UICC	Union for International Cancer Control
ULN	Upper limit of normal
VATS	Video-assisted thoracoscopic surgery
WTP	willingness to pay

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

B.1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication:

[redacted]

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adult patients with anaplastic lymphoma kinase (*ALK*)-positive non-small cell lung cancer (NSCLC) who have undergone tumour resection.	Per final scope	N/A
Intervention	Alectinib (Alecensa®)	Per final scope	N/A
Comparator(s)	Established adjuvant clinical management without alectinib, which may include: • Platinum-based chemotherapy • Active monitoring • Pembrolizumab (subject to NICE appraisal)	• Platinum-based chemotherapy • Active monitoring	Regarding active monitoring: • UK clinicians consider active monitoring as an option for a small portion of patients (typically less than 10%). However, this would only apply to those for whom the risks of adjuvant treatment outweigh the benefits. This approach is generally reserved for patients with a high risk of disease recurrence and issues related to treatment compliance. Clinician decisions are also influenced by the patient's age, post-surgical recovery, comorbidities, performance status, and patient preference. Some clinicians indicated they would not advocate for active monitoring due to high risk of disease recurrence.

			• As a result, although active monitoring was listed as a comparator, it was only included in the scenario analyses where its efficacy was assumed to match that of platinum-based chemotherapy, due to limited studies demonstrating its effectiveness. In these analyses, the treatment costs for active monitoring were set as zero, and the follow up healthcare resource use was kept as the same as chemotherapy. The Company does not consider pembrolizumab as an appropriate comparator for this appraisal, and therefore, has not been included in the economic analysis: • The Company consulted with four national UK clinical experts regarding the use of pembrolizumab for *ALK*+ NSCLC. The consensus was that pembrolizumab is not an appropriate treatment for *ALK*+ NSCLC patients, and that they would not prescribe pembrolizumab for patients with this specific genetic alteration. This viewpoint is supported by the British Thoracic Oncology Group (BTOG), which reflected this stance in their comments during a consultation conducted by NICE.

			• The IMMUNOTARGET registry, also referenced in the European Society for Medical Oncology (ESMO) guidelines for oncogenic-addicted metastatic NSCLC (1), noted the lack of clinical activity in the *ALK* group when retrospectively studying patients receiving immune checkpoint inhibitors (ICI) as monotherapy for advanced NSCLC with at least one oncogenic driver alteration. This trend was also seen in patients with other driver alterations and it was discussed that ICI should only be considered after exhaustion of targeted therapies and in some cases, potentially in all other therapies including standard and salvage chemotherapies (2). • The PEARLS/ KEYNOTE-091 trial studying pembrolizumab vs placebo as adjuvant therapy for completely resected stage IB-IIIA NSCLC did not mandate *ALK* status for inclusion in the trial (61% of patients receiving pembrolizumab had unknown status of *ALK* and 38% were negative for this alteration). As such, no subgroup analysis was performed to evaluate the efficacy of pembrolizumab in these patients (3).

			• NICE has agreed to exclude atezolizumab as a comparator in the current evaluation due to Cancer Drugs Fund (CDF) considerations. With both atezolizumab and pembrolizumab belonging to the same class of PD-1/PD-L1 inhibitors, the rationale for excluding atezolizumab should also be applicable to pembrolizumab. The availability and reimbursement status of these treatments do not affect their clinical appropriateness as comparators for *ALK*+ NSCLC patients.
Outcomes	The outcome measures to be considered include: • Disease-free survival • Overall survival • Adverse effects of treatment • Health-related quality of life	Per final scope	N/A
Subgroups to be considered	If the evidence allows it, the following subgroups will be considered: • Disease stage • Ethnicity	Per final scope	N/A

B.1.2 Description of the technology being evaluated

Table 2: Technology being evaluated

UK approved name and brand name	Alectinib (Alecensa®)
Mechanism of action	Alectinib is a highly selective and potent ALK and rearranged during transfection (RET) tyrosine kinase inhibitor. In pre-clinical studies, inhibition of ALK tyrosine kinase activity led to blockage of downstream signalling pathways including signal transducer and activator of transcription 3 (STAT 3) and phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) and induction of tumour cell death (apoptosis). Alectinib demonstrated *in vitro* and *in vivo* activity against mutant forms of the ALK enzyme, including mutations responsible for resistance to crizotinib. The major metabolite of alectinib (M4) has shown similar in vitro potency and activity. Based on preclinical data, alectinib is not a substrate of P-gp or BCRP, which are both efflux transporters in the blood brain barrier, and is therefore able to distribute into and be retained within the central nervous system.
Marketing authorisation/CE mark status	[redacted] Committee for Medicinal Products for Human Use (CHMP) opinion was received on 25 April 2024.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Proposed indication: [redacted]
Method of administration and dosage	[redacted]

	[redacted]
Additional tests or investigations	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 alectinib therapy.
List price and average cost of a course of treatment	List price = £5,032 Average cost of a course a treatment (list price) = £172,068 Average cost of a course a treatment (with alectinib PAS discount) = [redacted]
Patient access scheme (if applicable)	There is a simple patient access scheme (PAS) in place agreed with NHS England. There is a discount of [redacted] in place for alectinib. PAS price = [redacted]

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

B.1.3.1 Disease overview

B.1.3.1.1 Incidence and prevalence

In the UK, lung cancer is the third most common type of cancer, accounting for 13% of all new cancer diagnoses, with approximately 48,500 new cases annually between 2016 and 2018 (4). It is also the leading cause of cancer-related mortality, accounting for 21% of all cancer deaths from 2017−2019 (4). Within the spectrum of lung cancer subtypes, non-small cell lung cancer (NSCLC) is the most prevalent form, constituting about 91% of all lung cancer cases in England (5). Approximately 30% of NSCLC patients are diagnosed with early-stage disease (Stage I or II), around 10% are diagnosed with Stage IIIA; while most patients, approximately 60%, are diagnosed at advanced (Stage IIIB) or metastatic (Stage IV) stages (6). The survival rates vary significantly based on the stage at diagnosis: for advanced and metastatic NSCLC, the 5-year survival rate is very poor, ranging from 1−5% (6). For early-stages, the survival rates are higher, with 3- and 5-year survival rates ranging from 14-70%, depending on the disease's extent at diagnosis and the treatment options available (6-9).

B.1.3.1.2 Diagnosis and staging

The diagnosis process for NSCLC involves a multifaceted approach that begins with patient history and physical examination, and extends to advanced imaging and histological examination. Imaging techniques such as chest X-rays and computed tomography (CT) scans are pivotal for initial tumour visualisation and staging. NSCLC is classified into two primary histological types: squamous cell carcinoma and non-squamous carcinoma. Squamous cell carcinoma is frequently linked to smoking; non-squamous carcinoma, which predominantly includes adenocarcinoma, is the most common subtype among non-smokers (10). Accurate histological classification of NSCLC is essential for effectively guiding therapeutic strategies and prognostic assessments.

The extent of the NSCLC is evaluated by staging, which determines the most appropriate form of treatment and provides an indication of prognosis. The tumour, node, metastasis (TNM) system is the basis of staging in NSCLC according to the American Joint Committee on Cancer/Union for International Cancer Control system (11, 12). The TNM system categorises NSCLC into Stages 0 to IV, considering factors such as primary tumour size and spread, lymph node involvement, and presence of distant metastases.

The diagnosis of NSCLC also includes determining the molecular profile of the tumour, which is done by molecular testing for biomarkers such as anaplastic lymphoma kinase (*ALK*) rearrangements, epidermal growth factor receptor (*EGFR*) mutations, ROS proto-oncogene 1 (*ROS1*) mutations, or programmed death-ligand 1 (PD-L1) expression (13). It is expected that 4−5% of NSCLC cases contain the *ALK* fusion gene as a result of rearrangement on chromosome 2, leading to the production of an oncogenic ALK fusion protein (14, 15). UK clinical experts at an advisory board have validated a forecast figure of 2% based on real-world data (16). This genetic alteration inhibits processes that halt normal cell division, leading to the unchecked proliferation characteristic of cancer cells (17, 18). The identification of *ALK*-positive (+) NSCLC is critical as it directly impacts treatment strategy, guiding the use of ALK tyrosine kinase inhibitors (TKIs), which have been shown to significantly improve patient outcomes by specifically targeting and inhibiting abnormal *ALK* fusion protein activities.

In the UK, testing for ALK+ is primarily conducted using immunohistochemistry (IHC) on tumour biopsies, with confirmatory fluorescence in situ hybridisation (FISH) and next-generation sequencing (NGS) also used in some centres. The Company estimates that [redacted] of Stages IB–IIIA NSCLC patients are tested for *ALK*, based on a first-line (1L) *ALK* testing analogue of 85% (16). Testing can be carried out on tissue samples prior to surgery, particularly if patients are being considered for the current chemo-immunotherapy neoadjuvant treatment (confirmation that the tumour is *ALK*-negative is required), or post-resection (16). These tests are performed in-house or through the Genomic Laboratory Hubs (GLHs), as specified by the National Genomics Test Directory. The eligibility criteria for panel testing are defined as follows: "Molecular assessment will aid diagnosis or management. Indicated for all non-squamous NSCLC and in selected squamous cell lung cancer patients with clinical features suggesting a

higher likelihood of a targetable mutation (age <50 and non-smokers)." Feedback from the advisory board highlights variability in *ALK* testing practices across the country, not only in terms of when and where in the treatment pathway testing occurs, but also in the methods used and the patient eligibility criteria (16). Consequently, the National Disease Registration Service (NDRS) now systematically records and analyses *ALK* testing rates, including the number of patients tested for *ALK* mutations and other relevant biomarkers (19).

B.1.3.1.3 Clinical signs and quality of life

NSCLC manifests through various clinical signs and symptoms, which can be indicative of the disease's presence and progression. Common clinical presentations include persistent cough, dyspnoea, and chest pain, particularly in cases where the tumour invades the pleura or adjacent thoracic structures. Other symptoms may include fatigue, infections, haemoptysis, and unexplained weight loss, reflecting the diverse impacts of the tumour on lung function and overall health.

ALK+ NSCLC is associated with specific social and clinical features, including never- or light-smoking history, younger age, often economically active with dependents, and a predominance of adenocarcinoma in tumour histology. There is a significant propensity for these patients to develop brain metastases, affecting approximately 50−60% over their disease course (20, 21). If patients are suspected to have brain metastasis, further investigations and additional treatment may be required. Diagnostic procedures often include MRI scans, recommended at diagnosis and biannually if initial scans show no brain lesions, though there is no national guideline on this in the UK (22). The symptom burden from brain metastases can severely impact quality of life, with potential symptoms including headaches, shortness of breath, weakness, sickness, mood swings or behavioural changes, fits or seizures, coordination problems, confusion, lethargy, and difficulties with reading or talking. (23, 24) Therefore, patients diagnosed with brain metastasis are prohibited from driving by the Driver & Vehicle Licensing Agency (DVLA) (25). Patients with asymptomatic brain metastases exhibit a longer median overall survival post-diagnosis compared to those with symptomatic ones (11 months vs. 7 months; $p < 0.001$) (26).

ALK+ NSCLC is often diagnosed at an advanced stage, which generally precludes treatment with curative intent. This tendency towards late-stage diagnosis, compounded by specific clinical features highlighted above, significantly contributes to the poor prognosis of the disease. Additionally, the quality of life (QoL) for *ALK*+ NSCLC patients is heavily influenced by the type of *ALK* inhibitor treatment received. Research focuses on balancing the efficacy of these treatments with their impact on patients' well-being, assessing factors such as symptom management, overall health status, and the ability to perform daily activities. Optimising treatment regimens to improve both survival and QoL is a key goal in managing *ALK*+ NSCLC.

B.1.3.2 Current clinical practice in the UK

B.1.3.2.1 Surgical resection

As outlined in Section B.1.3.1.1, approximately 30% of newly diagnosed NSCLC patients are detected at an early-stage. For these patients, if clinically feasible, tumour resection is the preferred treatment approach. In 2022, 18% and 14% of patients diagnosed with NSCLC had a lung resection in England and Wales, respectively (27). However, despite this option of surgical resection with curative intent, patients with Stages I−III NSCLC still experience high recurrence rates, ranging from 41−76% (28-32). Furthermore, only 45% of patients are found to be alive five years post-surgery (33). This high recurrence rate may be attributed to micro-metastatic or distant spread of the disease, which underscores the rationale for adjuvant treatments (34, 35).

In managing post-surgery NSCLC patients, international guidelines recommend active monitoring with regular CT scans to detect recurrence early and assess recovery (36, 37). This active monitoring regimen typically involves regular follow-up visits, which may decrease in frequency from every few months to annually, depending on the patient's progress and the time elapsed since surgery. However, practices vary widely as NICE guidelines do not specify the type or frequency of imaging. In the event of disease recurrence in post-resection NSCLC patients, differentiating between locoregional and distant recurrences is crucial for tailoring appropriate interventions. Locoregional recurrence, occurring within the chest region, may be managed with localised treatment options such as radiation or additional surgery. On the other hand, distant recurrences, which often involve critical areas such as the central nervous

system, liver, bones, and lungs, require a more comprehensive approach due to their substantial impact on survival and quality of life.

Approximately 10–50% of patients treated for early-stage (I–III) resectable NSCLC will develop locoregional recurrence, and overall survival for these patients remains poor, with rates of 4.8% for supportive care only and 11.4% for active treatment. Post-treatment re-recurrence occurs in 35 to 72% of these cases (38). In Stage I–II disease, the 5-year risk of local or distant recurrence following resection is 36%, with the risk of recurrence increasing with disease advancement (from 45% at Stage IB to 76% at Stage III over an approximate 5-year follow-up, in one meta-analysis) (39, 40). Post-surgical recurrence often occurs rapidly: the median time to local or distant recurrence after resection is reported as 13.9 and 12.5 months, respectively (41).

The LuCaBis study indicated that brain metastases occurred in 41% of patients with recurrence, showcasing the gravity of CNS involvement in disease progression (42). Such metastases are associated with lower survival rates and highlights the need for vigilant monitoring and diverse therapeutic strategies to manage different recurrence patterns, such as systemic therapies capable of crossing the blood-brain barrier. Therefore, a proactive approach in monitoring and managing both locoregional and distant recurrences is essential to extend survival and enhance the quality of life for NSCLC patients. This includes regular imaging and the consideration of adjuvant therapies that can address potentially undetected microscopic disease.

B.1.3.2.2 Platinum-based chemotherapy

Patients with *ALK*+ early-stage NSCLC are currently treated similarly to patients without oncogenic driver alterations. Following resection, platinum-based chemotherapy is considered the standard of care for adjuvant treatment of *ALK*+ NSCLC (43-46), with 48−57% of patients with Stages IB−IIIA NSCLC undergoing treatment (32). Adjuvant chemotherapy can be offered to patients with resected Stage IIB and III NSCLC (TNM 8th edition), and can be considered in patients with T2bN0, Stage IIA resected primary tumour >4 cm. A 2015 Cochrane review examining adjuvant chemotherapy for resected early-stage NSCLC highlighted its limited efficacy, showing only a modest 4% increase in survival at five years, whether used alone or in combination with surgery and radiotherapy (47).

Additionally, platinum-based treatments are associated with significant side effects and disease recurrence. A study analysing the Surveillance, Epidemiology, and End Results (SEER)-Medicare database (2007-2019) found that that among 1,761 patients with early-stage, resected NSCLC who underwent adjuvant chemotherapy (40.6% in total), two-thirds experienced recurrence within 4.5 years. At 5 years, only 29.3% remained disease-free and 57.5% were alive (48). The high incidence of severe side effects, including neutropenia, anaemia, and nausea (49), underscores urgent need for more effective and tolerable adjuvant therapies. Although quality-of-life (QoL) analyses indicated that declines in QoL were generally modest and temporary, with most symptoms resolving within 3−9 months post-treatment (50, 51), the impact on patients' day-to-day well-being during this period raises concerns about the overall benefits of adjuvant chemotherapy for these patients. This emphasises the necessity for alternative adjuvant therapies to better support the overall well-being of these patients.

Given the relatively modest benefits associated with chemotherapy for certain cases of NSCLC, coupled with the potential for significant adverse events (AEs), some patients may opt for active monitoring or routine surveillance instead. This involves regularly scheduled medical check-ups and diagnostic tests to closely monitor the patient's condition without the immediate use of chemotherapy.

In recent years, beyond traditional chemotherapy, there has been growing evidence of the benefit of targeted therapies and immunotherapies as adjuvant treatments for early stage NSCLC patients.

B.1.3.2.3 Novel adjuvant treatments

The adjuvant treatment landscape is constantly evolving with the discovery of new treatment options for patients diagnosed with early-stage NSCLC. Progress in the identification of biomarkers such as PD-L1 expression, or oncogenic driver alterations such as the presence of *EGFR* alterations, have demonstrated benefit as potential targets for treatment in early NSCLC. The IMpower010 study on atezolizumab for resected Stage II−IIIA NSCLC showed improved disease-free survival (DFS) compared to best supportive care, with a 19% reduction in disease recurrence risk (hazard ratio [HR], 0.81; 95% confidence level (CI), 0.67−0.99). Treatment-related

Grade 3 and 4 AEs occurred in 11% of patients and Grade 5 events in 1% (52). The ADAURA trial demonstrated that osimertinib significantly improved outcomes in resected early-stage NSCLC patients with *EGFR* mutations. At 24 months, 89% of patients on osimertinib were disease-free (95% CI, 85−92), compared to 52% on placebo (95% CI, 46−58). The overall HR for central nervous system (CNS) disease recurrence or death was 0.18 (95% CI, 0.10–0.33), indicating an 82% reduction in the risk of CNS disease recurrence or death with osimertinib. No new safety concerns were noted. The 5-year survival rates were 88% for osimertinib-treated patients, versus 78% for those on placebo (overall HR for death, 0.49; 95% CI, 0.34−0.70) (53). As a result, atezolizumab and osimertinib are recommended by NICE (45), ESMO (43, 46) and NCCN (44) for patients with PD-L1 positive or *EGFR* mutation positive early-stage NSCLC, respectively. In addition to its efficacy and safety, *EGFR* patients in the early-stage NSCLC setting have highlighted the convenience of an oral treatment taken daily compared to receiving intravenous (IV) chemotherapy (54).

For *ALK*+ patients, ALK-tyrosine kinase inhibitors (TKIs) have been successfully used in the advanced/ metastatic NSCLC setting (55). TKIs are pharmacological agents that target specific tyrosine kinase enzymes implicated in the signal transduction pathways regulating cellular processes such as proliferation, differentiation, and apoptosis. By inhibiting these enzymes, TKIs disrupt abnormal signalling pathways in cancer cells, leading to inhibited tumour growth and proliferation. Alectinib (Alecensa®) is a small-molecule, highly selective, and potent oral next-generation ALK inhibitor, with strong ability as a CNS penetrant (56). There are several approved ALK-TKIs, including alectinib for patients with *ALK*+ NSCLC that have been shown to provide favourable clinical outcomes compared with either older ALK-TKIs or platinum-based chemotherapy (57, 58). Two global Phase III studies, ALEX (Study BO28984) and ALUR (Study MO29750), have demonstrated significant clinical benefits of alectinib in advanced or metastatic *ALK*+ NSCLC (57, 59, 60). In the first-line setting of the ALEX study, alectinib demonstrated prolonged progression free-survival (PFS) (stratified HR, 0.43; 95% CI, 0.32–0.58) and higher 5-year OS (62.5% vs. 45.5%, data immature) when compared with crizotinib. Alectinib's mechanism of action allows it to cross the blood-brain barrier, offering benefits demonstrated in the ALEX trial for delaying CNS progression compared to crizotinib (61, 62). In the ALUR study, alectinib was compared with chemotherapy (docetaxel or pemetrexed) in crizotinib pre-treated

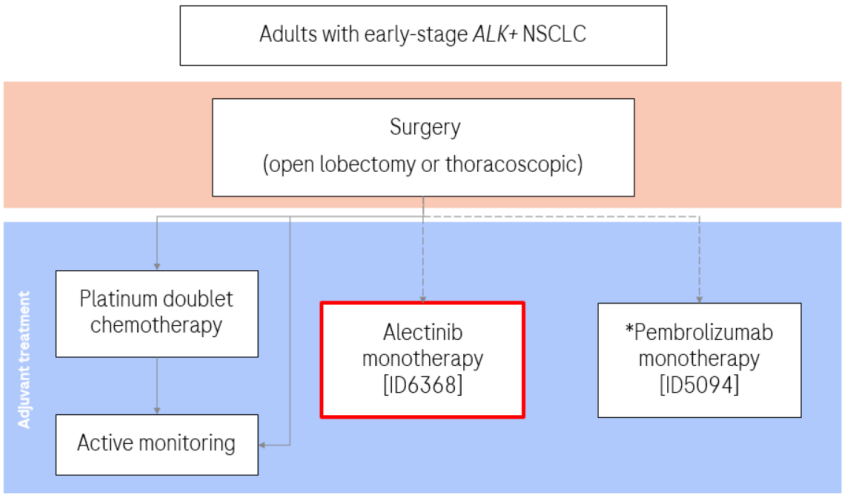
ALK+ NSCLC patients, and showed a PFS HR 0.15 (95% CI, 0.08–0.29), indicating a significant benefit despite a longer duration of treatment with alectinib (20.1 weeks vs. 6.0 weeks) (63). In addition to providing improvements in response duration and OS, TKIs are generally associated with fewer serious toxicities compared with traditional anti-neoplastic agents (64). In both studies, alectinib had lower instances of Grade ≥3 AEs than its comparators – 41% vs. 50% with crizotinib in ALEX, and 27.1% vs. 41.2% with chemotherapy in ALUR (57, 59, 60).

Despite these advances in treating metastatic *ALK*+ NSCLC, there remains a lack of studies evaluating the efficacy and safety of ALK-TKIs in earlier stages of the disease. Patients with early NSCLC, particularly those without a positive *EGFR* biomarker, have been limited to chemotherapy, which only offers modest improvements in outcomes. The pivotal ALINA study, a Phase III, global, multicentre, open-label, randomised trial appraised in the present company submission, aims to assess the benefits of alectinib compared to platinum-based chemotherapy early-stage *ALK*+ cases.

B.1.3.3 Disease management pathway

Based on the anticipated marketing authorisation indication, alectinib is positioned as [redacted], as presented in Figure 1 below.

Figure 1: Proposed positioning for alectinib for early-stage *ALK*+ NSCLC patients



The red box indicates the proposed positioning of adjuvant alectinib.
** Subject to NICE appraisal.*

B.1.4 Equality considerations

No equality issues have been identified.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

See Appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being evaluated.

B.2.2 List of relevant clinical effectiveness evidence

Table 3: Clinical effectiveness evidence

Study	ALINA Study (Study BO40366) (NCT03456076) (65)
Study design	Phase III, open-label, randomised study, with planned enrolment 255 patients (randomised 1:1 to experimental and control arms).
Population	Adult patients with completely resected (negative margins), histologically-confirmed, Stage IB (tumours≥4cm)-Stage IIIA (UICC/AJCC staging system 7th edition) (1) *ALK* positive NSCLC.
Intervention(s)	• Alectinib 600 mg orally twice daily (BID). Planned duration: 24 months.
Comparator(s)	Protocol-specified platinum-based chemotherapy: • Cisplatin 75 mg/m2 on Day 1 plus vinorelbine 25 mg/m2 on Days 1 and 8 • Cisplatin 75 mg/m2 on Day 1 plus gemcitabine 1250 mg/m2 on Days 1 and 8 • Cisplatin 75 mg/m2 on Day 1 plus pemetrexed 500 mg/m2 on Day 1 In case of intolerability to a cisplatin-based regimen, carboplatin could be administered instead of cisplatin. • Planned duration: four 21-day cycles
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	N/A

Study	ALINA Study (Study BO40366) (NCT03456076) (65)
Reported outcomes specified in the decision problem	• Investigator-assessed disease-free survival (DFS) • Overall survival • Adverse effects of treatment • Health-related quality of life: SF-36
All other reported outcomes	• Stratification factors: disease stage (IB ≥4cm vs. II vs. IIIA) and Race (Asian vs non-Asian)

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

The primary source of evidence for the clinical benefit of alectinib in adjuvant treatment of *ALK*+ NSCLC was derived from the ALINA study (Study BO40336) (65). ALINA was designed to explore the treatment effect of alectinib in patients with early-stage, *ALK*+ NSCLC after surgical resection. Alectinib could offer the potential for improved efficacy outcomes in the early lung cancer setting with a more manageable tolerability profile than platinum-based chemotherapy.

B.2.3.1 Study methodology

B.2.3.1.1 Study design

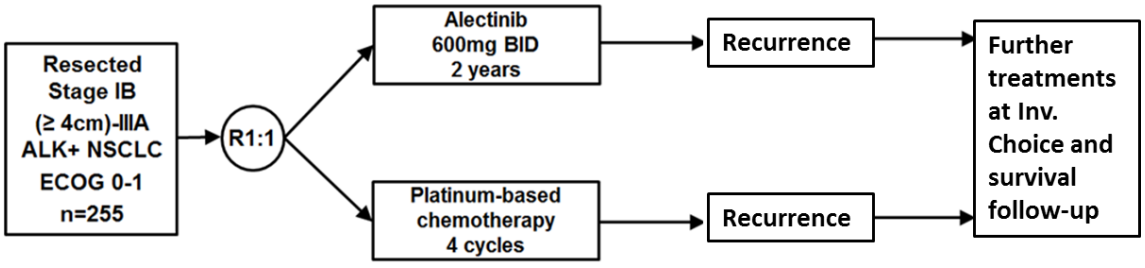
The ALINA study is a Phase III, global, multicentre, open-label, randomised study comparing the efficacy and safety of alectinib versus platinum-based chemotherapy as adjuvant therapy in patients with completely resected Stage IB (tumours ≥ 4 cm)−Stage IIIA *ALK*+ NSCLC (intention-to-treat [ITT] population), as per Union for International Cancer Control (UICC)/AJCC staging system, 7th edition. The primary endpoint of the study was investigator-assessed DFS (INV-DFS). The secondary and exploratory efficacy endpoints included overall survival (OS), time to CNS recurrence or death (CNS-DFS), quality of life and safety (See Appendix E for a full list of study endpoints).

Unless otherwise stated, results presented in this Company Submission were taken from the primary clinical study report (CSR), which includes analysis of study data collected from the date of first patient randomised (16th August 2018) to the clinical cut-off date (CCOD) of 26th June 2023 (efficacy and safety) for the protocol-specified interim analysis on DFS (65).

This study was conducted at 113 centres in 26 countries worldwide, including 3 centres in the UK. Central randomisation was performed via an interactive voice or Web-based response system (IxRS). Randomised patients were stratified by extent of disease (Stage IB [tumours ≥4 cm] vs. Stage II vs. Stage IIIA) and race (Asian vs. non-Asian). Relevant instructions were provided to each study site by the IxRS provider. Patients who met all required eligibility criteria were randomised in a 1:1 fashion, to receive either alectinib at 600 mg orally twice daily (BID) taken with food, or one of the protocol-specified platinum-based chemotherapy regimens. Screening and randomisation occurred 4−12 weeks after patients had undergone complete surgical resection (66). In case of intolerability to a cisplatin-based regimen, carboplatin was administered instead of cisplatin. Study drug (alectinib or platinum-based chemotherapy) was administered until the completion of the treatment period (24 months for alectinib and 4 cycles for chemotherapy), 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 (e.g. due to unacceptable toxicity) continued to be followed until disease recurrence. Data collection continued for each patient until death or study closure, whichever occurred first. No crossover was allowed between the two arms. However, patients initially receiving chemotherapy were allowed to receive alectinib as a subsequent treatment after disease recurrence, with decisions regarding these treatments made at the discretion of the Investigators.

The overall study design is shown in Figure 2.

Figure 2: ALINA study design



ALK+ = anaplastic lymphoma kinase–positive; BID = twice daily; ECOG = Eastern Cooperative Oncology Group (Performance Status); Inv. = investigator; NSCLC = non–small cell lung cancer; R1:1 = 1:1 randomisation.

B.2.3.1.2 Inclusion/exclusion criteria

Patients with completely resected, Stage IB−IIIA, *ALK*+ NSCLC were enrolled in the ALINA study. Key eligibility criteria are provided below. A full list of inclusion and exclusion criteria are provided in Appendix F.

Key inclusion criteria

Patients must have met the following criteria for inclusion in the study:

- Age ≥ 18
- Complete resection of histologically-confirmed, Stage IB (tumour ≥ 4 cm)−Stage IIIA NSCLC (as per UICC/AJCC, 7th edition), with negative margins
- Documented *ALK*-positive disease according to an Food and Drug Administration (FDA)-approved and CE-marked test
- Eastern Cooperative Oncology Group (ECOG) Performance Status of Grade 0 or 1
- Adequate haematologic and renal function as defined per protocol

Key exclusion criteria

Patients meeting any of the following criteria were excluded from the study:

- Pregnant or lactating women
- Prior adjuvant radiotherapy for NSCLC
- Prior exposure to systemic anti-cancer therapy
- Prior exposure to ALK inhibitors
- Liver disease as defined per protocol
- Patients with symptomatic bradycardia
- History of organ transplant
- Known human immunodeficiency virus (HIV) positivity or acquired immunodeficiency syndrome (AIDS)-related illness

B.2.3.1.3 Disease assessments

Patients must be disease-free at baseline and reassessed at each subsequent tumour evaluation once randomised into the study. 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 trial termination by the Sponsor, whichever occurred first (66). Disease recurrence was assessed by the Investigator using an integrated assessment of radiographic data, biopsy sample results (if clinically feasible), and clinical status:

- CT scan (with oral/ intravenous [IV] contrast unless contraindicated) of the chest and abdomen (including liver and adrenal glands).
- Magnetic resonance imaging (MRI) of the brain to rule out CNS metastasis. If MRI is not available, CT scans (with oral/IV contrast unless contraindicated) can be performed instead.
- Patients with metastatic disease are to be excluded from the ALINA study. Patients who have clinical signs, symptoms, biochemical abnormalities (including, but not limited to, alkaline phosphatase [ALP], lactate dehydrogenase [LDH], etc.), or radiological imaging that could be suggestive of bone metastases at baseline, must undergo further investigation to exclude the presence of bone metastases at study entry. Additional appropriate imaging techniques include but are not limited to positron emission tomography (PET) imaging and isotope bone scans.
- CT/MRI scans (with oral/IV contrast unless contraindicated) of the pelvis and neck should be included if clinically indicated
- The radiological assessments performed as per standard of care prior to obtaining informed consent and within 28 days before randomisation do not have to be repeated at screening.

B.2.3.2 Patient demographics and baseline characteristics

B.2.3.2.1 Study population and disposition

The study population comprises patients who have undergone complete resection with negative margins (R0) of histologically-confirmed Stage IB (tumours ≥ 4 cm) to Stage IIIA NSCLC per UICC/AJCC, 7th edition. Patients were randomised to receive either alectinib or platinum-based chemotherapy.

A total of 257 patients were randomised in the study: 130 in the alectinib arm and 127 in the chemotherapy arm. Of these patients, 9 did not receive study treatment after randomisation and were discontinued from the study: 2 patients in the alectinib arm (due to [redacted]) and 7 patients in the chemotherapy arm (due to [redacted]). The first patient was randomised on 16th August 2018 and the last patient was randomised on 8th December 2021. The clinical cut-off date was 26th June 2023.

Overall, 248 patients received study treatment: 128 in the alectinib arm and 120 in the chemotherapy arm. See Table 7 for a detailed breakdown on the population defined for the efficacy and safety analyses of ALINA.

As of the CCOD, study treatment was completed for 192 patients [redacted], and ongoing for 26 patients [redacted]. A total of 26 patients (20.3%) in the alectinib study was still receiving treatment (66). Study treatment had been discontinued for 30 patients (12.1%). A total of [redacted] overall discontinued from the study (Figure 3).

Figure 3: ALINA study disposition

B.2.3.2.2 Demographics and baseline characteristics

In the ALINA trial, 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%). Similar results were observed in the Stage II–IIIA subpopulation.

In the ITT population, demographics and baseline characteristics were generally well balanced between the alectinib and chemotherapy arms (Table 4). 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).

When consulting with UK clinical experts, it was noted that more patients with Stage IIIA disease, more Asian patients, more smokers, and fewer patients with squamous histology were recruited in the ALINA trial than would be expected for the UK *ALK*+ NSCLC population (16). The increased representation of Stage IIIA disease could be due to higher availability or willingness of Stage IIIA patients to participate in clinical trials, often seeking new treatments at a critical disease stage. The higher proportion of Asian patients aligns with the greater prevalence of *ALK* rearrangements in this population globally. The true proportion of smokers in the ALINA trial may be higher than reported, as some participants who were labelled as "never smokers" might have been occasional or social smokers, especially in their youths. Lastly, the lower incidence of patients with squamous histology aligns with its rarer association with *ALK* mutations, which is more prevalent among non-squamous *ALK*+ NSCLC patient.

Table 4: Demographic and baseline characteristics (ITT patients)

	Alectinib (N=130)	Chemotherapy (N=127)	All patients (N=257)
Age (yr)			
n	130	127	257
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	54	57	56

Min - Max	[redacted]	[redacted]	[redacted]
Age group 1 (yr)			
n	130	127	257
<65	103 (79.2%)	93 (73.2%)	196 (76.3%)
>=65	27 (20.8%)	34 (26.8%)	61 (23.7%)
Age group 2 (yr)			
n	[redacted]	[redacted]	[redacted]
18-40	[redacted]	[redacted]	[redacted]
41-60	[redacted]	[redacted]	[redacted]
>60	[redacted]	[redacted]	[redacted]
Sex			
n	130	127	257
Male	55 (42.3%)	68 (53.5%)	123 (47.9%)
Female	75 (57.7%)	59 (46.5%)	134 (52.1%)
Ethnicity			
n	130	127	257
Hispanic or Latino	[redacted]	[redacted]	[redacted]
Not Hispanic or Latino	[redacted]	[redacted]	[redacted]
Not Stated	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
Race (eCRF)			
n	130	127	257
Asian	72 (55.4%)	71 (55.9%)	143 (55.6%)
Black or African American	1 (0.8%)	0	1 (0.4%)
White	55 (42.3%)	52 (40.9%)	107 (41.6%)
Unknown	2 (1.5%)	4 (3.1%)	6 (2.3%)
Race (IxRS)			
n	130	127	257
Asian	72 (55.4%)	71 (55.9%)	143 (55.6%)
Non-Asian	58 (44.6%)	56 (44.1%)	114 (44.4%)
Weight (kg) at baseline			
n	130	127	257
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min - Max	[redacted]	[redacted]	[redacted]
ECOG performance status at baseline			
n	130	127	257
0	72 (55.4%)	65 (51.2%)	137 (53.3%)
1	58 (44.6%)	62 (48.8%)	120 (46.7%)
Tobacco use history			
n	130	127	257

Never	84 (64.6%)	70 (55.1%)	154 (59.9%)
Current	5 (3.8%)	3 (2.4%)	8 (3.1%)
Previous	41 (31.5%)	54 (42.5%)	95 (37.0%)
Female fertility status			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Baseline disease characteristics

The study arms were comparable with respect to baseline disease characteristics. The majority of patients in the ITT population had Stage IIIA disease ([redacted]) and non-squamous histology (96.5%). A minority of patients had Stage IB disease ([redacted]) (Table 5). *ALK*-positivity was confirmed either by a locally performed test or central testing in all patients for enrolment into the study.

Table 5: Lung cancer history (ITT patients)

	Alectinib (N=130)	Chemotherapy (N=127)	All patients (N=257)
Time from initial diagnosis to randomisation (months)			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min - Max	[redacted]	[redacted]	[redacted]
Site of primary tumour			
n	130	127	257
Left	[redacted]	[redacted]	[redacted]
Right	[redacted]	[redacted]	[redacted]
Largest tumour diameter (cm)			
n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min - Max	[redacted]	[redacted]	[redacted]
Histology			
n	130	127	257
Squamous	6 (4.6%)	3 (2.4%)	9 (3.5%)
Non-squamous	124 (95.4%)	124 (97.6%)	248 (96.5%)
Subtype histology in non-squamous			

n	124	124	248
Adenocarcinoma	[redacted]	[redacted]	[redacted]
Mixed (Not Including small cell)	[redacted]	[redacted]	[redacted]
NSCLC/NOS	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Primary tumour stage per AJCC 7th edition			
n	[redacted]	[redacted]	[redacted]
T1a	[redacted]	[redacted]	[redacted]
T1b	[redacted]	[redacted]	[redacted]
T2a	[redacted]	[redacted]	[redacted]
T2b	[redacted]	[redacted]	[redacted]
T3	[redacted]	[redacted]	[redacted]
T4	[redacted]	[redacted]	[redacted]
Regional lymph node stage			
n	130	127	257
N0	21 (16.2%)	18 (14.2%)	39 (15.2%)
N1	45 (34.6%)	43 (33.9%)	88 (34.2%)
N2	64 (49.2%)	66 (52.0%)	130 (50.6%)
Distant metastasis stage			
n	130	127	257
M0	[redacted]	[redacted]	[redacted]
Initial diagnosis staging per AJCC 7th edition (eCRF)			
n	130	127	257
Stage IB	[redacted]	[redacted]	[redacted]
Stage IIA	[redacted]	[redacted]	[redacted]
Stage IIB	[redacted]	[redacted]	[redacted]
Stage IIIA	[redacted]	[redacted]	[redacted]
Initial diagnosis staging per AJCC 7th edition (IxRS)			
n	130	127	257
Stage IB	14 (10.8%)	12 (9.4%)	26 (10.1%)
Stage II	47 (36.2%)	45 (35.4%)	92 (35.8%)
Stage IIIA	69 (53.1%)	70 (55.1%)	139 (54.1%)

All patients in the study were required to undergo a complete resection of their tumour prior to receiving study treatment. The reported surgical procedures was comparable between treatment arms, with lobectomy being the most commonly reported procedure (96.9% in the alectinib arm and 92.1% in the chemotherapy arm), and mediastinal lymph node dissection being the most commonly reported lymph node assessment procedure (83.1% in the alectinib arm and 82.7% in the chemotherapy arm) (Table 6).

The median time between complete resection of NSCLC to randomisation was similar in both arms ([redacted] in the alectinib arm vs. [redacted] in the chemotherapy arm).

Table 6: Summary of lung cancer surgery (ITT patients)

	Alectinib (N=130)	Chemotherapy (N=127)	All patients (N=257)
Total number of patients with at least one surgery	130 (100%)	127 (100%)	257 (100%)
Total number of surgeries	130	127	257
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%)
Time from last surgery to randomisation (months)			
n	130	127	257
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	1.71
Min - Max	[redacted]	[redacted]	[redacted]
Mediastinal lymph node dissection (MLND)			
n	130	127	257
Yes	108 (83.1%)	105 (82.7%)	213 (82.9%)
No	[redacted]	[redacted]	[redacted]
Lymph node (LN) sampling conduction			
n	130	127	257
Yes	19 (14.6%)	15 (11.8%)	34 (13.2%)
No	[redacted]	[redacted]	[redacted]
Reason MLND and LN sampling not done			
Patients have documented N2 disease in one level	[redacted]	[redacted]	6 (2.3%)
Preoperative staging imaging results negative in the mediastinum	[redacted]	[redacted]	4 (1.6%)

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

B.2.4.1 Analysis population

The analysis sets defined for the efficacy and safety analyses of the ALINA study are shown in Table 7. See Appendix E for a full list of study endpoints.

Table 7: Analysis sets

Population	Definition	No of patients	
		Alectinib	Chemo
ITT	All randomised patients, whether or not the participant received the assigned treatment. Participants will be grouped according to the treatment assigned at randomisation by the IxRS.	130	127
Stage II–IIIA	All patients in the ITT population with Stage II–IIIA NSCLC as per IxRS data.	116	115
Safety-evaluable	All patients who received at least one dose of study treatment. Patients were assigned to treatment groups as treated, and all patients who received any dose of alectinib was included in the alectinib treatment arm.	128	120

ITT = intent-to-treat; IxRS = interactive voice or web-based response system.

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

Critical appraisal of the ALINA was performed using established risk of bias tools recommended for HTA submissions. The complete quality assessment is presented in Appendix D. A summary is presented below in Table 8**Error! Reference source not found.**.

Table 8: Clinical effectiveness evidence quality assessment for ALINA

Study question	ALINA
Random sequence generation	Yes
Allocation concealment	Yes
Comparability of groups	Yes

Blinding	No
Imbalance in dropouts	No
Selective reporting	No
Incomplete reporting	Yes
Overall rating for risk of bias	Low

B.2.4.2 Analysis methods

B.2.4.2.1 Efficacy endpoints

Primary endpoint analysis

The ALINA study was designed to demonstrate superiority of alectinib compared with chemotherapy with 80% power to detect a target HR of 0.55 in the Stage II–IIIA subpopulation, and HR of 0.58 in the ITT population (Stage IB–IIIA) in the primary analysis of DFS per investigator. This corresponded to 89 DFS events in the Stage II–IIIA subpopulation.

A pre-planned interim analysis was to be conducted after ~67% of events (59 events) were observed in the Stage II–IIIA subpopulation. A testing hierarchy was used to control the overall type I error rate at 5% with regards to DFS in the Stage II–IIIA subpopulation and ITT population.

The stopping boundaries for the DFS interim analysis were computed with use of the Lan-DeMets approximation to the O'Brien Fleming boundaries. The stopping boundaries for early rejection of the null hypothesis for an overall two-sided 5% significance level are:

- Stage II–IIIA subpopulation: with 59 events, $p \leq 0.0118$
- ITT population: with [redacted], $p \leq 0.0077$

DFS in the Stage II–IIIA subpopulation was first tested at an overall two-sided α level of 0.0118. Since a significant effect was observed in the Stage II–IIIA subpopulation, DFS in the ITT population was then tested. Since the boundaries were crossed at the pre-specified interim analysis, no further hypothesis testing will be performed at later CCODs. This interim analysis therefore became the primary analysis.

Table 9: Efficacy endpoints and analysis

Endpoint	Definition	Analysis
Primary endpoint: Investigator-assessed disease-free survival (DFS)	Time from randomisation 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.	The treatment comparison of DFS is based on a stratified log-rank test, according to the protocol-defined stratification factors as entered in the IxRS: • Race (Asian vs. non-Asian) for the analysis in the Stage II–IIIA subpopulation, • Race (Asian vs. non-Asian) and disease stage (Stage IB [tumours ≥ 4 cm] vs. Stage II vs. Stage IIIA) for the analysis in the ITT population • Cox proportional hazards model, stratified as shown above, are used to estimate the HR between the two treatment arms and its 95% confidence interval (CI). Kaplan-Meier methodology is used to estimate the median DFS for each treatment arm, and the Kaplan-Meier curves are constructed to provide a visual description of the difference between the treatment and control arms. Brookmeyer-Crowley methodology is used to construct the 95% CI for the median DFS for each treatment arm (67).
Landmark DFS	The DFS rates at 3, 4 and 5 years	DFS rates are estimated within the Stage II–IIIA subpopulation and the ITT population using Kaplan-Meier methodology for each treatment arm, with 95% CIs calculated using Greenwood's formula.
Overall survival (OS)	Time from the date of randomisation to death due to any cause.	Similar methodology to that described for the primary endpoint of DFS.
CNS recurrence	Time from randomisation to the first documented recurrence of disease in the CNS or death from any cause, whichever occurs first.	Similar methodology to that described for the primary endpoint of DFS.

B.2.4.2.2 Patient-reported outcomes (PROs)

The benefits associated with treatment in the post-resection adjuvant setting must be weighed with its residual short- and long-term impact on patients' health-related quality of life (HRQoL) and function (68-70).

In ALINA, PRO data was collected from patients using the SF-36v2® Health Survey, which yields 2 component summary scores (i.e., physical and mental) and 8 health domains (i.e., physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health) that provide a generic assessment of HRQoL. In addition, in order to inform pharmacoeconomic modelling, health-status utility scores were collected using the EQ-5D-5L Questionnaire.

B.2.4.2.3 Safety reporting and analyses

After initiation of study drug, all AEs were collected until 28 days after last dose of alectinib or 28 days after end of last cycle of chemotherapy (7 weeks after day one of last cycle). After the end of the AE reporting period, serious adverse events believed to be related to prior exposure to study drug were to be collected. Deaths reported during the study treatment period and those reported during the follow-up period after treatment completion/discontinuation are summarised by treatment arm.

AEs are summarised in standard incidence tables, by intensity (according to NCI CTCAE v5.0) and causality (investigator-assessment of relationship to treatment).

B.2.6 Clinical effectiveness results of the relevant studies

Alectinib significantly improved DFS as compared with platinum-based chemotherapy, and reduced disease recurrence in the early, potentially curative setting for patients with resected *ALK*+ NSCLC of Stages IB, II, or IIIA (see overview in Table 10):

- The ALINA study met its primary endpoint of DFS, at the pre-planned interim analysis, demonstrating statistically significant and clinically meaningful improvement with alectinib over chemotherapy in both the Stage II–IIIA subpopulation as well as the ITT population (Stage IB–IIIA). The benefit of alectinib treatment was consistent across the pre-specified subgroups analysed.
- The secondary endpoint of OS was immature with low event-to-patient ratio (6 events: 2/130 deaths in the alectinib arm vs. 4/127 deaths in the chemotherapy arm) in the ITT population.
- Alectinib showed CNS efficacy with a clinically meaningful prolongation of time to time to CNS recurrence or death (CNS−DFS) or death compared to the chemotherapy arm in the ITT population.

B.2.6.1 Overview of efficacy

At the CCOD of 26th June 2023, the median duration of exposure to alectinib was 23.9 months (range: [redacted]). A total of 59 DFS events had occurred in the Stage II−IIIA subpopulation and 65 DFS events in the ITT population. The pre-specified DFS interim analysis was conducted by an independent Data Monitoring Committee (iDMC) and the stopping boundaries for both populations were crossed. An overview of efficacy results for INV-DFS, OS, and CNS-DFS in the Stage II−IIIA subpopulation and ITT population (Stage IB−IIIA) are provided in Table 10.

Table 10: Overview of efficacy

	Alectinib	Chemotherapy
Primary efficacy endpoint		
DFS in Stage II–IIIA	N = 116	N = 115
Patients with event (%)	14 (12.1%)	45 (39.1%)
Median DFS (95% CI), months	NE (NE, NE)	44.4 (27.8, NE)
Stratified HR (95% CI)	0.24 (0.13, 0.45)	

	Alectinib	Chemotherapy
p-value (stratified log-rank)	< 0.0001	
24 Month DFS% (95% CI)	93.8 [redacted]	63.0 [redacted]
Patients remaining at risk	67	48
36 Month event free rate (%) (95% CI)	88.3 [redacted]	53.3 [redacted]
Patients remaining at risk	35	23
DFS in ITT (Stage IB–IIIA)	N = 130	N = 127
Patients with event (%)	15 (11.5%)	50 (39.4%)
Median DFS (95% CI), months	NE (NE, NE)	41.3 (28.5, NE)
Stratified HR (95% CI)	0.24 (0.13, 0.43)	
p-value (stratified log-rank)	< 0.0001	
24 Month DFS% (95% CI)	93.6 [redacted]	63.7 [redacted]
Patients remaining at risk	74	55
36 Month DFS% (95% CI)	88.7 [redacted]	54.0 [redacted]
Patients remaining at risk	39	27
Secondary efficacy endpoint		
OS in ITT (Stage IB–IIIA)	N = 130	N = 127
Median duration of survival follow-up (months)	27.8	28.4
Patients with event (%)	2 (1.5%)	4 (3.1%)
Median OS (95% CI), months	[redacted]	[redacted]
Stratified HR (95% CI)	[redacted]	
Exploratory efficacy endpoint		
CNS–DFS in ITT (Stage IB–IIIA)	N = 130	N = 127
Patients with event (%)	5 (3.8%)	18 (14.2%)
Median time to CNS recurrence (95% CI), months	[redacted]	[redacted]
Stratified HR (95% CI)	0.22 (0.08, 0.58)	
24 Month CNS-DFS% (95% CI)	98.4 (96.11, 100.00)	85.8 (78.83, 92.82)
Patients remaining at risk	74	57
36 Month CNS-DFS% (95% CI)	95.5 [redacted]	79.7 [redacted]
Patients remaining at risk	39	27

DFS = disease-free survival; HR = hazard ratio; ITT = intent-to-treat; NE = not estimable; OS = overall survival; CNS-DFS = time to CNS recurrence or death.

B.2.6.2 Primary efficacy endpoint

The primary endpoint was met as the pre-specified interim analysis alpha boundary was crossed with 59 DFS events occurred in Stage II–IIIA population. The median

duration of follow-up for survival was 27.8 months (27.8 months in the alectinib arm and 28.4 months in the chemotherapy arm).

B.2.6.2.1 Stage II–IIIA

In the Stage II–IIIA population, 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; p value < 0.0001; Table 11), 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 in the chemotherapy arm. The KM curves began to separate at approximately 3 months after randomisation in favour of the alectinib arm and was maintained thereafter (Figure 4).

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% vs. 63.0%, respectively), and at 3 years (88.3% vs. 53.3%, respectively).

The next planned analysis is expected in [redacted] and will include an updated descriptive DFS analysis.

Table 11: Disease-free survival, Stage II–IIIA patients (Hierarchical population)

	Alectinib (N=116)	Chemotherapy (N=115)
Patients with event (%)	14 (12.1%)	45 (39.1%)
Earliest contributing event		
Death	0	1
Disease recurrence	14	44
Patients without event (%)	102 (87.9%)	70 (60.9%)
Time to event (months)		
Median	NE	44.4
95% CI	NE	(27.8, NE)
25% and 75%-ile	[redacted]	[redacted]
Range	[redacted]	[redacted]
Stratified analysis		
p-value (log-rank)	<.0001	
Hazard ratio	0.24	
95% CI	(0.13, 0.45)	
Unstratified analysis		

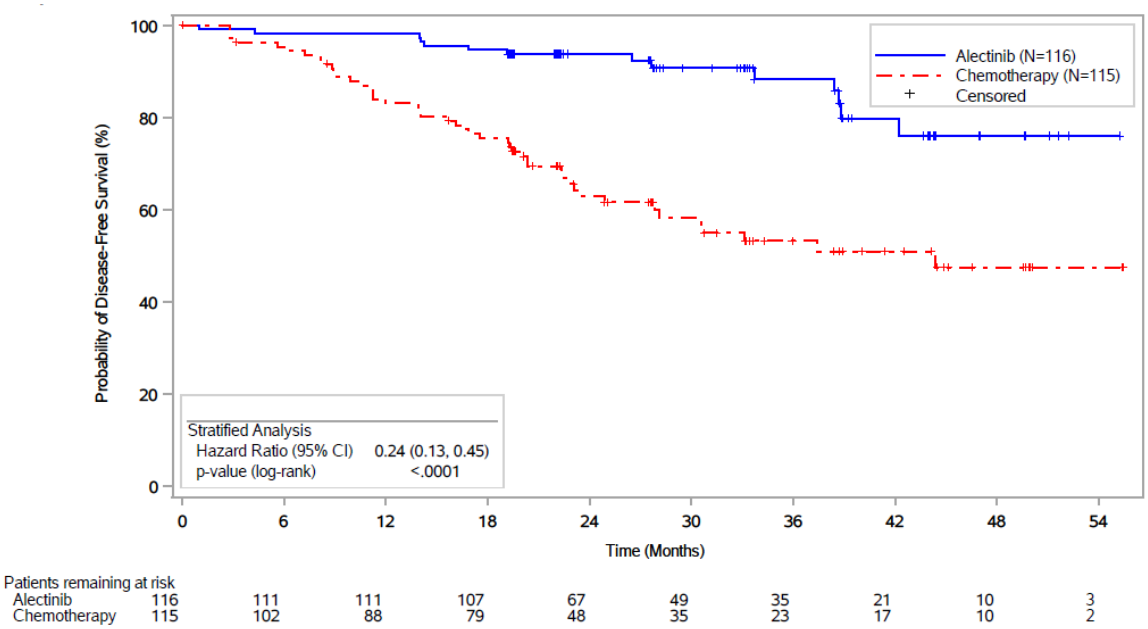
p-value (log-rank)		
Hazard ratio		
95% CI		
2 years		
Patients remaining at risk	67	48
Event free rate (%)	93.81	63.01
95% CI		
Difference in event free rate		
95% CI		
p-value (Z-test)		
3 years		
Patients remaining at risk	35	23
Event free rate (%)	88.33	53.25
95% CI		
Difference in event free rate		
95% CI		
p-value (Z-test)		
4 years		
Patients remaining at risk	10	10
Event free rate (%)		
95% CI		
Difference in event free rate		
95% CI		
p-value (Z-test)		

** Censored observation.*

Summaries of DFS (median, percentiles) are Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley. Strata are: race from IxRS (Asian vs. non-Asian). Hazard ratios were estimated by Cox regression.

Disease recurrence events include local recurrence, regional recurrence, distant recurrence and new primary NSCLC events.

Figure 4: Kaplan-Meier plot of disease-free survival, Stage II–IIIA patients



B.2.6.2.2 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; p value < 0.0001; Table 12), 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. The KM curves began to separate at approximately 3 months after randomisation in favour of the alectinib arm and was maintained thereafter (Figure 5).

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% vs. 63.7%, respectively), and at 3 years (88.7% vs. 54.0%, respectively).

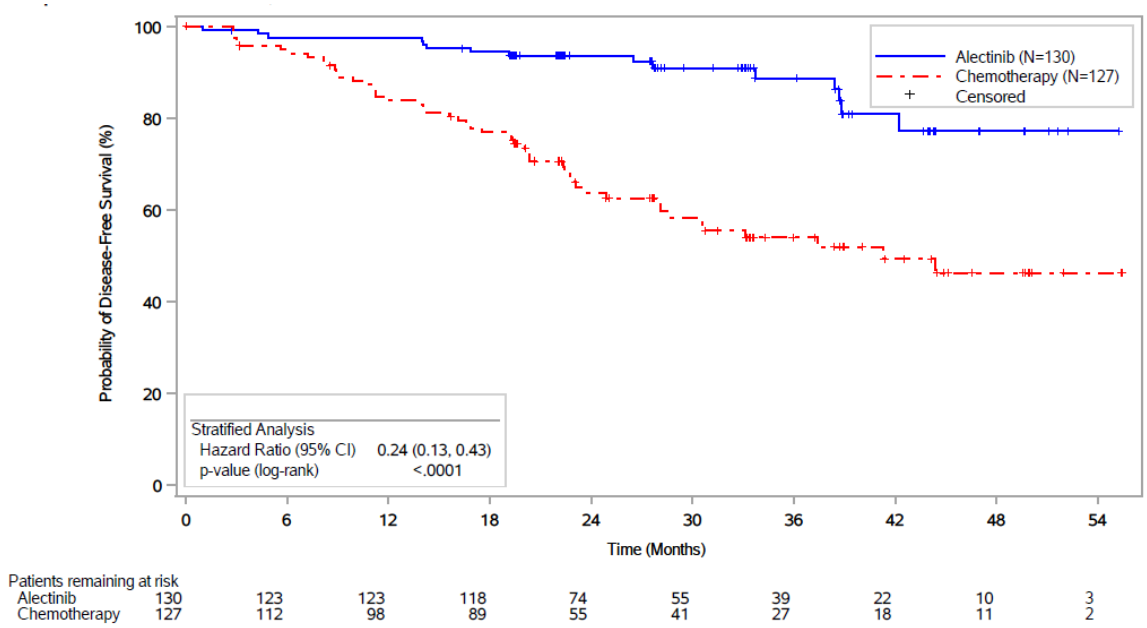
Table 12: Disease-free survival (ITT patients)

	Alectinib (N=130)	**Chemotherapy (N=127)**
Patients with event (%)	15 (11.5%)	50 (39.4%)
Earliest contributing event		
Death	0	1
Disease recurrence	15	49
Patients without event (%)	115 (88.5%)	77 (60.6%)
Time to event (months)		
Median	NE	41.3
95% CI	NE	(28.5, NE)
25% and 75%-ile	[redacted]	[redacted]
Range	[redacted]	[redacted]
Stratified analysis		
p-value (log-rank)	<.0001	
Hazard ratio	0.24	
95% CI	(0.13, 0.43)	
Unstratified analysis		
p-value (log-rank)	[redacted]	
Hazard ratio	[redacted]	
95% CI	[redacted]	
2 years		

Patients remaining at risk	74	55
Event free rate (%)	93.64	63.74
95% CI	[redacted]	[redacted]
Difference in event free rate	[redacted]	
95% CI	[redacted]	
p-value (Z-test)	[redacted]	
3 years		
Patients remaining at risk	39	27
Event free rate (%)	88.69	53.97
95% CI	[redacted]	[redacted]
Difference in event free rate	[redacted]	
95% CI	[redacted]	
p-value (Z-test)	[redacted]	
4 years		
Patients remaining at risk	10	11
Event free rate (%)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Difference in event free rate	[redacted]	
95% CI	[redacted]	
p-value (Z-test)	[redacted]	

** Censored observation. Summaries of DFS (median, percentiles) are Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley. Strata are: race from IxRS (Asian vs. non-Asian) and stage from IxRS (IB vs. II vs. IIIA). Hazard ratios were estimated by Cox regression. Disease recurrence events include local recurrence, regional recurrence, distant recurrence and new primary NSCLC events.*

Figure 5: Kaplan-Meier plot of disease-free survival, ITT patients



The robustness of the DFS results was assessed by pre-specified sensitivity analyses. Alternative censoring rules were applied to assess the impact of stratification errors, missing disease assessments, and Ukraine-Russia conflict. The statistically significant and clinically meaningful improvement in DFS for the alectinib arm compared to the chemotherapy arm in the Stage II–IIIA and the ITT NSCLC populations was also observed in the DFS sensitivity analyses.

B.2.6.2 Secondary efficacy endpoint

B.2.6.2.1 Overall survival

At the CCOD, the OS data were immature with low event-to-patient ratio (alectinib arm: 2/130 deaths; chemotherapy arm: 4/127 deaths). In the ITT population, there were 2 deaths in the alectinib arm vs. 4 deaths in the chemotherapy arm (Table 13). There was an additional death in the chemotherapy arm where only the year was reported for the date of death. This event was censored at the last date the patient was known to be alive. The KM curve is provided in Figure 6.

The next OS data cut-off date is expected in [redacted] and will be descriptive only.

Table 13: Overall survival (ITT patients)

	Alectinib (N=130)	Chemotherapy (N=127)
Patients with event (%)	2 (1.5%)	4 (3.1%)
Earliest contributing event		
Death	2	4
Patients without event (%)	128 (98.5%)	123 (96.9%)
Time to event (months)		
Median	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
25% and 75%-ile	[redacted]	[redacted]
Range	[redacted]	[redacted]
Stratified analysis		
p-value (log-rank)	[redacted]	
Hazard ratio	[redacted]	
95% CI	[redacted]	
Unstratified analysis		
p-value (log-rank)	[redacted]	
Hazard ratio	[redacted]	
95% CI	[redacted]	
2 years		
Patients remaining at risk	[redacted]	[redacted]
Event free rate (%)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Difference in event free rate	[redacted]	

95% CI	
p-value (Z-test)	
3 years	
Patients remaining at risk	
Event free rate (%)	
95% CI	
Difference in event free rate	
95% CI	
p-value (Z-test)	
4 years	
Patients remaining at risk	
Event free rate (%)	
95% CI	
Difference in event free rate	
95% CI	
p-value (Z-test)	

** Censored observation.*
Summaries of OS (median, percentiles) are Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley. Strata are: race from IxRS (Asian vs. non-Asian) and stage from IxRS (IB vs. II vs. IIIA). Hazard ratios were estimated by Cox regression.

Figure 6: Kaplan-Meier plot of overall survival, ITT patients

B.2.6.3 Exploratory endpoints

B.2.6.3.1 Time to CNS recurrence or death (CNS-DFS)

At the CCOD, the exploratory endpoint CNS-DFS in the ITT population showed clinically meaningful prolongation of CNS-DFS with alectinib compared to

chemotherapy. A higher proportion of patients in the chemotherapy arm (14.2% [18 patients]) had experienced CNS recurrence or death compared to the alectinib arm (3.8% [5 patients]) (Table 14), with a stratified HR of 0.22 (95% CI: 0.08, 0.58). 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% vs. 85.8%, respectively), and at 3 years (95.5% vs. 79.7%, respectively). The KM curve is provided in Figure 7.

Table 14: Time to CNS recurrence or death (ITT patients)

	Alectinib (N=130)	**Chemotherapy (N=127)**
Patients with event (%)	5 (3.8%)	18 (14.2%)
Earliest contributing event		
CNS disease recurrence	4	14
Death	1	4
Patients without event (%)	[redacted]	[redacted]
Time to event (months)		
Median	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
25% and 75%-ile	[redacted]	[redacted]
Range	[redacted]	[redacted]
Stratified analysis		
p-value (log-rank)	[redacted]	
Hazard ratio	0.22	
95% CI	(0.08. 0.58)	
Unstratified analysis		
p-value (log-rank)	[redacted]	
Hazard ratio	[redacted]	
95% CI	[redacted]	
2 years		
Patients remaining at risk	74	57
Event free rate (%)	98.36	85.82
95% CI	(96.11, 100.00)	(78.83, 92.82)
Difference in event free rate	[redacted]	
95% CI	[redacted]	
p-value (Z-test)	[redacted]	
3 years		
Patients remaining at risk	39	27
Event free rate (%)	95.49	79.73
95% CI	[redacted]	[redacted]
Difference in event free rate	[redacted]	
95% CI	[redacted]	
p-value (Z-test)	[redacted]	

4 years		
Patients remaining at risk	10	11
Event free rate (%)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Difference in event free rate	[redacted]	
95% CI	[redacted]	
p-value (Z-test)	[redacted]	

** Censored observation.*
Summaries of time to CNS recurrence or death (median, percentiles) are Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Strata are: race from IxRS (Asian vs. non-Asian) and stage from IxRS (IB vs. II vs. IIIA).
Hazard ratios were estimated by Cox regression.

Figure 7: Kaplan-Meier plot of time to CNS recurrence or death (ITT patients)

[redacted]

B.2.6.3.2 Patterns of disease recurrence

At the CCOD, a higher proportion of patients in the chemotherapy arm (38.6% [49 patients]) compared to the alectinib arm (11.5% [15 patients]) had experienced disease recurrence (Table 15). Fewer patients in the alectinib arm (3.8% [5 patients]) had distant recurrence of lung cancer compared to the chemotherapy arm (21.3% [27 patients]), with the most common sites of distant recurrence as brain (alectinib arm: 3.1% [4 patients] vs. chemotherapy arm: 11% [14 patients]) and bone (alectinib arm: 0.8% [1 patient] vs. chemotherapy arm: 6.3% [8 patients]). One patient in alectinib arm developed a new primary lung cancer.

Table 15: Location of first documented recurrence or new primary NSCLC (ITT patients)

	Alectinib (N=130)	Chemotherapy (N=127)
Patients with event	15 (11.5%)	49 (38.6%)
Local recurrence of lung cancer	[redacted]	[redacted]
Regional recurrence of lung cancer	[redacted]	[redacted]
Distant recurrence of lung cancer	5 (3.8%)	27 (21.3%)
New primary lung cancer	1 (0.8%)	0
Sites of distant recurrence		
Adrenal gland	0	3 (2.4%)
Bone	1 (0.8%)	8 (6.3%)
Brain	4 (3.1%)	14 (11.0%)
Kidney	0	1 (0.8%)
Lymph Node	0	2 (1.6%)
Other	1 (0.8%)	0
Peritoneum	0	1 (0.8%)
Site of new primary lung cancer		
Not applicable	1 (0.8%)	0

B.2.6.3.3 Patient-reported outcomes

Patients randomised to the chemotherapy arm could receive 4 (21-day) cycles of treatment whereas patients randomised to the alectinib arm could continue to receive treatment up to Week 104. Due to this difference in the treatment schedules, PRO comparisons between arms were only made up to and including Week 12. The analysis presented below is focused on the ITT population; similar results were observed in the Stage II–IIIA subpopulation.

Completion rate

Completion rate at baseline for the Short Form 36-Item Health Survey, version 2 (SF-36v2) was [redacted] and [redacted] for the alectinib and chemotherapy arms, respectively. Completion rates remained high [redacted] for the alectinib arm up to and including the [redacted]. For the chemotherapy arm, completion rates were also high [redacted] during treatment and off-treatment periods up to and including [redacted]. At only one time was the completion rate [redacted] Similarly high completion rates were observed with the Stage II–IIIA subpopulation.

PRO assessment

With the SF-36v2, norm-based scoring is applied to the 8 health domains and the 2 component summary scores such that each has a mean of 50 and standard deviation of 10 (based on a national sample of the general U.S. adult population). Higher scores indicate better health. Mean scores below 45 (0.5 SD below the norm of 50) are indicative of lower health-related quality of life (HRQoL) in that domain the ITT population is provided in Table 16 (71). Similar trends were observed for the Stage II–IIIA subpopulation.

At baseline, mean scores for 6 out of the 8 health domains, as well as the Mental Component Summary (MCS) score and Physical Component Summary (PCS) score were comparable between treatment arms, the baseline means of General Health were [redacted] in the alectinib arm vs. [redacted] in the chemotherapy arm, and [redacted] vs. [redacted] for Social Functioning.

Patients in both treatment groups had low baseline mean scores [redacted] domains, and for the chemotherapy arm in the [redacted]. In contrast, the baseline mean scores for the [redacted] were near the norm for both treatment arms. Overall, the baseline mean scores for MCS and PCS scores suggests patients in both arms experienced somewhat lower mental and physical well-being at baseline, compared to the general population.

For the alectinib arm, mean scores [redacted] The mean change from baseline scores for [redacted] and MCS met or exceeded by at least one point the minimal important difference (MID) by Week 12 through Week 96; the MID was also met or exceeded for the [redacted] and the PCS by Week 96 (Table 17). Overall, there was no evidence of detrimental impact on HRQoL over the 96 weeks of treatment with alectinib. HRQoL was maintained on all aspects of health assessed by the SF-36v2 up to Week 96 with alectinib.

For the chemotherapy arm, mean scores for the 8 health domains, MCS and PCS tended to be lower during treatment, compared to their respective mean scores during the off-treatment Disease Follow-Up period. During treatment, the [redacted] domains exceeded their MIDs for worsening whereas no change was observed for the other health domains, MCS and PCS. During the off-treatment period, the positive MID was met or exceeded for the MCS, PCS and 5 of the health domains (Table 17). During the off-treatment period, the mean scores for the [redacted] domains as well as the PCS reached near, or above, the norm of 50.0. Overall, these results suggest a trend to numerically higher scores as assessed by the SF-36v2 once treatment with chemotherapy was completed.

Table 16: Summary of SF-36v2 domains and component summary scores at baseline, Week 12, Week 96 (alectinib) and Disease Follow-Up Visit 7* (chemotherapy, mean [SD]) (ITT patients)

Assessment scores (mean [SD])	Alectinib			Chemotherapy		
	Baseline	Week 12	Week 96	Baseline	Week 12	Week 96
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						

SF-36v2 = Short Form 36-Item Health Survey, version 2; ITT = intent-to-treat; MCS = Mental Component Summary score; PCS = Physical Component Summary score; DFV7 = Disease Follow-Up visit 7.

The scales including Physical Functioning, Role Physical, and Bodily Pain contribute most to the PCS. The scales including Mental Health, Role Emotional, and Social Functioning contribute most to the MCS.

**Due to differences in treatment administration schedules, the Disease Follow-Up Visit 7 should not be compared to the Week 96 visit*

Table 17: Minimal important difference (MID)

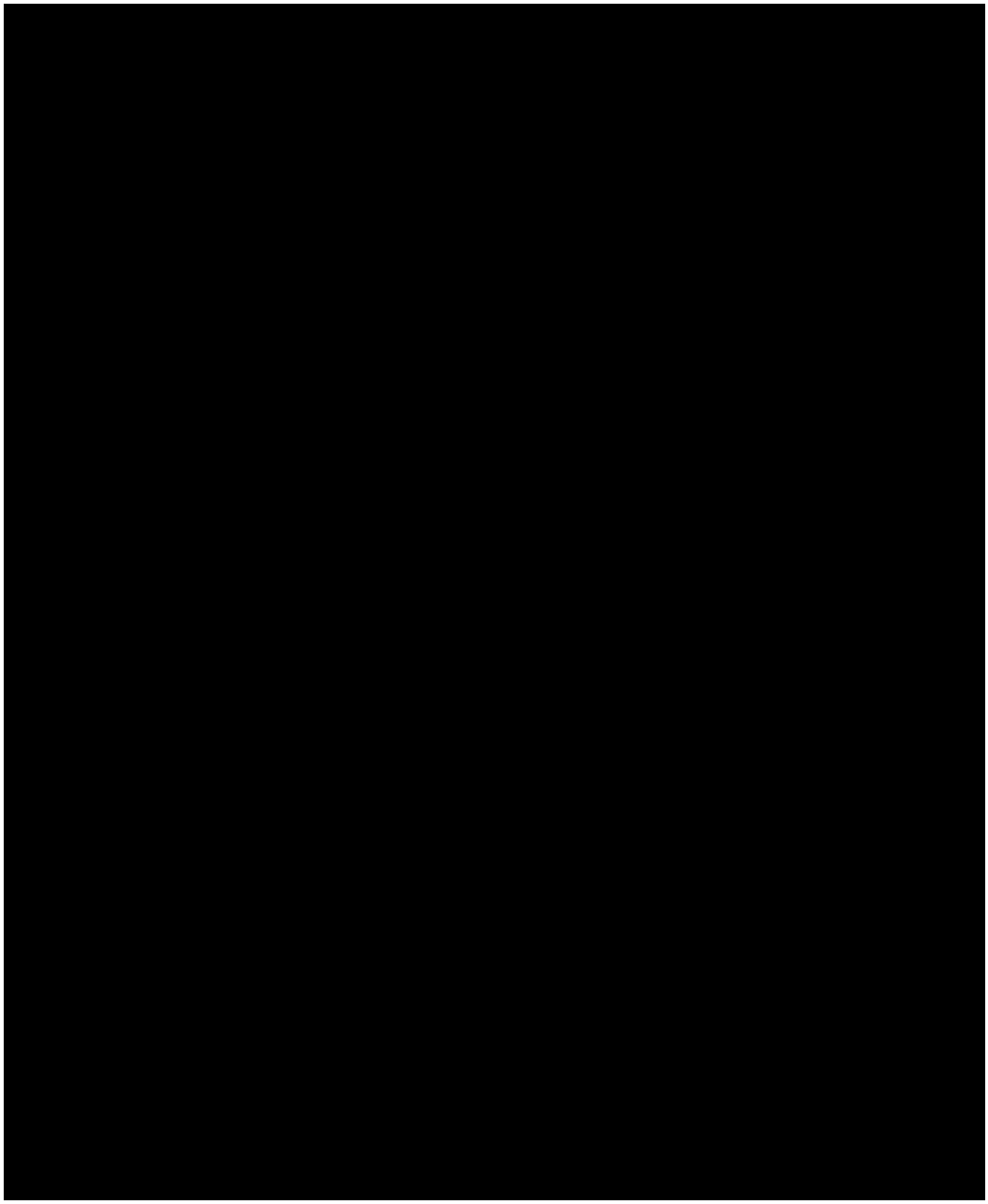
Domain	MID	Change from baseline			
		Alectinib		Chemotherapy	
		Week 12	Week 96	Week 12	Week 12
[redacted]					

MID = minimal important difference; SF-36v2 = Short Form 36-Item Health Survey, version 2; ITT = intent-to-treat; MCS = Mental Component Summary score; PCS = Physical Component Summary score; DFV7 = Disease Follow-Up visit 7.
The scales including Physical Functioning, Role Physical, and Bodily Pain contribute most to the PCS. The scales including Mental Health, Role Emotional, and Social Functioning contribute most to the MCS.
**Due to differences in treatment administration schedules, the Disease Follow-Up Visit 7 should not be compared to the Week 96 visit.*

B.2.7 Subgroup analysis

Consistent with the observation in the primary efficacy analysis of DFS, the subgroup analyses also demonstrated a clinically meaningful prolongation of DFS, and the alectinib treatment effect on DFS was generally consistent across the predefined subgroups in the ITT population (Figure 8).

Figure 8: Forest plot for subgroup analysis of disease-free survival (ITT patients)



Results of the safety analyses based on subgroups defined by baseline characteristics (age, race, sex, and stage) were generally consistent with the overall population. The most notable differences are highlighted below:

The AEs by PT with notable differences between male and female patients in the alectinib arm were (male and female patients, respectively):

- [redacted]

The AEs by preferred term (PT) with notable differences [redacted] between Asian ([redacted] and non-Asian [redacted] patients in the alectinib arm were (Asian and non-Asian patients, respectively):

- [redacted]
- [redacted]
- [redacted]
- [redacted]

Differences are seen between age groups (aged < 65 years and ≥ 65 years), and by Disease Stage (Stage IB, Stage II, and Stage IIIA), are difficult to interpret owing to the small number of patients in certain subgroups.

B.2.8 Meta-analysis

Meta-analysis is not included in this submission as the comparator (platinum-based chemotherapy) was included in the ALINA trial. There are limited studies to demonstrate the efficacy of active monitoring, therefore, its efficacy was assumed to match that of platinum-based chemotherapy.

B.2.9 Indirect and mixed treatment comparisons

Indirect treatment comparisons (ITCs) were not conducted as the ALINA trial included relevant comparators.

B.2.10 Adverse reactions

B.2.10.1 Overview of safety

A total of 248 patients (128 patients in the alectinib arm and 120 patients in the chemotherapy arm) received at least one study treatment and were considered for the safety-evaluable population.

The proportion of patients who experienced at least one AE in the alectinib arm (98.4% [126 patients]) was comparable to the chemotherapy arm (93.3% [112 patients]), despite the longer duration of alectinib treatment.

Adverse events of any grade that were considered by the Investigator to be related to treatment were reported in 93.8% (120 patients) of the patients in the alectinib arm and 89.2% (107 patients) of those in the chemotherapy arm; Grade 3 or 4 treatment-related adverse events occurred in 18.0% and 27.5%, respectively.

Most patients reported low severity (Grade 1 or 2) AEs. The proportion of patients who experienced at least one Grade 3−5 AE in the alectinib arm (29.7% [38 patients]) was comparable to the chemotherapy arm (30.8% [37 patients]). No Grade 5 AEs were reported.

Most patients reported non-serious AEs. 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.

There was a lower frequency of AEs leading to treatment discontinuation in the alectinib arm (5.5% [7 patients]) compared with the chemotherapy arm (12.5% [15 patients]). The proportion of patients who experienced at least one AE leading to treatment dose reduction or interruption in the alectinib arm (25.8% [33 patients] and 27.3% [35 patients], respectively) was higher than the chemotherapy arm (10.0% [12 patients] and 18.3% [22 patients], respectively).

The median duration of exposure to treatment and follow-up time for safety was longer in the alectinib arm than in the chemotherapy arm (23.9 months vs 2.1 months).The data showed that alectinib was well-tolerated and that the safety profile was consistent with previous experience in the metastatic setting.

An overview of the key safety results is provided in Table 18.

Table 18: Overview of adverse events (safety-evaluable patients)

	Alectinib (N=128)	Chemotherapy (N=120)
All AEs		
Total number of patients with at least one AE	126 (98.4%)	112 (93.3%)
Total number of AEs	[redacted]	[redacted]
Total number of patients with at least one		
AE with fatal outcome (Grade 5)	0	0
Grade 3-5 AE	38 (29.7%)	37 (30.8%)
Serious AE	17 (13.3%)	10 (8.3%)
Serious AE leading to withdrawal from treatment	1 (0.8%)	4 (3.3%)
Serious AE leading to dose modification/interruption	7 (5.5%)	4 (3.3%)
Related serious AE	2 (1.6%)	8 (6.7%)
AE leading to withdrawal from treatment	7 (5.5%)	15 (12.5%)
AE leading to dose modification/interruption	[redacted]	[redacted]
Related AE	120 (93.8%)	107 (89.2%)
Related AE leading to withdrawal from treatment	[redacted]	[redacted]
Related AE leading to dose modification/interruption	[redacted]	[redacted]
Selected AEs*		
Total number of patients with at least one selected AE		
Any grade	[redacted]	[redacted]
Grade 3-5 AE	[redacted]	[redacted]
Serious AE	[redacted]	[redacted]
Leading to discontinuation	[redacted]	[redacted]
Leading to dose modification	[redacted]	[redacted]

Investigator text for AEs encoded using MedDRA version 26.0. Percentages are based on N in the column headings.
Multiple occurrences of the same AE in one individual are counted only once except for "Total number of AEs" row in which multiple occurrences of the same AE are counted separately.
Includes AEs with onset from first dose of study drug.
**Selected AEs include: Gastrointestinal AEs, Haematologic Abnormalities, Muscular AEs/CPK increases, Hepatocellular or cholestatic damage AEs, Abnormal liver function tests, Dysgeusia, Oedema, Bradycardia, Vision Disorders, and Interstitial Lung Disease.*

B.2.10.2 Exposure to treatment

B.2.10.2.1 Exposure to alectinib

As of the CCOD (26th June 2023), the median duration of exposure to alectinib was 23.9 months ([redacted]). The median dose intensity of alectinib was 99.4% [redacted]. The majority of patients ([redacted]) had received alectinib >18 months, of which [redacted] had received alectinib >24 months (Table 19).

Table 19: Exposure to alectinib (safety-evaluable patients)

	Alectinib (N=128)
Treatment duration (months)	
n	128
Mean (SD)	[redacted]
Median	23.9
Min - Max	[redacted]
Treatment duration (months)	
n	128
0 - <=6	[redacted]
>6 - <=12	[redacted]
>12- <=18	[redacted]
>18 - <=24	[redacted]
>24 - <=30	[redacted]
Dose intensity (%)	
n	128
Mean (SD)	[redacted]
Median	99.4
Min - Max	[redacted]
Number of doses	
n	128
Mean (SD)	[redacted]
Median	[redacted]
Min - Max	[redacted]
Total cumulative dose (mg)	
n	128
Mean (SD)	[redacted]
Median	[redacted]
Min - Max	[redacted]

Treatment duration is the date of the last study drug administration minus the date of the first study drug administration plus one day.
Dose intensity is the amount of study drug actually received divided by the expected amount to the time of the last administered dose.

B.2.10.2.2 Exposure to chemotherapy

Patients in the chemotherapy arm (n = 120) completed a median of 4 cycles of platinum-based chemotherapy (range: 1–4 cycles).

The most common chemotherapy regimen was [redacted]), of whom [redacted] completed 4 cycles, followed by [redacted]), of whom

[redacted] completed 4 cycles. [redacted] received [redacted] and completed 4 cycles.

Carboplatin could be substituted for cisplatin, when cisplatin was not tolerated by patients. In the chemotherapy arm, [redacted] were exposed to carboplatin either with [redacted] or [redacted] (Table 20).

Table 20: Exposure to chemotherapy (safety-evaluable patients)

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

[redacted]

B.2.10.3 Common adverse events

The most frequent AEs by preferred term (PT) (≥ 10% of patients in either arm) were (alectinib arm and chemotherapy arm, respectively):

- Nausea (7.8% [10 patients] and 72.5% [87 patients])

- Blood creatine phosphokinase (CPK) increased (43.0% [55 patients] and 0.8% [1 patient])
- Constipation (42.2% [54 patients] and 25.0% [30 patients])
- Aspartate aminotransferase (AST) increased (41.4% [53 patients] and 5.0% [6 patients])
- Alanine aminotransferase (ALT) increased (33.6% [43 patients] and 9.2% [11 patients])
- Blood bilirubin increased (33.6% [43 patients] and 0.8% [1 patient])

A summary of common AEs with an incidence rate of at least 10% in either treatment arm is provided in Table 21.

Table 21: Summary of common adverse events (≥ 10% incidence in either treatment arm)

MedDRA System Organ Class MedDRA Preferred Term	Alectinib (N=128)	Chemotherapy (N=120)
Gastrointestinal disorders		
Nausea	10 (7.8%)	87 (72.5%)
Constipation	54 (42.2%)	30 (25.0%)
Vomiting	9 (7.0%)	30 (25.0%)
Diarrhoea	16 (12.5%)	10 (8.3%)
Investigations		
Aspartate aminotransferase increased	53 (41.4%)	6 (5.0%)
Blood creatine phosphokinase increased	55 (43.0%)	1 (0.8%)
Alanine aminotransferase increased	43 (33.6%)	11 (9.2%)
Blood bilirubin increased	43 (33.6%)	1 (0.8%)
Blood alkaline phosphatase increased	32 (25.0%)	4 (3.3%)
Blood creatinine increased	19 (14.8%)	6 (5.0%)
White blood cell count decreased	2 (1.6%)	23 (19.2%)
Neutrophil count decreased	3 (2.3%)	21 (17.5%)
Weight increased	17 (13.3%)	1 (0.8%)
General disorders and administration site conditions		
Fatigue	18 (14.1%)	16 (13.3%)
Asthenia	14 (10.9%)	19 (15.8%)

Malaise	6 (4.7%)	16 (13.3%)
Oedema peripheral	13 (10.2%)	1 (0.8%)
Infections and infestations		
COVID-19	37 (28.9%)	1 (0.8%)
Metabolism and nutrition disorders		
Decreased appetite	7 (5.5%)	35 (29.2%)
Blood and lymphatic system disorders		
Anaemia	30 (23.4%)	31 (25.8%)
Neutropenia	2 (1.6%)	19 (15.8%)
Musculoskeletal and connective tissue disorders		
Myalgia	36 (28.1%)	2 (1.7%)
Skin and subcutaneous tissue disorders		
Rash	18 (14.1%)	7 (5.8%)
Nervous system disorders		
Headache	14 (10.9%)	8 (6.7%)
Dysgeusia	13 (10.2%)	3 (2.5%)
Respiratory, thoracic and mediastinal disorders		
Cough	19 (14.8%)	4 (3.3%)
Dyspnoea	13 (10.2%)	3 (2.5%)
Injury, poisoning and procedural complications		
Product dose omission issue	[redacted]	[redacted]
Product dose omission in error	[redacted]	[redacted]

Investigator text for AEs encoded using MedDRA version 26.0. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. Includes AEs with onset from first dose of study drug.

B.2.10.4 Grade 3–5 adverse events

Most patients reported only low severity (Grade 1 or 2) AEs. The proportion of patients who experienced at least one Grade 3–5 AE in the alectinib arm (29.7% [38 patients]) was comparable to the chemotherapy arm (30.8% [37 patients]). No patients experienced Grade 5 AEs.

The most frequent Grade ≥ 3 AE by PT was blood CPK increased in the alectinib arm (6.3% [8 patients]) and neutrophil count decreased in the chemotherapy arm (10% [12 patients]).

A summary of Grade 3–5 AEs with an incidence rate of at least 2% in either treatment arm is provided in Table 22.

Table 22: Grade 3–5 adverse events with a difference in incidence rate of at least 2% between treatment arms (safety-evaluable patients)

MedDRA System Organ Class MedDRA Preferred Term	Alectinib (N=128)	Chemotherapy (N=120)
Investigations		
Neutrophil count decreased	0	12 (10.0%)
Blood creatine phosphokinase increased	8 (6.3%)	1 (0.8%)
White blood cell count decreased	0	4 (3.3%)
Gastrointestinal disorders		
Nausea	0	5 (4.2%)
Infections and infestations		
Appendicitis	4 (3.1%)	0
Blood and lymphatic system disorders		
Neutropenia	0	10 (8.3%)
General disorders and administration site conditions		
Asthenia	0	3 (2.5%)

Investigator text for AEs encoded using MedDRA version 26.0. Grading based on NCI CTCAE 5.0. Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. Includes AEs with onset from first dose of study drug.

B.2.10.5 Serious adverse events

Overall, the frequency of SAEs was low in both treatment arms. Most SAEs were Grade 3 or less in severity and had resolved by the CCOD. The frequency of treatment discontinuations or dose modifications due to SAEs was low, showing a good tolerability profile of treatments and patient adherence to treatment.

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 (Table 23). The only SAE by PT 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). All SAEs that were considered to be related to treatment with alectinib were resolved.

Table 23: Serious adverse events (safety-evaluable patients)

MedDRA System Organ Class MedDRA 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	[redacted]	[redacted]

Infections and infestations		
Total number of patients with at least one adverse event	[redacted]	[redacted]
Total number of events	[redacted]	[redacted]
Appendicitis	4 (3.1%)	0
Pneumonia	3 (2.3%)	1 (0.8%)
Influenza	[redacted]	[redacted]
Lower respiratory tract infection	[redacted]	[redacted]
Pneumonia viral	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
Urosepsis	[redacted]	[redacted]
Gastrointestinal disorders		
Total number of patients with at least one adverse event	[redacted]	[redacted]
Total number of events	[redacted]	[redacted]
Nausea	0	2 (1.7%)
Abdominal pain	[redacted]	[redacted]
Colitis	[redacted]	[redacted]
Epigastric discomfort	[redacted]	[redacted]
Gastritis erosive	[redacted]	[redacted]
Ileus paralytic	[redacted]	[redacted]
Pancreatitis acute	[redacted]	[redacted]
Regurgitation	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders		
Total number of patients with at least one adverse event	[redacted]	[redacted]
Total number of events	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]
Pulmonary embolism	[redacted]	[redacted]
Cardiac disorders		
Total number of patients with at least one adverse event	[redacted]	[redacted]
Total number of events	[redacted]	[redacted]
Acute myocardial infarction	2 (1.6%)	0
Investigations		
Total number of patients with at least one adverse event	[redacted]	[redacted]
Total number of events	[redacted]	[redacted]
Neutrophil count decreased	0	2 (1.7%)
Reproductive system and breast disorders		
Total number of patients with at least one adverse event	[redacted]	[redacted]

Total number of events	[redacted]	[redacted]
Benign prostatic hyperplasia	[redacted]	[redacted]
Uterine prolapse	[redacted]	[redacted]
Blood and lymphatic system disorders		
Total number of patients with at least one adverse event	[redacted]	[redacted]
Total number of events	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]
General disorders and administration site conditions		
Total number of patients with at least one adverse event	[redacted]	[redacted]
Total number of events	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Total number of patients with at least one adverse event	[redacted]	[redacted]
Total number of events	[redacted]	[redacted]
Bladder cancer	[redacted]	[redacted]
Vascular disorders		
Total number of patients with at least one adverse event	[redacted]	[redacted]
Total number of events	[redacted]	[redacted]
Embolism	[redacted]	[redacted]

Investigator text for AEs encoded using MedDRA version 26.0. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same SAE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately. Includes AEs with onset from first dose of study drug.

B.2.10.6 Adverse events of special interest (AESIs)

B.2.10.6.1 Hy's law

[redacted]

[redacted]

B.2.10.7 Adverse events leading to dose modification or treatment discontinuation

The proportion of patients who experienced AEs requiring dose modification was higher with alectinib than with chemotherapy: 27.3% vs 18.3% required treatment interruption and 25.8% vs 10.0% required dose reduction (alectinib vs chemotherapy, respectively). The higher incidence of AEs requiring dose modification in the alectinib arm was attributable to [redacted].

Despite these interruptions and modifications, the proportion of patients who stopped treatment due to AEs in the alectinib arm (5.5% [7 patients]) was lower than in the chemotherapy arm (12.5% [15 patients]). At a UK advisory board, clinicians were reassured by the relatively low rate of treatment withdrawals with alectinib, highlighting that, based on their experience, treatment interruptions are typically more frequent in the adjuvant setting due to adverse events (16).

The most frequent AEs by PT (≥ 1% of patients in either arm) that led to treatment discontinuation were (alectinib arm and chemotherapy arm, respectively):

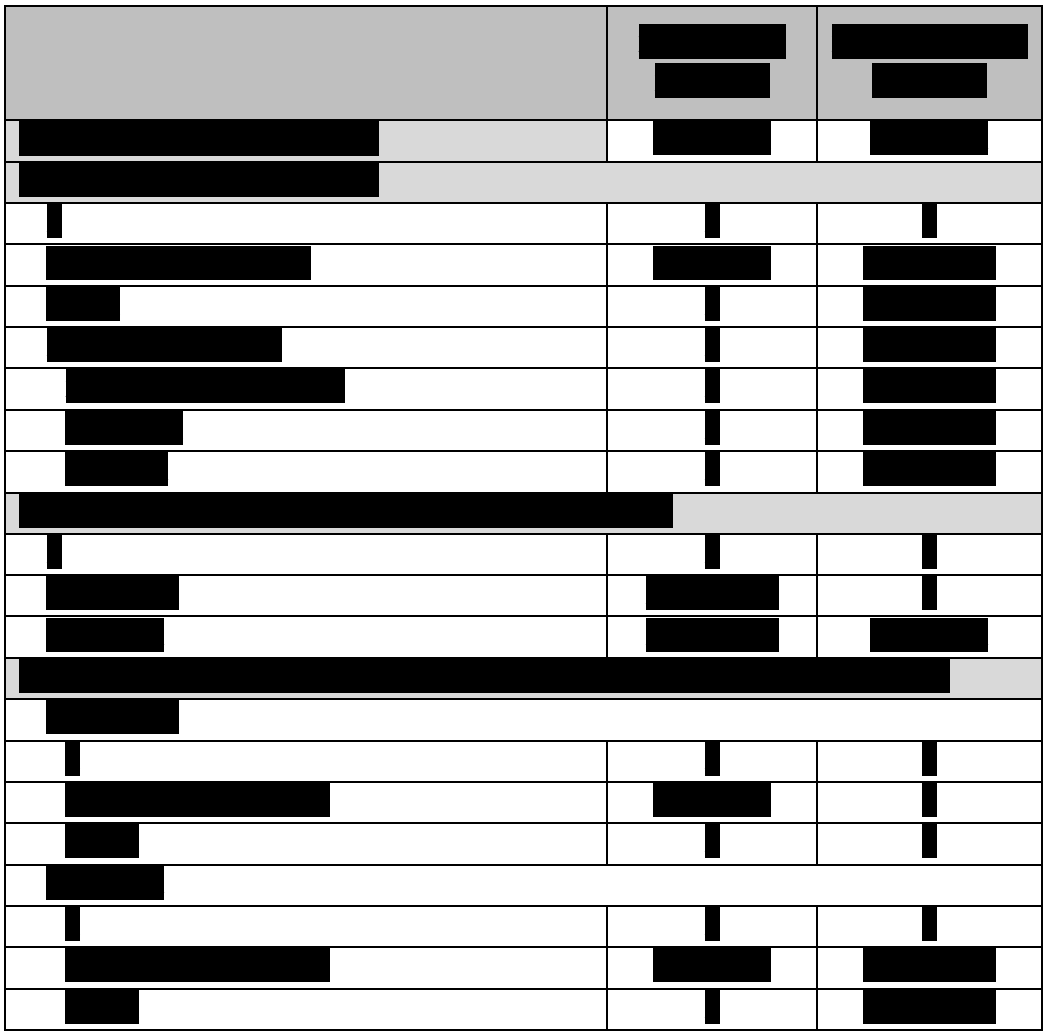
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

B.2.10.8 Deaths

A total of [redacted] in the alectinib arm and [redacted] in the chemotherapy arm died. The death cases occurred during the follow-up period (off-treatment, outside of the AE reporting period). There were no Grade 5 AEs.

In the alectinib arm, [redacted] (Table 24).

Table 24: Deaths (safety-evaluable patients)



Percentages for total number of deaths are relative to total N.
All other percentages are relative to n within each module.
For post-study deaths identified through public records, cause of death is not collected and is displayed as "post-study reporting of death".

B.2.10.9 Subsequent follow up anti-cancer therapy

No crossover was allowed between the two arms in the adjuvant setting. In the ITT population, [redacted] received subsequent follow-up anti-cancer systemic therapy after study treatment: [redacted] from the alectinib arm and [redacted] from the chemotherapy arm. Off-study alectinib or 'alectinib hydrochloride' was the most commonly used agent by patients from both arms ([redacted] in the alectinib arm and [redacted] in the chemotherapy arm).

In the ITT population, [redacted] received follow-up radiotherapy [redacted] in the alectinib arm vs. [redacted] in the chemotherapy arm), with the [redacted] as the most common site ([redacted] in the alectinib arm vs. [redacted] in the chemotherapy arm), followed by the [redacted] ([redacted] in the alectinib arm vs. [redacted] in the chemotherapy arm).

Follow-up cancer surgery was reported in a small proportion (1.6% [4 patients]) of patients, of whom [redacted] in the alectinib arm underwent surgery at a location in [redacted], while [redacted] in the chemotherapy arm underwent surgery at locations reported as [redacted]

Clinical experts consulted at a UK advisory board agreed that the subsequent therapies given following disease recurrence in the ALINA trial were reflect of UK clinical practice (16). An overview of these treatments is detailed below in Table 25.

Table 25: Subsequent anticancer systemic therapy by preferred name (ITT patients)

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

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

Treatments are coded using the WHODRUG GLOBAL B3 MARCH 1, 2023 dictionary. Multiple uses of a specific medication for a patient were counted once in the frequency for the medication. For frequency counts in "Total number of treatments", multiple uses of the same medication for a patient were counted separately.

After disease recurrence, at least one subsequent treatment was given to 13 patients in the alectinib arm and 43 patients in the chemotherapy arm. Table 26 presents any subsequent therapy reported on or after date of earliest contributing event to disease recurrence. Patients may have received more than one subsequent anti-cancer therapy.

Table 26: Post-recurrence subsequent therapy

Number of patients with disease recurrence, n (%)	Alectinib (n=15)	Chemotherapy (n=49)
Patients with any subsequent therapy	13 (87)	43 (88)
Systemic therapy	13 (87)	38 (78)
ALK-TKI	7 (47)	37 (76)
Alectinib	4 (27)	29 (59)
Brigatinib	4 (27)	4 (8)
Crizotinib	0	4 (8)
Lorlatinib	0	2 (4)
Ceritinib	0	1 (2)
Chemotherapy	6 (40)	2 (4)
Immunotherapy	1 (7)	1 (2)
Other anti-cancer therapy	1 (7)	1 (2)
Radiotherapy	5 (33)	9 (18)
Surgery	1 (7)	3 (6)

B.2.11 Ongoing studies

Aside from ALINA (Study BO40366) (65), alectinib is being investigated in the ALEX trial (Study BO28984), a randomised, active controlled, multicentre Phase III open-label study designed to evaluate the efficacy and safety of alectinib compared with crizotinib treatment in participants with treatment-naive *ALK*+) advanced NSCLC (63). Patients were randomised at the CCOD of 9 February 2017 and is expected to last approximately 144 months.

B.2.12 Interpretation of clinical effectiveness and safety evidence

ALINA met its primary endpoint of investigator−assessed DFS at the pre-specified interim analysis, demonstrating statistically significant and clinically meaningful improvement with alectinib over chemotherapy in both the Stage II−IIIA subpopulation as well as the ITT population (Stage IB−IIIA) (HR=0.24; 95% CI: 0.13, 0.43; p value < 0.0001, corresponding to a 76% relative risk reduction of disease recurrence or death when compared to chemotherapy). The benefit of alectinib treatment was generally consistent across the pre-specified subgroups. The secondary endpoint of OS was immature with low event-to-patient ratio (6 events: 2/130 deaths in the alectinib arm vs. 4/127 deaths in the chemotherapy arm) in the ITT population. The exploratory endpoint time of CNS recurrence or death showed clinically meaningful prolongation of time to CNS recurrence or death in the alectinib arm compared to the chemotherapy arm in the ITT population.

In terms of safety outcomes, a total of 248 patients (128 patients in the alectinib arm and 120 patients in the chemotherapy arm) received at least one study treatment and were considered for the safety-evaluable population. The safety results from this study demonstrated that alectinib 600 mg BID was generally well tolerated in patients with Stage IB−IIIA *ALK*+ NSCLC after surgical resection. The proportion of patients who experienced at least one AE in the alectinib arm (98.4% [126 patients]) was comparable to the chemotherapy arm (93.3% [112 patients]), despite the differences in treatment duration. Most patients reported low severity (Grade 1 or 2) AEs. The proportion of patients who experienced at least one Grade 3−5 AE in the alectinib arm (29.7% [38 patients]) was comparable to the chemotherapy arm (30.8% [37 patients]). No Grade 5 AEs were reported. These safety outcomes are of particular note

considering the extended duration of treatment, and therefore drug exposure for patients receiving alectinib compared with chemotherapy. A total of [redacted] in the alectinib arm and [redacted] in the chemotherapy arm died. The death cases occurred during the follow-up period (off-treatment, outside of the AE reporting period). [redacted]

There was a lower frequency of AEs leading to treatment discontinuation in the alectinib arm (5.5% [7 patients]) compared with the chemotherapy arm (12.5% [15 patients]).

The primary analysis data from the ALINA trial demonstrated a statistically significant and clinically meaningful improvement in DFS with alectinib compared with chemotherapy, in patients with resected early-stage *ALK*+ NSCLC. The study met its first primary efficacy endpoint, and associated subgroup analyses indicated potential broad applicability within these patient populations. At the time of primary analysis, alectinib appeared to be well-tolerated with a manageable toxicity profile, and the observed safety data is consistent with the known risks of alectinib. UK clinical experts at an advisory board agreed that DFS was an appropriate primary endpoint in ALINA (16), and cited the noteworthy translation of benefit from DFS to OS as observed in osimertinib, which indicated a promising correlation between improved DFS and extended overall survival rates. The experts also noted the significant advantages of alectinib over chemotherapy in terms of DFS, that alectinib's benefits are consistent across all disease stages, and highlighted alectinib's acceptable safety profile, particularly in early-stage settings (16). These benefits are particularly relevant for patients diagnosed at an early stage who are eligible for complete resection, a group with a significant unmet medical need due to the limited survival benefits provided by current therapies, with metastatic spread and poor prognosis. As discussed in Section B.1.3.1.3, the high risk of brain metastases in *ALK*+ NSCLC can significantly deteriorate quality of life. ALINA data showed a clinically meaningful delay in CNS recurrence which highlighted the benefit of alectinb’s mechanism of action, further emphasising the potential impact of the treatment in improving outcomes for patients across disease stages. Lastly, there was a consensus among the experts on the desirability of having the option to prescribe both adjuvant chemotherapy and alectinib

for both early- and late-stage diseases. This reinforces the need for *ALK* testing in patients with early-stage disease, not only to determine neoadjuvant eligibility, but also to identify patients who are likely to benefit from adjuvant alectinib. Overall, these findings demonstrate that alectinib offers a substantial advantage over existing treatment options, or as an additional treatment option for *ALK*+ NSCLC patients in the UK. Experts noted that the robust data from the ALINA trial are compelling enough to influence and potentially change clinical practices across the nation (16).

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

A systematic literature review (SLR) was conducted to identify published cost effectiveness studies in the adjuvant treatment of patients with *ALK*+ NSCLC patients. Detailed descriptions of the search strategy and extraction methods, as well as an overview of the identified studies are provided in Appendix G.

B.3.1.1 Summary of identified studies and results

An SLR was conducted in September 2023 (72), identifying a total of 64 publications that met the eligibility criteria for the economic evaluation SLR (full publications, n=36; conference abstracts, n=22; HTA submissions, n=5; NICE guidelines, n=1). Due to limited reporting and the difficulties associated with meaningful quality assessment, studies presented as conference abstracts only were isolated and tagged.

The review identified a total of 36 published economic evaluations presented as full publications considering interventions for early-stage NSCLC. A range of different treatment comparisons were considered, covering first-line treatment options (surgery and/or radiotherapy), adjuvant or neoadjuvant therapy, and supportive care. The analyses were primarily based across the US, Canada, China, and Europe. The majority of studies were cost-utility analyses reporting the cost per quality-adjusted life year (QALY) gained for the interventions of interest (n=26). The most commonly cited published sources of utility values across these studies was Chouaid *et al* (2013) (73); however, this study reported utilities for health states associated with advanced stages

of NSCLC. This indicates a lack of suitable utility values specifically for patients with early-stage NSCLC for use in economic evaluations.

A total of 25 of the published economic evaluations in the adjuvant lung setting reported use of a model. A high level of variation was observed across the studies, with regard to the selected disease states and pathways used in the models. The traditional three-state model typically utilised in oncology indications was not generally used; model structures were more complex and included a variety of alternative health states, including those for local/regional recurrence, metastasis/distant recurrence/advanced disease, no evidence of disease (NED), progression-free survival, progression, treatment with radiotherapy, treatment with robotic-assisted thoracoscopic surgery (RATS)/open thoracotomy/video-assisted thoracoscopic surgery (VATS), and treatment-related AEs (including dysphagia, dyspnoea, pneumonitis, and oesophagitis).

Quality assessment of the published economic evaluations presented as full publications revealed that, in general, the identified studies had well-defined objectives, treatments, and populations, and clearly reported methodologies. However, key modelling decisions (e.g. choice of model, discount rate, and variables for sensitivity analysis) were often not justified. While results were generally clearly reported, there was variability in the extent to which individual study caveats were discussed; and issues relating to the generalisability of results were not consistently addressed.

Further details and results for the identified cost effectiveness studies and abstracts can be found in Appendix G. Overall, no published studies were found that assessed the cost effectiveness of adjuvant treatment with alectinib in patients with Stage IB–IIIC NSCLC.

B.3.2 Economic analysis

The cost effectiveness studies described in Section B.3.1.1 were intended to inform the structure for the model used in the economic analysis. However, there is a lack of consensus relating to modelling approaches and model structures/frameworks. In addition, no literature were identified on alectinib in the adjuvant setting for patients

with Stage IIB–IIIA NSCLC. Therefore, a *de novo* economic model was built to inform decision making, which reflects the disease pathway in this therapeutic area.

B.3.2.1 Patient population

The cost effectiveness model (CEM) compared the clinical and economic outcomes of alectinib versus adjuvant platinum-based chemotherapy (PBC) in patients with completely resected Stage IB (tumours ≥ 4cm) to Stage IIIA *ALK*+ NSCLC. This aligns with the patient population described in the final scope of this appraisal ("adults with *ALK*-positive NSCLC who have undergone surgical resection").

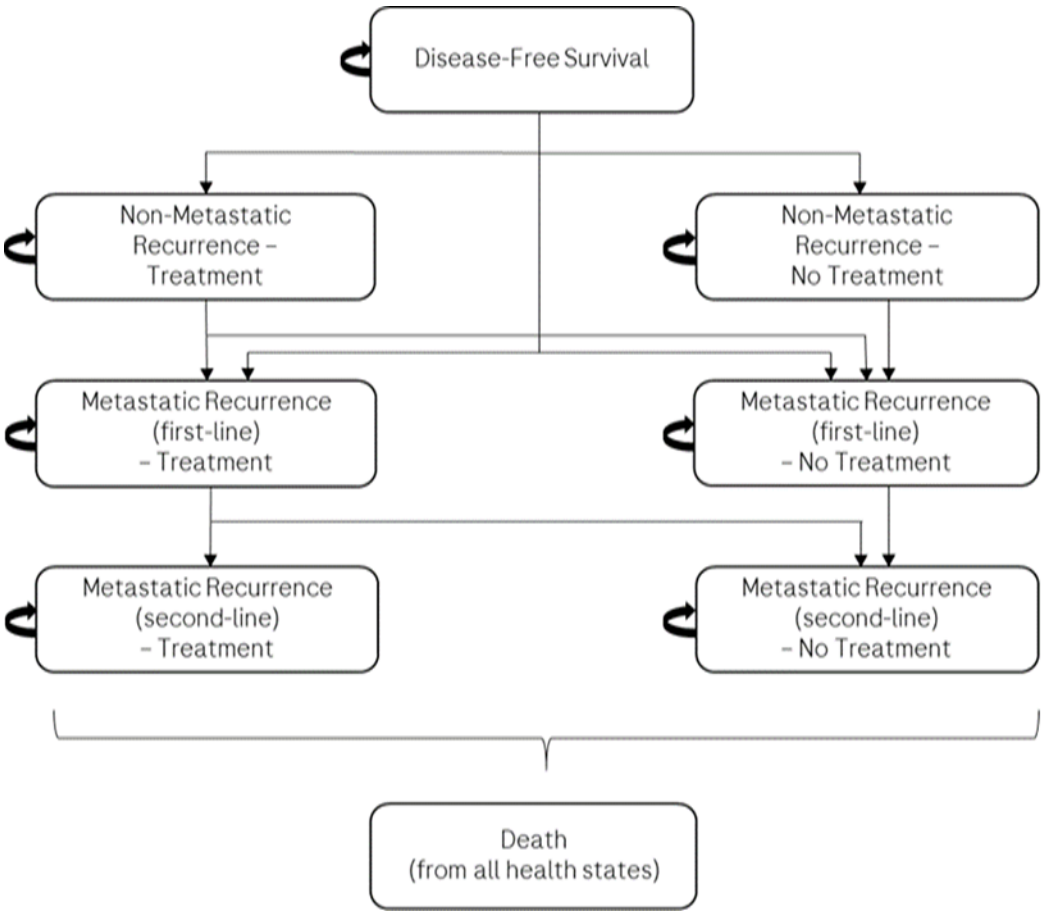
B.3.2.2 Model structure

A cohort-level semi-Markov Markov model was developed in Microsoft Excel® as this model structure allows for consideration of the long-term clinical and economic outcomes associated with early NSCLC. In February 2024, a UK advisory board was held with UK oncologists which provided valuable insights on the model's validity (i.e. model structure, assumptions, and inputs values). The advisory board followed some principles of a structured expert elicitation, as per NICE guidelines, in an attempt to reduce risk of bias and uncertainty (16).

The UK clinicians confirmed that the structure of the model accurately represents the disease and treatment pathways of early NSCLC in the *ALK*+ setting (16). In addition, the SLR carried out to identify relevant economic evaluations (see Appendix G) noted that despite the broad use of Markov models, the SLR shows that considerable variation exists in the health states used by the economic models indicating that a general approach on the modelling of interventions in early NSCLC does not exist. Further details on model validation are outlined in Section B.3.14.

The eight health states in the economic model are disease-free survival, non-metastatic recurrence (treatment and no treatment), metastatic recurrence (first-line: treatment and no treatment), metastatic recurrence (second-line: treatment and no treatment) and death. Figure 9 presents the model's structure and its eight health states.

Figure 9: Model structure and health states



The economic base case used a lifetime time horizon of 40 years, which was considered sufficiently long enough to capture all clinical and economic outcomes of the disease and full treatment pathway for the modelled cohort. The time horizon takes into account typical age at diagnosis and expected survival times following the treatment pathway.

The model used a cycle length of one month, with proportion of patients in each health state calculated each month, as it was expected that any differences in the timing of transitions between the model and reality would be less significant with shorter cycle lengths. This aligns with the expected speed of progression in people with early NSCLC. This is consistent with previous adjuvant NSCLC HTA appraisals (54, 74). Half cycle corrections were not applied in the model, given that it is expected to have a minimal impact on the results.

Discounting was set to 3.5% with the perspective of the NHS and personal social services (PSS) adopted, as per the NICE reference case (75).

For each health state, a specific cost and utility was assigned for each time period (represented by a model cycle). Costs and utilities were multiplied by state occupancy to calculate the weighted costs and quality-adjusted life years (QALYs) per cycle. These were then added across all cycles in the model time horizon to find the total costs and QALYs, which in turn were used to calculate incremental cost per life years gained (LYG) and the incremental cost per QALY gained.

B.3.2.3 Health states

The possible transitions between each of the health states are described below. Where possible, health state transitions were based on best available sources of evidence, full details are outlined in Section B.3.2.4.

B.3.2.3.1 Disease free survival

Patients entered the model in the DFS health state. Patients in the intervention arm received alectinib for 24 months whilst those in the platinum-based chemotherapy arm received treatment 21-day cycles for a total of 4 cycles. Patients who had non-metastatic or metastatic recurrence, or died, transitioned to the non-metastatic recurrence, metastatic recurrence or death health states, respectively.

B.3.2.3.2 Non-metastatic recurrence

Patients transitioned to this health state from DFS if they had non-metastatic recurrence and could either receive subsequent treatment or no treatment. In TA823, UK clinical experts advised that some patients might have less tolerance for subsequent treatment, therefore the model accounted for patients who could may or may not receive subsequent treatment (74).

Patients on curative treatment for non-metastatic recurrence, who then developed metastatic recurrence or died, transitioned to the first line metastatic recurrence or death health states, respectively.

B.3.2.3.3 Metastatic recurrence (1L)

Patients transitioned to this health state from DFS and non-metastatic recurrence if they had metastatic recurrence, and were split by whether they received treatment or no treatment. The model used this separation to account for patients who may or may not receive treatment, as this choice would affect the clinical and economic outcomes. Patients on treatment who progressed or died, transitioned to metastatic recurrence (second-line treatment) or death health states. Patients not receiving treatment could only transition to the death health state.

B.3.2.3.4 Metastatic recurrence (2L)

Patients transitioned to this health state from metastatic recurrence (first-line treatment) if they had disease progression and were split by whether they were treated and not treated. The model used this separation to account for patients who may or may not receive treatment, as this choice would affect the clinical and economic outcomes.

Patients from the 2L metastatic recurrence health state could only transition to the death health state. The model did not include subsequent lines of metastatic treatment; when validating the model with UK clinical oncologists , they agreed the proportion of patients treated were lower at later lines and excluding further lines of metastatic treatment would have a minimal impact on the results from the model. This is in line with the TA823 appraisal (74).

B.3.2.3.5 Death

Patients in all health states can progress to the death. Death is an absorbing health state where all patients transitioned by the end of the model's (lifetime) time horizon.

B.3.2.4 Transition probabilities

The transition probabilities and efficacy for all health states were not able to be informed by the ALINA trial. Therefore, data from published literature were used to estimate the probability of a patient transitioning from one health state to another. An overview of the transition probabilities, efficacy and data sources used per transition is outlined in Table 27.

ALINA does not systematically collect data on disease progression after first recurrence. An SLR was conducted on the transition probabilities, efficacy and safety of interventions for *ALK*-positive NSCLC to identify evidence that could assist it in informing the PFS and OS of patients who do or do not treat after relapsing.

As the study does not have access to the individual patient data (IPD) of the studies that it has identified with the SLRs, approximated datasets were produced by extrapolating the Kaplan-Meier estimates of PFS and OS and transforming them to IPD (76). Similarly to 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 mortality adjustment if it leads to a higher proportion of patients transitioning to death.

B.3.2.4.1 Non-metastatic recurrence

Radiotherapy

The clinical SLR that was conducted for ALINA to identify studies studying the efficacy and safety of interventions for advanced *ALK*+ NSCLC did not identify any studies focussing on the use of radiotherapy for patients with advanced *ALK*+ NSCLC.

A targeted literature review (TLR) was conducted in 2021 to identify studies studying the clinical outcomes of early-stage NSCLC after locoregional recurrence for IMpower010. The TLR identified two studies that investigated the clinical outcomes of patients who received radiotherapy for the treatment of locoregional recurrence (77, 78). While Wu *et al.* uses a greater sample size, does not focus solely on Asian patients, and contains a greater proportion of patients who received adjuvant chemotherapy after surgical resection, their sample contains patients who did and did not receive concurrent/sequential chemotherapy. Therefore, Nakamichi *et al.* was used in the CEM.

Surgery

The SLR and TLR mentioned above did not identify any studies focusing on the use of surgery for patients with locally advanced *ALK*+ NSCLC or who experienced locoregional recurrence. It was assumed that the efficacy of patients who receive surgery is similar to that of patients who receive radiotherapy. In the absence of available data, this may be deemed appropriate despite the limitations with using such an approach (e.g. the clinical outcomes of patients on surgery would not exactly match what we would expect).

Alectinib

The SLR and TLR did not identify any studies focusing on the use of alectinib for patients with only locally advanced *ALK*+ NSCLC or who experienced locoregional recurrence. It was assumed that the efficacy and safety of patients who receive alectinib for non-metastatic recurrence is similar to that of patients who receive alectinib for advanced NSCLC. Therefore, the current data that is included in the model on the efficacy and safety of alectinib as first-line metastatic treatment was used to inform this treatment option. In the absence of available data, this may be deemed appropriate despite the limitations with using such an approach (e.g. the clinical outcomes of patients on alectinib for non-metastatic recurrence would not exactly match what we would expect).

Chemotherapy

The SLR and TLR did not identify any studies focusing on the use of alectinib for patients with only locally advanced *ALK*+ NSCLC or who experienced locoregional recurrence after initial *ALK*+ early-stage NSCLC diagnosis. However, the SLR identified three studies that focus on the use of chemotherapy as first-line treatment for patients with locally advanced and metastatic *ALK*+ NSCLC (79-81). The Profile 1007 study was not considered as the study compares crizotinib with chemotherapy in patients with locally advanced or metastatic ALK+ lung cancer who had received one prior platinum-based regimen (i.e. 2L treatment).

The Soria *et al.* (2014) study was used to inform the clinical outcomes of early-stage ALK+ NSCLC patients who experience non-metastatic recurrence, in the absence of more appropriate data. While the other studies could have also been used, Solomon

et al. (2014) contains a similar sample of patients in terms of characteristics but uses a smaller sample to conduct the analysis (80), and Wu *et al.* (2018) only focus on Chinese patients (79).

B.3.2.4.2 Metastatic recurrence (1L)

The SLR identified four studies that investigated the PFS of first-line metastatic treatment with alectinib (82-85). The first of the four studies is used as it is does not focus solely on an Asian population and the IPD from the ALEX trial is used in the CEM.

The SLR identified one study each that investigated the PFS of first-line metastatic treatment with brigatinib and lorlatinib (Camidge, *et al.*, 2021; Solomon, et al., 2023) (86, 87) which is used in the CEM. It is assumed that the efficacy for chemotherapy is the same as chemotherapy used in non-metastatic recurrence.

B.3.2.4.3 Metastatic recurrence (2L)

The SLR identified three studies that study the OS of second-line metastatic treatment with alectinib (88-90). The CEA does not consider Hotta *et al.* (2022) as this study only focuses solely on an Asian population therefore is not representative of the UK population. While Yang *et al.* (2023) (91) and Novello *et al.* (2018) (92) focused 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.

The above SLR did not identify any studies focussing on the use of lorlatinib as second-line treatment for patients with metastatic NSCLC. In the absence of data on this matter, an assumption was made that the efficacy, safety and treatment discontinuation of second-line lorlatinib is similar to second-line alectinib, despite limitations inherent with this (e.g. the clinical outcomes of patients on lorlatinib would not exactly match what we would expect).

No treatment

The SLR did not identify any studies that study the PFS or OS of patients who do not receive any treatment. Thus, the CEM uses Wong *et al.* (2016) to inform the OS of

patients with non-metastatic, first-line and second-line metastatic recurrence who do not receive treatment (93).

Table 27: Overview of the data source used per transition

Disease state	Treatment options	Estimate	Variance	Standard Deviation	Parameter Incorporating Uncertainty	Inputs to inform Transitions	Source
Non-metastatic recurrence	Radiotherapy	3.07	0.03	0.17	3.33	0.05	Nakamichi *et al.* (2017) (78)
	Surgery	3.07	0.03	0.17	3.33	0.05	Assume same efficacy as radiotherapy Nakamichi *et al.* (2017) (78)
	Alectinib	3.42	0.06	0.25	3.35	0.03	Assumed safe efficacy as alectinib in disease free survival health state (ALINA)
	Chemotherapy	2.54	0.01	0.09	2.45	0.08	Soria *et al.* (2014)
	No treatment	2.53	0.01	0.12	2.52	0.08	Wong *et al.* (2016) (93)
Metastatic recurrence (1L)	Alectinib	3.82	0.01	0.11	4.02	0.02	ALEX (Intent-to-Treat Patients, clinical cut-off: 30.11.2018) (63)
	Chemotherapy	2.54	0.01	0.09	2.53	0.08	Solomon *et al.* (2023) (86)
	Brigatinib	3.78	0.01	0.12	4.03	0.02	Camidge *et al.* (2021) (87)
	Lorlatinib	4.42	0.03	0.16	4.41	0.01	Solomon *et al.* (2023) (86)
	No treatment	2.23	0.01	0.09	2.40	0.11	Wong *et al.* (2016) (93)
Metastatic recurrence (2L)	Alectinib	3.62	0.03	0.17	3.44	0.03	ALUR (Intent-to-Treat Patients, clinical cut-off: 10.2018)
	Lorlatinib	3.62	0.03	0.17	3.68	0.03	Assumed same efficacy as second line alectinib
	Chemotherapy	2.54	0.01	0.09	2.72	0.08	ALUR (Intent-to-Treat Patients, clinical cut-off: 10.2018) (59, 60)
	No treatment	2.23	0.01	0.09	2.27	0.11	Wong *et al.* (2016) (93)

B.3.2.5 Features of the economic analysis

An overview of how the economic analysis of alectinib compared to previous evaluations for adjuvant treatment in early NSCLC is provided in Table 28. Although these appraisals are not for *ALK*+ NSCLC, both appraisals have a similar population for adjuvant treatment of NSCLC after resection.

Table 28: Features of the economic analysis

Factor	Previous evaluations		Current evaluation	
	Atezolizumab [TA823] (74)	Osimertinib [TA761] (54)	Chosen values	Justification
Model structure	Markov with five health states	Markov with five health states	Cohort level semi markov model	Allowed consideration of the long-term clinical and economic outcomes associated with early NSCLC. Aligned with previous NSCLC appraisals
Time horizon	40 years	37 years	40 years	Aligned with NICE reference case Time horizon sufficiently long enough to reflect any differences between clinical and cost outcomes between the technologies being compared
Cycle length	1 month	4 weeks (28 days)	1 month	Aligned with previous NSCLC appraisals and to mitigate bias

Half-cycle correction	Yes	Yes	No	Adding half cycle corrections to the model will significantly increase the size of the model and will make it more complex. Half cycle corrections will have a minimal impact to the results.
Discounting	3.5% for costs and benefits	3.5% for costs and benefits	3.5% for costs and benefits	In line with NICE reference case
Treatment waning effect	Not in base case- included in scenario analysis	No	No- included in scenario analysis	In-line with previous HTAs in this disease area
Source of utilities	Utility sources identified via an SLR. Disease-free survival: Yang *et al.* 2014 Locoregional recurrence: Chouaid et al 2013 (curative), Van den Hout *et al.* 2006 (palliative) 1L metastatic recurrence : IMpower150 2L metastatic recurrence : IMpower150	DF and LRR: SF-36 data from ADAURA mapped to EQ-5D-3L. DM1: EORTC QLQ-C30 data from FLAURA63 mapped to EQ-5D-3L. DM2: Labbé *et al.*	EQ-5D-5L data from ALINA mapped to EQ-5D-3L	In-line with guidance in NICE reference case
Source of costs	NHS Reference Costs PSSRU BNF eMIT	NHS Reference Costs PSSRU BNF eMIT	NHS Reference Costs PSSRU BNF eMIT	Widely used and accepted sources of cost and resource use data

BNF, British national formulary; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.

B.3.2.6 Intervention technology and comparators

The intervention technology, alectinib, and the comparator, platinum based chemotherapy, in the ALINA trial are consistent with the final NICE scope outlined in Section B.1.1. The population of interest is completely resected Stage IB (tumours ≥ 4cm) to Stage IIIA *ALK*+ NSCLC, which is aligned to the [redacted].

Pembrolizumab was not included as a comparator, as this is an ongoing appraisal for adults with NSCLC who have undergone complete surgical resection with or without adjuvant chemotherapy (ID3907) (94). UK clinicians unanimously agreed that pembrolizumab is not a suitable treatment option for patients who are *ALK*+. This is based on clinical practice, guidelines and study data, suggesting that pembrolizumab would not be prescribed for this patient group due to lack of efficacy or clinical rationale. Further rationale for the exclusion of pembrolizumab as a comparator can be found in Table 1, Section B.1.1.

Although UK clinicians consider active monitoring an option for a small portion of patients (typically less than 10%), this would only apply to those for whom the risks of adjuvant treatment outweigh the benefits. This approach is generally reserved for patients with a high risk of disease recurrence and issues related to treatment compliance. Clinician decisions are also influenced by the patient's age, post-surgical recovery, comorbidities, performance status, and patient preference. Some clinicians indicated they would not advocate for active monitoring due to the high risk of disease recurrence.

There are limited studies to demonstrate the efficacy of active monitoring, this comparator has been included in the scenario analyses. Efficacy is assumed equal to platinum-based chemotherapy and treatment costs will be set to zero. The follow up healthcare resource use will remain the same as platinum-based chemotherapy.

B.3.3 Clinical parameters and variables

The primary data source for the economic model is the Phase III, open-label randomised clinical trial, ALINA (CCOD: 26th June 2023), comparing adjuvant alectinib (intervention) to adjuvant platinum based chemotherapy (comparator) (65). This study

is the data source for the clinical outcomes (DFS, OS), adverse events and quality of life for both the comparator and intervention. Alectinib is an oral medication, administered orally BID twice a day (600 mg; four 150 mg capsules) for a duration of 24 months, or until disease progression or unacceptable toxicity. PBC was administered for a total of 4 cycles (21 day cycles) and which included one of the following regimens:

- Cisplatin 75 mg/^{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 could be administered instead of cisplatin in one of the above combinations.

Adjuvant chemotherapy used in the ALINA trial is reflective of current UK clinical practice, therefore the responses and outcomes seen in the ALINA trial are expected to be reflective of UK clinical practice. All treatment options were validated by UK clinical experts at an advisory board held in February 2024 (16).

DFS data was extrapolated over a lifetime time horizon of 40 years and the curves were adjusted to avoid overestimating patients who have recurrences in the longer term. This involved fitting seven parametric curves to the ALINA Kaplan Meir data as per NICE Decision Support Unit methodology (95). The cure assumption was derived from modified structured expert elicitation from UK clinicians and curves were adjusted with the ten-year “cure” assumption (16). A ramping period was not introduced to address the unrealistic “kink” in the DFS curve. This was not accepted by the External Assessment Group (EAG) and NICE committee in the TA823 appraisal (74); therefore, it was not applied in this CEM.

All parametric models were then assessed against the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) for statistical fit to the observed data. Curves were also visually inspected and validated by UK clinical experts during an advisory board to help identify the most plausible survival model (16).

B.3.3.1 DFS extrapolation

Patients remain in the DFS health state while they are disease-free and alive. The probability of remaining in the DFS health state is derived from patient-level data in the ALINA trial. Given the relatively short median follow-up period in the ALINA trial, and the fact that a large proportion of events had not occurred by the end of the available follow-up period, extrapolation techniques were essential to model DFS over a (lifetime) time horizon of 40 years. Guidance from the NICE DSU was followed to identify parametric survival models for DFS in the base case of the cost effectiveness model. The following steps were followed to identify the base-case model:

- Testing the proportional hazard (PH) assumption, to assess whether joint or separate statistical models were more appropriate. The log-cumulative hazard plot was used to assess the proportional hazard assumption.
- The AIC and BIC goodness-of-fit statistics were calculated to assess the goodness of fit to the observed data.
- Within the various parametric survival models explored, visual inspection was used to assess the fit of the curves to the observed clinical trial data.
- Clinical expert validation was conducted to select the most appropriate parametric distribution.

B.3.3.1.1 Unadjusted curves

The Kaplan Meier (KM) data from the ALINA trial for the alectinib and platinum based chemotherapy arm is presented in Figure 12. Based on the latest clinical cut-off date, this data is only available up to approximately month 50. To determine which distribution was the most appropriate fit to the observed data, seven parametric distributions (Exponential, Weibull, Log-normal, Generalised Gamma, Log-logistic, Gamma and Gompertz) were fitted to the observed alectinib DFS data. All parametric distributions without the cure assumption applied is presented in Figure 13 for alectinib arm and Figure 14 for the PBC arm. A Schoenfield test was conducted to test the PH assumption. In curve selection, distributions which support the proportional hazards assumption were preferred, as the PH assumption was not violated. Figure 10 presents the log-cumulative hazard plot of investigator-assessed DFS and Figure 11 presents a Schoenfeld test which support this conclusion.

Figure 10: Log-cumulative hazard plot – investigator-assessed DFS (ALINA; CCOD 26/Jun/23)

Figure 11: Schoenfeld residuals – investigator-assessed DFS (ALINA; CCOD 26/Jun/23)

Figure 12: Kaplan-Meier estimates – investigator-assessed DFS (ALINA; CCOD 26/Jun/23)

ALE; Alectinib. CHT; chemotherapy

Figure 13: Projected investigator-assessed DFS by parametric survival model for alectinib arm (ALINA; CCOD 26/Jun/23)

Figure 14: Projected investigator-assessed DFS by parametric survival model for platinum based chemotherapy arm (ALINA; CCOD 26/Jun/23)

B.3.3.1.2 Statistical tests

The AIC and BIC goodness-of-fit statistics were calculated to assess the goodness of fit to the observed data. When assessing the best statistical fit based on AIC and BIC tests, a difference of five or more between AIC and BIC statistics of models is generally considered meaningful. Thus, when extrapolations have a narrow statistical difference, visual inspection and clinical plausibility become paramount. Table 29 presents the AIC and BIC scores for the different parametric survival models. The scores indicate that the model assuming that investigator-assessed DFS following a log-logistic distribution appears to provide the best fit to the observed data.

Table 29: AIC and BIC scores of parametric survival models of investigator-assessed DFS (ALINA; CCOD 26/Jun/23)

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)

A comparison of the DFS events at different time points was carried out. Table 30 presents the proportion of patients who did not experience a DFS event at 10, 20, and 30 years according to the parametric extrapolations of the Kaplan-Meier data.

Table 30: Expected proportion (%) patients who are disease-free event-free at 5, 10 and 20 years after treatment initiation for alectinib and platinum- based chemotherapy

Distribution	5 years		10 Years		20 Years	
	ALE	PBC	ALE	PBC	ALE	PBC
Exponential	78.8%	37.8%	62.1%	14.3	38.6%	2.00%
Weibull	75.6%	31.2	50.9%	6.00	19.6%	0.10%
Log-normal	74.9%	41.0	55.9%	22.7	35.4%	10,1%
Generalized Gamma	75.3%	34.9	52.9%	12.5	26.6%	2.10%
Log-logistic	75.0%	35.6	52.0%	16.7	28.2%	6.80%
Gompertz	75.1%	30.6	39.5%	2.20	4.00%	0.00%
Gamma	75.3%	32.0	50.8%	7.70	21.2%	0.40%

B.3.3.1.3 Adjusting the DFS curves

Cure adjustment

The median follow-up of ALINA is around [redacted]. As most recurrences occur within 5 years, the DFS projections can underestimate long-term DFS (96). In order for the cost effectiveness analysis (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 a certain number of years.

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. 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. As patients with the *ALK* mutation are generally younger and non-smokers (i.e. have less comorbidities), the use of this study may not be appropriate.

In an attempt to validate this evidence, discussions with UK clinicians were held from which it was concluded that patients who remain disease-free for 10 years might be considered cured but that 0–10% of them may still experience recurrence, and that this should not depend on whether they were treated with adjuvant alectinib or chemotherapy. Using the modified structured expert elicitation method, UK clinicians were asked to estimate the most likely cure assumption rate at year 5, 10 and 20; as well as the lowest and highest plausible limit. The mean estimates for cure assumption are presented in Table 31. The CEA assumes that 92% and 94% of patients will be considered cured for 10 years in the PBC and alectinib arm (i.e. can only experience background mortality).

Table 31. Mean estimates for the proportion of patients cured at 5-, 10- and 20-years

	Mean lowest plausible limit, % (range)	Mean mostly likely estimate, % (range)	Mean highest plausible limit, % (range)
Chemotherapy			
5 years	63 (20–80)	79 (60–90)	91 (80–100)
10 years	77 (25–95)	92 (80–100)	98 (90–100)
20 years	94 (80–100)	98 (90–100)	100 (99–100)
Alectinib			
5 years	66 (30–80)	83 (70–90)	92 (80–100)
10 years	83 (70–95)	94 (90–100)	99 (95–100)
20 years	95 (70–100)	99 (80–100)	100 (90–100)

Treatment waning effect

The CEM allows for the treatment effect of the adjuvant alectinib to decrease over time and eventually cease. When this process begins, the CEM assumes that the clinical

outcomes for patients in the drug arm are informed by the chemotherapy arm. This adjustment is not applied in the base case. While longer-term follow-up data from ALINA would be needed to determine the appropriateness of this adjustment, current results suggest it may not be suitable. Disease-free survival in Figure 15 does not appear to be converging across arms, despite most patients on alectinib completing 24 months of treatment.

Figure 15: Projected investigator-assessed DFS with log-logistic parametric survival model and cure, mortality and treatment effect adjustments (ALINA; CCOD 26/Jun/23)

Mortality adjustment

The cost effectiveness model uses UK lifetable statistics to inform the probability of death of patients who it considers cured after Year 10 (97). Discussions were held with UK clinical experts to validate the evidence from which it was concluded that *ALK*+ patients who are considered cured may confront a similar probability of death as an age- and sex-adjusted individual from the general population (16). As patients with *ALK*+ NSCLC are typically non-smokers, it was assumed that these patients were less likely to develop co-morbidities in comparison to patients with other types of lung cancer. Thus, the CEA assumes that patients who are considered cured after year 10 confront a similar probability of death as someone from the general population. The model adjusts the probability of death of these patients with a standardised mortality

ratio of 1.25 (25% more cases of death than the general population) to account for excess mortality faced by these lung cancer survivors. This estimate was based on Janssen-Heijnen et al. (2012)[1] who reported a 10-year conditional relative survival of 69–82% with a sample of Stage I–III patients (dependent on stage and age at diagnosis) (98) and in line with appraisal TA823 (74). The KM data with the selected distribution curve (log- logistic) with the cure assumption applied in presented in Figure 16.

Figure 16: Projected investigator-assessed DFS with log-logistic parametric survival model and cure, mortality and treatment effect adjustments (ALINA; CCOD 26/Jun/23)

B.3.3.2 Overall survival

Although overall survival was collected in the ALINA trial, the data is immature for this clinical data cut-off, due to a low event-to-patient ratio. This indicates that the current findings may not fully capture the long-term survival benefits of alectinib

It is unlikely that the data will be available for some time due to expected treatment effect. The next data cut-off date is expected in [redacted] and will be descriptive

[1] A structured review was carried out in June 2021 to identify evidence on clinical burden and treatment patterns for patients with early NSCLC in the DFS and locoregional recurrence health state (see Appendix M)

only. In Figure 17, OS is modelled using the log logistic distribution; the KM data is not visible due to insufficient events.

In the absence of mature OS data, which is considered the gold standard in oncology outcomes, DFS was utilised as a surrogate endpoint in the ALINA trial. This decision is backed by consultations with UK clinicians, who agreed that the significant improvements in DFS observed with alectinib are likely to translate into corresponding OS benefits (16). This perspective is informed by historical precedents in oncology where enhanced DFS has been shown to predict improved OS, particularly in treatments targeting specific cancer mechanisms, like *ALK*+ NSCLC.

Figure 17: Overall survival modelled using the log-logistic distribution

B.3.4 Measurement and valuation of health effects

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

ALINA administered the EuroQoL 5-dimension, 5-level questionnaire (EQ-5D-5L) with different frequencies for patients in the intervention and control arms (65). 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.

B.3.4.2 Mapping

The EQ-5D-5L utility values were mapped to EQ-5D-3L using the Hernández Alava *et al.* 2017 algorithm and 'EEPRU dataset' as per NICE DSU guidance (95).

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

An SLR was conducted on 14th September 2023 to identify studies of clinical evidence (efficacy and safety), HRQoL, and other PROs associated with adjuvant treatments for completely resected Stage I-III NSCLC. Detailed descriptions of the search strategy and extraction methods, as well as an overview of the identified studies are provided in Appendix H.

B.3.4.4 Adverse reactions

The CEA does not consider Grade 1–2 AEs as these events were defined by mild to moderate symptoms which may not require any intervention. It only considers Grade 3–5 treatment emergent AEs as these events were treatment-related and produced severe to life threatening symptoms that may require an invasive or emergency intervention. Table 32 presents the AEs observed in ALINA to inform their occurrence during adjuvant treatment. 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.

Table 32: Occurrence of Grade 3–5 treatment emergent adverse events during adjuvant treatment (ALINA; safety-evaluable patients; CCOD 26/Jun/23)

Adverse events	Intervention arm (N = 128)		Control arm (N = 120)	
	Total follow-up = 4,092 months		Total follow-up = 3,842 months	
	Occurrence	Probability	Occurrence	Probability
Neutrophil count decreased	0	0.0000	12	0.0031
Blood creatine phosphokinase increased	8	0.0020	0	0.0000
White blood cell count decreased	0	0.0000	4	0.0010
Alanine aminotransferase increased	2	0.0005	0	0.0000
Blood bilirubin increased	2	0.0005	0	0.0000

Aspartate aminotransferase increased	1	0.0002	0	0.0000
Blood creatine increased	1	0.0002	0	0.0000
Liver function test increased	1	0.0002	0	0.0000
Neutropenia	0	0.0000	10	0.0026
Anaemia	0	0.0000	1	0.0003
Febrile neutropenia	0	0.0000	1	0.0003
Leukopenia	0	0.0000	1	0.0003
Nausea	0	0.0000	5	0.0013
Constipation	1	0.0002	1	0.0003
Vomiting	0	0.0000	2	0.0005
Abdominal pain	0	0.0000	1	0.0003
Diarrhoea	1	0.0002	0	0.0000
Epigastric discomfort	0	0.0000	1	0.0003
Regurgitation	0	0.0000	1	0.0003
Stomatitis	1	0.0002	0	0.0000
Asthenia	0	0.0000	3	0.0008
Fatigue	1	0.0002	2	0.0005
Decreased appetite	0	0.0000	1	0.0003
Hypertriglyceridaemia	1	0.0002	0	0.0000
Type 2 diabetes mellitus	0	0.0000	1	0.0003
Appendicitis	1	0.0002	0	0.0000
Urinary tract infection	0	0.0000	1	0.0003
Cough	1	0.0002	0	0.0000
Pneumonitis	1	0.0002	0	0.0000
Pulmonary embolism	0	0.0000	1	0.0003
Rash	1	0.0002	0	0.0000
Rash maculo-papular	1	0.0002	0	0.0000
Embolism	0	0.0000	1	0.0003
Lymphoedema	1	0.0002	0	0.0000
Hyperbilirubinaemia	1	0.0002	0	0.0000
Myalgia	1	0.0002	0	0.0000

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

The health utility values and sources used in the cost effectiveness analysis is presented in Table 33 below. The utility values were validated by UK clinical experts (16).. UK clinicians highlighted that the utility value of 0.77 for non-metastatic recurrence was deemed too high for patients in this health state, however, this has been tested in scenario analysis. The CEM 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 0.70 for patients who are in the non-metastatic and metastatic recurrence health states.

Table 33: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	Justification
Alectinib - On-treatment	0.83 (0.01)	Derived from ALINA trial
Alectinib - Off-treatment	0.86 (0.014)	Derived from ALINA trial
Chemotherapy - On-treatment	0.81 (0.011)	Derived from ALINA trial
Chemotherapy - Off-treatment	0.86 (0.011)	Derived from ALINA trial
Non-metastatic Recurrence	0.77 (0.03)	Literature source-Chouaid *et al.* (2013) (73)
Metastatic recurrence	0.70 (0.04)	Model calculation

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

An SLR was conducted to identify recent studies presenting cost and resource use data associated with early-stage NSCLC in the adjuvant or neoadjuvant settings, to inform the economic model for this appraisal. Detailed descriptions of the search strategy, search terms and extraction methods, as well as details of the included studies, are provided in Appendix I.

Overall, 133 publications met the eligibility criteria of the review were identified for final inclusion (full publications, n=92; conference abstracts, n=41). A total of 42 studies reported direct medical cost data and the economic burden of early-stage NSCLC was consistently demonstrated to be substantial. Costs were observed to increase with increasing pathological stage of disease, with patients with advanced disease incurring higher costs than those with early-stage disease. Cost drivers also varied according to disease stage, with surgery being the predominant contributor to costs in the early-stages of disease, and radiotherapy, medical therapy, treatment for progression, and supportive care becoming increasingly important with more

advanced disease stages. Treatment approach was also found to influence direct medical costs, with minimally invasive surgery options generally incurring less costs than the more traditional open surgical approaches. A summary of studies with UK-specific costs are provided in Table 34.

Table 34: UK costs related to adjuvant treatment of resectable NSCLC identified from the SLR

Study, country, currency (yr.), follow up period	Study design & objective(s)	Population (sample size)	Direct medical costs	Resource use
Andreas, 2018 (42) Multi-national (France, Germany, UK) EUR (2013) – follow up >1 year	Study design: cost analysis Objective(s): to estimate the burden and cost-of-illness associated with completely resected stage IB-IIIA NSCLC in France, Germany and the UK	Patients aged ≥18 years who had undergone complete resection (no residual disease) of stage IB-IIIA NSCLC (N=306)	Mean total direct costs per patient over follow up period (95% CI): UK: €8,377 (€7,310, €9,518) Mean total community care direct costs per patient (95% CI): UK: €794 (€415, €1,231) Mean monthly direct cost per patient (95% CI): UK: €492 (€405, €587) Mean monthly community care direct cost per patient (95%CI): UK: €71 (€35, €120)	Mean number of episodes per patient over follow up period (SD): Oncologist visits: 5.3 (4.1) Surgeon visits: 2.6 (2.2) Pulmonologist/respiratory physician: 4.6 (3.5) Palliative care physician (Germany & UK): 0 Other specialist visit: 3.2 (3.3) Nurse visits (UK): 1.6 (0.8) Hospitalisations: 1.8 (1.4) ED visits: 1.2 (0.6) CT scans: 3.5 (2.3) MRI: 1.4 (1.1) PET scans: 1.2 (0.4) PET-CT combination: 2.4 (2.2) Ultrasound: 2.5 (2.4) Gamma-knife procedure: 1.0 (-) Nuclear medicine scans: 1.4 (0.8) Ambulance transports: 1.7 (1.8)

				Other paid transport services: 6.9 (8.0) Radiotherapy courses: 9.8 (12.1) Radiotherapy fractions: 44.2 (15.6) Mean duration of hospitalisation, days (SD): 12.3 (15.2)
Kennedy, 2016 (99) UK GBP (2013/ 2014) – follow up ≤1 year	Study design: retrospective cohort (January 2008 to October 2014; follow up period, 12 months) Objective(s): to evaluate the direct costs of hospital care in the diagnosis and management of lung cancer in a single large UK teaching hospital using routine NHS data, and to identify factors that were predictive of high costs	Patients with a diagnosis of lung cancer (N=1,883)	The total direct cost of hospital care over 12 months for the 3,274 patients included in the study was £32,768,229. The mean cumulative costs at 90 days and one year were £5,852 (95% CI: £5,694, £6,027) and £10,009 (95% CI: £9,717 to £10,278), respectively.	NR
Incremental mean UK costs for patients who had complete information for all resource use items: EBUS/EUS procedure: €1,651 Surgical staging procedure: -€1,793 Thoracotomy with lymph node dissection: -€997	Number of patients using each resource use item in the UK, n (%): (a) EBUS/EUS (N=11): EBUS/EUS procedure: 11 (100) Surgical staging procedure: 5 (45) Thoracotomy with lymph node dissection: 6 (55)	Patients with confirmed or suspected potentially resectable NSCLC requiring mediastinal staging based on CT and PET-CT (N=241)		

Total chemotherapy costs in first 2 months: €169 Total radiotherapy cost in first 2 months: -€89 Total hospital admission costs in the first 2 months: -€19 Hospice admission in the first 2 months: €0 Surgery between months 2 and 6: -€116 Total chemotherapy cost between months 2 and 6: -€108 Total radiotherapy cost between months 2 and 6: €264 Total hospital admission costs between months 2 and 6: €25 Hospice admission between months 2 and 6: €12	Chemotherapy in first 2 months: 4 (36) Radiotherapy in first 2 months: 0 (0) Hospital admission in first 2 months: 2 (18) Hospice admission in first 2 months: 0 (0) Surgery between months 2 and 6: 1 (9) Chemotherapy between months 2 and 6: 6 (55) Radiotherapy between months 2 and 6: 6 (55) Hospital admission between months 2 and 6: 5 (45) Hospice admission between months 2 and 6: 1 (9) (b) Surgical staging (N=10): EBUS/EUS procedure: 0 (0) Surgical staging procedure: 10 (100) Thoracotomy with lymph node dissection: 7 (70) Chemotherapy in first 2 months: 5 (50) Radiotherapy in first 2 months: 0 (0) Hospital admission in first 2 months: 2 (20)			

	Hospice admission in first 2 months: 0 (0) Surgery between months 2 and 6: 1 (10) Chemotherapy between months 2 and 6: 6 (60) Radiotherapy between months 2 and 6: 3 (30) Hospital admission between months 2 and 6: 2 (20) Hospice admission between months 2 and 6: 0 (0) Median hospital LOS following thoracotomy, days (IQR): Belgium: 13 (9-13) Netherlands: 8 (7-11) UK: 10 (8-15)			

EBUS, endobronchial ultrasound; IQR, interquartile range.

B.3.5.1 Intervention and comparators' costs and resource use

B.3.5.1.1 Drug acquisition costs

Drug acquisition costs for the treatment regimens included in the economic model are summarised in Table 35. For medicines only available to the NHS as proprietary medicines, prices were taken as the list price stated in the 2024 British National Formulary (BNF) (100). Follow-up costs were taken from NHS Reference Costs 2021-2022 (101) and the Personal Social Services Research Unit 2022 (102). Alectinib has a patient access scheme (PAS) which offers a discount of [redacted] All other treatments are assumed to be list price. Although it should be noted that the other treatments may have a confidential PAS discount within the UK.

The average weight (kg) and body surface area (BSA) (m^2 using the Dubois formula) from the ALINA study (69.63 kg and 1.77 m^2) (65) were used to estimate the average cost per dose per patient for the treatments with dosing according to weight or BSA.

Table 35: Drug acquisition costs

Drug	Small vial/small pack		Large vial/large pack		Source
	Vial size /pack size	List price per pack (£)	Vial size /pack size	List price per pack (£)	
Alectinib	150mg	5,032.00 [redacted]	-	-	-
Crizotinib	250mg	4,698.00	-	-	BNF 2024 (100)
Brigatinib	180mg	4,900.00	-	-	BNF 2024 (100)
Lorlatinib	100mg	5,283.00	-	-	BNF 2024 (100)
Ceritinib	150mg	2,757.13	-	-	BNF 2024 (100)
Cisplatin	50	27.98	100	29.27	eMIT 2023 (103)
Carboplatin	50	9.28	600	71.44	eMIT 2023 (103)
Pemetrexed	100	24.52	500	159.35	eMIT 2023 (103)
Vinorelbine	10	75.16	50	172.56	eMIT 2023 (103)
Gemcitabine	1,000	18.17	1,000	45.96	eMIT 2023 (103)

B.3.5.1.2 Administration costs

Table 36 provides the administration costs assumed for the intervention and comparators. The administration costs for all therapies are sourced from the NHS reference costs (101) and PSSRU 2023 (102).

Table 36: Drug administration costs

Drug	Type of administration	Administration	Unit cost	Cost per subsequent administration	Source
Alectinib Crizotinib Brigatinib Lorlatinib Ceritinib	Oral	12 minutes pharmacist time every 4 weeks, hospital pharmacist (band 6)	£50 per hour	£10.00	PSSRU 2023 (102)
Cisplatin Carboplatin Pemetrexed Vinorelbine Gemcitabine	IV	Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance (SB14Z)	-	£475.94	NHS reference costs 2021/2022 (101)
		Deliver subsequent elements of a chemotherapy cycle – (SB15Z)	-	£368 44	

B.3.5.1.3 Health-state unit costs and resource use

The types of resource are derived from previous line-agnostic advanced NSCLC technology appraisals (TA823 (74) and TA761 (54)); these data were verified by UK clinical experts (16). Frequency of each healthcare resource use was estimated by UK clinicians, resource use estimates per cycle for each disease state are presented in Table 37.

Unit costs for healthcare resources were sourced from NHS Reference costs 2021/22 and are presented in Table 38. The monthly cost of supportive care for each health state is as follows: disease free survival £79.67, non-metastatic recurrence £119.64, metastatic recurrence (1L) £201.54, non-metastatic recurrence (2L) £349.93. A summary of the total health state costs is provided in Table 39.

Table 37: Healthcare resource use by health state

Resource type	Healthcare resource use per month			
	Disease free survival	Non-metastatic recurrence	Metastatic recurrence (1L)	Metastatic recurrence (2L)
Chest radiography	0.08	0.08	0.08	0.08
Outpatient visit	0.12	0.33	1.00	0.12
Community nurse visit	0.10	0.10	0.10	0.10
Clinical Nurse Specialist	0.14	0.14	0.14	0.14
GP surgery visit	0.23	0.23	0.23	0.23
Echocardiogram	0.00	0.00	0.21	0.21
MRI brain scan	0.08	0.08	0.08	0.17
Complete blood count	0.33	0.33	1.00	1.00
Liver function test	0.33	0.33	1.00	1.00
Renal function test	0.33	0.33	1.00	1.00

MRI, magnetic resonance imaging.

Table 38: Healthcare resource use unit costs

Resource type	Cost (£)	Source
Radiotherapy cost, cost per fraction:	244.23	NHS reference costs 2021-2022, Weighted average: SC22Z, SC31Z and SC52Z. (101)
Cost of surgical resection	588.30	NHS reference costs 2021-2022, DZO2K Complex Thoracic Procedures, 19 years and over, with CC Score 0-2(101)
CT scan	119.01	NHS Reference Costs 2021/2022 (101), Diagnostic Imaging, Outpatient, HRG code RD 24Z (two areas with contrast)
ALK test	50.00	Adult Immunohistochemistry Laboratory
Chest radiography	38.28	NHS reference costs 2021/2022 (101), DAPF
Echocardiogram	363.09	NHS Reference costs 2021/22 (101), EY50Z
Outpatient visit	194.71	NHS Reference costs 2021/22 (101), Code 370 outpatient medical oncology
Community nurse visit	82.00	Band 8a, Cost per hour. Personal Social Service Research Unit in UK, 2023 (102)
Complete blood count	2.96	NHS Reference costs 2021/22 (101), DAPS05 – Haematology
Liver Function test	1.55	NHS reference costs 2021/22 (101), DAPS04 – Clinical biochemistry
Renal function test	1.55	NHS reference costs 2021/22 (101), DAPS04 – Clinical biochemistry
Clinical Nurse Specialist	94.00	Band 8b, Cost per hour. Personal Social Service Research Unit in UK, 2023 (102)
MRI scans	223.00	NHS Reference costs 2021/22 (101), RD05Z - Magnetic Resonance Imaging Scan of Two or Three Areas, with Contrast
GP surgery visit	50.50	Average cost per surgery consultation lasting 10 minutes. Personal Social Service Research Unit in UK, 2022 (102)

CT scan, Computerised Tomography Scan.

Table 39: Healthcare resource use, cost per health state per model cycle

Health state	Monthly cost for patients in disease state
Disease free survival	£79.67
Non-metastatic recurrence	£119.64
Metastatic recurrence (1L)	£201.54
Metastatic recurrence (2L)	£349.93

The frequency of follow up CT scans for patients in each disease state is presented in Table 40, this was validated by UK clinical experts (16). The type of radiotherapy and

the total treatment dose is informed by radiotherapy dose fractionation, fourth edition. The most conservative approach was taken for radiotherapy, resulting in 66gy in 33 fractions over 6.5 weeks as per the Royal college of radiologists guidance on fractionation (104).

Table 40: Frequency of follow-up CT scans for patients who remain disease-free after surgery

Health state	Input	Value	Reference
Disease-free	Frequency of CT scans within the first 24 months (2 years) after surgery	Every 6 months	UK clinical expert opinion from NICE appraisal TA823 (74)
	Frequency of CT scans between 25 to 60 months (5 years) after surgery	Every 12 months	UK clinical expert opinion from NICE appraisal TA823 (74)
	Month at which CT scans cease	60 months after surgery	UK clinical expert opinion from NICE appraisal TA823 (74)
Non-metastatic recurrence	Frequency of CT scans	Every 3 months	UK clinical expert opinion from NICE appraisal TA823 (74)
Metastatic recurrence (1st line)	Frequency of CT scans	Every 3 months	UK clinical expert opinion from NICE appraisal TA823 (74)
Metastatic recurrence (2nd line)	Frequency of CT scans	Every 3 months	UK clinical expert opinion from NICE appraisal TA823 (74)

Subsequent treatment

The economic model included costs and resource use of subsequent treatment for patients who have progressed beyond DFS health state. The distribution of subsequent treatments was multiplied by the acquisition and administration costs of each subsequent treatment and applied based on individual treatment regimen. Those patients who were not modelled to receive a subsequent treatment were modelled to receive active monitoring. For each disease health state, the model used the four

treatment options presented and the market shares estimated by UK clinical oncologists are presented in Table 41.

Table 41: Subsequent treatment options and estimated market shares for each disease state

	Inputs	Option 1	Option 2	Option 3	Option 4
Non-metastatic recurrence	Treatment option	Radiotherapy	Surgery	Alectinib	Chemotherapy (cisplatin + pemetrexed)
	Chemotherapy arm	25.0%	10%	42%	23%
	Alectinib arm (Re-challenge disallowed)	47.4%	21.3%	0%	31.3%
	Alectinib arm (Re-challenge allowed)	38%	17%	20%	25%
Metastatic recurrence (1L)	Treatment option	Alectinib	Chemotherapy	Brigatinib	Loratinib
	Chemotherapy arm	54.6%	3.9%	40%	1.5%
	Alectinib arm (Re-challenge disallowed)	0%	17%	34%	49%
	Alectinib arm (Re-challenge allowed)	23%	13%	26%	38%
Metastatic recurrence (2L)	Treatment option	Alectinib	Loralatinib	Chemotherapy	
	Chemotherapy arm	38.5%	46.2%	15.3%	-
	Alectinib arm (Re-challenge disallowed)	0%	58.3%	41.7%	-
	Alectinib arm (Re-challenge allowed)	16%	49%	35%	-

B.3.5.1.4 Adverse reaction unit costs and resource use

For disease-free survival, Grade 3–4 treatment-related AEs that occurred with a difference in incidence rate of at least 2% between treatment arms in the ALINA trial were included in the model. The costs of managing AEs were applied as a monthly cost and were sourced from the NHS reference costs 2021-2022 (101). The cost and source of each AE is presented in Table 42.

Table 42: Adverse event costs

Name of event	Unit cost to manage event (£)	Source
Neutrophil count decreased	0.00	NICE TA428 (105)
Blood creatine phosphokinase increased	0.00	NICE TA531 (106)
Alanine aminotransferase increased	0.00	Assumption
Glutamyltransferase increased	0.00	Assumption
White blood cell count decreased	0.00	NICE TA428 (105)
Neutropenia	625.11	Inflated from TA812 (107)
Nausea	1,059.60	TA812 (107)
Asthenia	0.00	NICE TA531 (106)
Appendicitis	4,376.75	NHS reference costs 2021/22 - FF37D (101)
Febrile neutropenia	0.00	NICE TA531 (106)
Hypercholesterolaemia	0.00	Assumption
Hypertriglyceridaemia	0.00	Assumption
Weight increased	0.00	Assumption
Hypertension	770.10	NHS Reference costs 2021/22 - EB04Z (101)
Lipase increased	0.00	Assumption

B.3.5.1.5 Miscellaneous unit costs and resource use

Testing costs

A one-off *ALK* mutation testing cost was applied in the first model cycle to all patients on alectinib and PBC arm. The cost of immunohistochemistry (IHC) testing was estimated by applying the cost of IHC (£50) to all non-squamous NSCLC patients who would be tested upfront. The cost of an *ALK* test was sourced from the Adult Immunohistochemistry Laboratory (108).

End of life costs

An end of life cost was included in the model and applied to patients who enter the death state as a one-off cost, in line with NICE appraisal TA705 (109) and TA823 (74). The model differentiated end-of-life cost based on whether the death was all-cause or disease related. Patients in the DFS health state who died incurred the all-cause death related end-of-life cost, while patients in the post-DFS health states incurred the disease-related death end-of-life cost. The end of life costs are presented in Table 43.

Table 43: End of life cost

Death	AE management cost	Reference
All-cause	£0	PSSRU 2023 (102)
Disease related	£19,934 per episode	

B.3.6 Severity

No severity analyses are presented as part of this submission.

B.3.7 Uncertainty

Uncertainty analyses are presented in Section B.3.11 Exploring uncertainty.

B.3.8 Managed access proposal

A managed access proposal is not applicable for this submission. Alectinib is not a suitable candidate for managed access given the strength of evidence already available from the ALINA trial. It is anticipated that future data cut offs will have insufficient data for overall survival due to expected treatment effect.

B.3.9 Summary of base-case analysis inputs and assumptions

B.3.9.1 Summary of base-case analysis inputs

Table 44 summarises all key variable applied in the base case of the economic model.

Table 44: Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
General model parameters			
Time horizon	40 years	Fixed	B.3.2.2 Model structure
Discount rate - efficacy	3.5%	Fixed	
Discount rate - costs	3.5%	Fixed	
Population parameters			
Age	54.90 years	Fixed	NR
Body weight	69.63 kg	Fixed	
Height	165.80 cm	Fixed	
Body surface area	1.77 m^2	Fixed	
Clinical inputs			
DFS	Investigator assessed	Fixed	B.3.2.3.1 Disease free survival
Parametric curves			
PFS – alectinib	Log-logistic	Multivariate normal	B.3.2.3.1 Disease free survival
PFS – PBC	Log-logistic	Multivariate normal	
OS – alectinib	Log-logistic	Multivariate normal	
OS – PBC	Log-logistic	Multivariate normal	
Utilities – base case			
Disease free survival	0.83	Beta	B.3.4.1
Non-metastatic recurrence	0.77	Beta	
Metastatic recurrence	0.70	Beta	
Technology acquisition costs per pack (unit costs at list price)			
Alectinib	£5,032.00 [redacted]	Fixed	B.3.5.1
Platinum based chemotherapy	£1,429.00	Fixed	
Administration costs: Intervention and Comparator – per administration			
Alectinib	£10.00	Fixed	B.3.5.1
Platinum based chemotherapy-first attendance	£475.94	Fixed	
Platinum based chemotherapy-subsequent attendance	£368,44	Fixed	
Cost of *ALK* test			

Cost of identifying a person with the *ALK* mutation	£50.00	Fixed	B.3.5.1.5 Miscellaneous unit costs and resource use

B.3.9.2 Assumptions

The key assumptions applied in the base case of the economic model are specified in Table 45.

Table 45: Key assumptions used in the economic model (base case)

Area	Assumption	Justification
Time horizon	40 years	Aligned with NICE reference case (75). Time horizon sufficiently long to reflect any differences in costs or outcomes between the technologies being compared
Clinical inputs	Treatment effect duration	Treatment effect in maintained over time in the base case. In the scenario analysis, a five-year treatment effect was chosen as this aligns with previous NSCLC appraisals
	"Cure" proportion assumptions	Validated with UK clinical oncologists that a small proportion of patients can be considered "cured" if disease-free for ten years.
	Transition probabilities	External sources were used to inform the transition probabilities to non-metastatic and metastatic recurrence health states. Data from other clinical trials were used in absence of specific clinical trial data. This data was appraised in previous NICE appraisals.
	DFS extrapolations	Extrapolation of DFS curves was based on NICE DSU recommendation. Best fit according to statistical and visual fit to observed data and long-term clinical plausibility.
HRQoL	Source utilities	Utility values for the disease free state were collected in the ALINA trial, and therefore applied in the CEM. Utility values after recurrence is taken from the literature (Chouaid *et al.* (2013))
	AEs	The CEA does not include 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.
	AE disutilities not included	Disutilities associated with AEs were not included to avoid double counting, as impact on utilities from AEs may have already been accounted for in the ALINA trial and the identified utility source.
Costs and resource use	NHS reference costs, PSSRU	Aligned with NICE reference case and validated with UK clinical experts.

B.3.10 Base-case results

B.3.10.1 Base-case incremental cost-effectiveness analysis results

The results for the economic model base case for alectinib versus platinum-based chemotherapy (with PAS price applied to alectinib) are presented in Table 46. In these comparisons, all comparators (and therapies included in the treatment pathway) are at list price. Patients in the alectinib arm attained [redacted] QALYs at a total cost of [redacted] The base case results with list price for all medicines are presented in Table 47.

In comparison to the platinum-based chemotherapy arm, alectinib provides an incremental LYG of [redacted] and incremental QALY gain of [redacted] at a total incremental cost of [redacted] This represents an ICER of [redacted] per LYG and an ICER of [redacted] per QALY gained. The results demonstrate that alectinib is a cost effective treatment option compared to platinum based chemotherapy in the base case results at both PAS and list price.

Table 46: Base-case results (with PAS price for alectinib)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/LYG)	ICER (£/QALY)
Alectinib	[redacted]	12.40	9.90	-	-	-	-	-
Platinum- based chemotherapy	[redacted]	8.51	6.60	[redacted]	3.89	3.30	[redacted]	[redacted]

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

Table 47: Base-case results (List price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/LYG)	ICER (£/QALY)
Alectinib	170,742	12.40	9.90	-	-	-	-	-
Platinum- based chemotherapy	112,729	8.51	6.60	58,013	3.89	3.30	16,307	19,227

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

The net health benefit at a willing-to-pay threshold (WTP) of £20,000 and £30,000 per QALY is presented in Table 48. NMB is calculated as (incremental benefit x threshold) – incremental cost.

Table 48: Net health benefit (with PAS price for alectinib)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Alectinib	[redacted]	9.90	-	-	-	-
Platinum- based chemotherapy	[redacted]	6.60	[redacted]	3.18	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; NHB, net health benefit.

The clinical outcomes and disaggregated base-case cost-effectiveness results are presented in Appendix J.

B.3.11 Exploring uncertainty

B.3.11.1 Summary of sensitivity analyses results

- Extensive sensitivity and scenario analyses were conducted in the economic model to demonstrate the uncertainty around the parameters used, assess the plausibility of different scenarios and approaches, and help understand what key variables and assumptions potentially have a major impact on cost effectiveness results.
- The PSA ICER results when comparing alectinib with PAS to platinum based chemotherapy was [redacted], consistent with the deterministic base case.
- The deterministic sensitivity analyses (DSA) showed treatment types after metastatic recurrence, proportion of patients initiating treatment after 1L metastatic recurrence and proportion of DFS events being non metastatic recurrence are the most influential parameters on the ICER.
- These results help to quantify and understand the impact of the uncertainty in the analysis on cost effectiveness and decision-making. Overall, the results show that the model results are robust. The results demonstrates that alectinib is cost effectiveness in all scenarios presented.

B.3.11.2 Probabilistic sensitivity analysis

To assess the uncertainty surrounding the variables included in the cost effectiveness model, a PSA was undertaken using 1,000 iterations to ensure results had converged. Results of the PSA compared to deterministic results at list price are presented in Table 49. The list price equivalent comparison is presented in Table 50.

Table 49: Probabilistic sensitivity analysis results (with PAS price for alectinib)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/LYG)	ICER (£/QALY)
Alectinib	[redacted]	12.35	9.87	-	-	-	-	-
Platinum-based chemotherapy	[redacted]	8.53	6.64	[redacted]	[redacted]	3.23	[redacted]	[redacted]

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

Table 50: Probabilistic sensitivity analysis results (List price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/LYG)	ICER (£/QALY)
Alectinib	172,249	12.35	9.86	-	-	-	-	-
Platinum-based chemotherapy	106,799	8.51	6.62	65,450	3.84	3.240	17,065	20,198

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

The incremental cost effectiveness planes in Figure 18 and Figure 19 show the individual PSA iterations for the comparisons of alectinib to platinum based chemotherapy at list and PAS price, respectively. Alectinib was cost effective in all of the simulations; supporting the view that alectinib is a valuable treatment option for *ALK*+ Stage IIB–III NSCLC within the NHS.

Figure 18: Incremental cost effectiveness plane – alectinib versus platinum based chemotherapy (with PAS applied to alectinib)

ALE, Alectinib; CHT, chemotherapy.

Figure 19: Incremental cost effectiveness plane – alectinib versus platinum based chemotherapy (with alectinib list price)

ALE, Alectinib; CHT, chemotherapy.

Cost effectiveness acceptability curves for the comparisons of alectinib to platinum based chemotherapy at PAS and list price are presented in Figure 20 and Figure 21.

In all scenarios, alectinib remained cost effective versus PBC at the £30,000 WTP threshold.

Figure 20: Cost effectiveness acceptability curve (with PAS applied to alectinib)

ALE, Alectinib; CHT, chemotherapy.

Figure 21: Cost effectiveness acceptability curve (alectinib list price)

ALE, Alectinib; CHT, chemotherapy.

B.3.11.3 Deterministic sensitivity analysis

Deterministic sensitivity analyses with PAS results are presented in Figure 22

Based on the deterministic sensitivity analyses at PAS price, the most influential parameters are the treatment types after metastatic recurrence, proportion of patients

initiating treatment after 1L metastatic recurrence and proportion of patients initiating on treatment after 1L metastatic . All results are cost effective at the £30,000 threshold. The results of the deterministic sensitivity analyses were as expected due to the number of parameters included within the model and number of progressive states – no individual input would be expected to have a significantly large impact.

Figure 22: Tornado diagram (with PAS price applied to alectinib)

Figure 23: Tornado diagram (list price)

B.3.11.4 Scenario analysis

Scenario analyses were conducted to assess uncertainty around remaining parameter inputs and structural assumptions in the model and are presented in Table 51. All scenario results remain cost-effective; the cure rate proportions and treatment effect had the biggest impact on the ICER.

Table 51: Scenario analyses results (with PAS price for alectinib)

Parameter	Value	Alectinib			PBC			ALE vs. PBC	
		Life Years	QALYS	Costs	Life Years	QALYS	Costs	Inc. costs per LY gained	Inc. costs per QALY gained
Base case		**12.4**	**9.9**	[redacted]	**8.5**	**6.6**	[redacted]	[redacted]	[redacted]
Time horizon	10.00	7.5	6.1	[redacted]	6.4	5.0	[redacted]	[redacted]	[redacted]
	20.00	10.7	8.7	[redacted]	7.9	6.2	[redacted]	[redacted]	[redacted]
	30.00	12.1	9.7	[redacted]	8.4	6.5	[redacted]	[redacted]	[redacted]
DFS distributions	Exponential	13.1	10.5	[redacted]	8.4	6.5	[redacted]	[redacted]	[redacted]
	Weibull	12.3	9.8	[redacted]	7.7	5.9	[redacted]	[redacted]	[redacted]
	Log-normal	12.6	10.1	[redacted]	9.1	7.1	[redacted]	[redacted]	[redacted]
	Generalized Gamma	12.5	9.9	[redacted]	8.2	6.3	[redacted]	[redacted]	[redacted]
	Log-logistic	12.4	9.9	[redacted]	8.5	6.6	[redacted]	[redacted]	[redacted]
	Gompertz	11.3	9.0	[redacted]	7.4	5.6	[redacted]	[redacted]	[redacted]
	Gamma	12.3	9.8	[redacted]	7.8	6.0	[redacted]	[redacted]	[redacted]
Maximum "cure" proportion	0%	11.6	9.2	[redacted]	8.5	6.6	[redacted]	[redacted]	[redacted]
	30%	11.8	9.4	[redacted]	8.5	6.6	[redacted]	[redacted]	[redacted]
	70%	12.1	9.6	[redacted]	8.5	6.6	[redacted]	[redacted]	[redacted]
	100%	12.5	10.0	[redacted]	8.5	6.6	[redacted]	[redacted]	[redacted]
"Cure" proportion implementation	5 years	13.8	11.1	[redacted]	9.7	7.6	[redacted]	[redacted]	[redacted]
	20 years	11.7	9.3	[redacted]	8.2	6.3	[redacted]	[redacted]	[redacted]
Trial data used to inform recurrence type split	Pooled across Arms	12.4	9.9	[redacted]	8.5	6.6	[redacted]	[redacted]	[redacted]

Treatment effect	Limited in Time	11.2	8.8	[redacted]	8.5	6.6	[redacted]	[redacted]	[redacted]
Standardised mortality rate	1.70	11.9	9.5	[redacted]	8.3	6.5	[redacted]	[redacted]	[redacted]
	2.30	11.2	9.0	[redacted]	8.1	6.3	[redacted]	[redacted]	[redacted]
Cost of *ALK*+ testing	Exclude	12.4	9.9	[redacted]	8.5	6.6	[redacted]	[redacted]	[redacted]
	NGS	12.4	9.9	[redacted]	8.5	6.6	[redacted]	[redacted]	[redacted]
Utility Values after recurrence	0.60	12.4	9.6	[redacted]	8.5	6.1	[redacted]	[redacted]	[redacted]
Active Monitoring as a comparator	Assumed same efficacy as chemotherapy, costs of treatment set to zero.	12.4	9.9	[redacted]	8.5	6.6	[redacted]	[redacted]	[redacted]

B.3.11.5 Summary of sensitivity analyses results

- The PSA simulations produced a mean ICER of [redacted] per QALY gained, this is in line with the base case results. Furthermore, the cost effectiveness acceptability curve showed that the alectinib arm had a more than 98% probability of being a cost effective treatment at PAS price at the £20,000 WTP threshold.
- The results of the DSA showed that the model drivers were treatment types after metastatic recurrence, proportion of patients initiating treatment after 1L metastatic recurrence and proportion of DFS events being non metastatic recurrence.
- A number of scenario analyses were conducted as part of this submission. The parameters varied included those pertaining to the model settings, clinical parameters, health state utilities, and cost and resource use. ICERs produced by the scenario analysis ranged from [redacted] per QALY gained.

B.3.12 Subgroup analysis

No subgroup analysis was conducted in the economic analysis.

B.3.13 Benefits not captured in the QALY calculation

All health benefits of the technology have been adequately captured in the QALY calculation.

B.3.14 Validation

B.3.14.1 Validation of cost-effectiveness analysis

The modelling approach and structure is consistent with the following NICE appraisals looking at a similar population: Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection (TA761) (54) and atezolizumab for adjuvant treatment of resected non-small-cell lung cancer (TA823) (74).

The economic model was developed specifically from the UK NHS perspective. The structure is consistent with previous adjuvant NSCLC submissions to NICE (54, 74). All costs are sourced from UK published sources including NHS reference costs, PSSRU, published literature and previous NICE NSCLC appraisals. In addition, the model approach and inputs were validated by a number of UK clinical experts to ensure the model is reflective of clinical practice. This includes, but is not limited to model structure, health state inclusion, relevant comparators, healthcare resource use, subsequent treatment, selection of parametric distribution curves, cure approach.

The modelling approach and inputs were cross-referenced with previous technology appraisals and subsequently validated by UK clinical experts at an advisory board (16). The feedback provided confirmed that the structure of the model accurately represents the disease and treatment pathways of early NSCLC. These validations ensured that the model was robust and reflective of current UK clinical practice.

Selection of the appropriate parametric distributions was driven by statistical fit to the data, visual fit to the Kaplan-Meier and clinical plausibility of the outcomes as per an advisory board with clinical experts.

Clinical data for the DFS health state have been incorporated into the model from the ALINA trial and the clinical outcomes in both arms of the model have been compared with published evidence and clinical expert opinion.

Internal quality control and validation of the model was conducted by an external consultancy. A technical cell by cell verification of formulas, functions, and coding was performed as part of this process. A number of 'pressure tests' were also conducted using extreme values and these were compared to expected outputs to assess the functional accuracy.

B.3.15 Interpretation and conclusions of economic evidence

This is the first economic evaluation focused on assessing the cost effectiveness of alectinib for the adjuvant treatment of patients with *ALK*+ NSCLC versus platinum based chemotherapy from a UK health system perspective. The base case results demonstrated that alectinib is a cost effective treatment for the NHS and is supported by the extensive sensitivity and scenario analyses.

B.3.15.1 Strengths of the evaluation

- Efficacy, safety and HRQoL data was directly collected in the ALINA trial and therefore were used in the CEM.

- The long-term efficacy extrapolations from the model were made using methodologies to follow NICE guidance and validated by UK clinical experts to ensure the clinical plausibility of the model.

- Resource utilisation used in the analysis is derived from previous NICE appraisals relating to advanced NSCLC and clinical expert opinion. Unit costs used in the analysis are reflective of UK clinical practice and were mainly derived from UK published sources and previous NICE appraisals.

- Cure assumption rate, treatment types after DFS and proportion of patients receiving treatment in health state was validated by UK clinical experts.

- To account for any potential uncertainty, extensive sensitivity and scenario analyses were conducted in the economic model to inform the uncertainty

around the parameters used and help understand what key variables and assumptions potentially have a major impact on cost-effectiveness results.

B.3.15.2 Limitations of the evaluation

- DFS as a surrogate for OS – In the absence of long-term OS data (the 'gold standard' in terms of outcomes for oncology), DFS is used in the model. We validated this with UK clinical oncologists who considered that the DFS benefit will translate into OS benefit.

- Data was not identified in published literature for some transition probabilities between health states as well as efficacy and safety inputs for some treatment options in non- metastatic recurrence and 1L metastatic recurrence.

- The study's stratification by race and disease stage, along with a high proportion of Asian participants could affect the generalisability of the results.

- Challenges in interpretation may arise from the study's open-label design, and the limited maturity of OS data.

- The comparison compared to active monitoring is not robust as there is no available efficacy data and therefore the clinical benefit of active monitoring has been overestimated in the scenario analysis.

- There is uncertainty about later treatments with or without adjuvant alectinib (including retreatment with alectinib).

Several measures have been implemented to address limitations of the evaluation. For example, by adopting conservative assumptions and employing a robust methodology where possible, testing the impact on the ICER, providing thorough sensitivity and scenario analyses, and ultimately delivering an appropriate cost-effectiveness analysis to aid decision-making.

B.3.15.3 Conclusions

Currently there is high unmet need for *ALK*+ NSCLC patients in the adjuvant setting. Alectinib is an innovative treatment offering a potentially curative benefit and

represents a paradigm shift to patients and healthcare providers, in a disease area with high unmet need.

Alectinib is a highly efficacious and well tolerated as demonstrated by the primary analysis data from the ALINA trial. The study demonstrated a statistically significant and clinically meaningful improvement in DFS with alectinib compared to chemotherapy in patients with resected early-stage *ALK*+ NSCLC.

In addition to the clinical benefits of alectinib to patients, it is also a highly cost effective treatment when compared to platinum-based chemotherapy reporting an ICER of [redacted]. This ICER is well below the conventional NICE thresholds of £20,000–£30,000 per QALY and at a WTP threshold of £20,000 per QALY, alectinib has a 100% probability of being cost-effective.

In conclusion, these findings underscore that alectinib represents a substantial improvement over current treatment options and represents a cost effective treatment option for *ALK*+ NSCLC patients within the NHS.

B.4 References

1. Hendriks LE, Kerr KM, Menis J, Mok TS, Nestle U, Passaro A, et al. Oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up[☆]. Annals of Oncology. 2023;34(4):339-57.
2. Mazieres J, Drilon A, Lusque A, Mhanna L, Cortot AB, Mezquita L, et al. Immune checkpoint inhibitors for patients with advanced lung cancer and oncogenic driver alterations: results from the IMMUNOTARGET registry. Ann Oncol. 2019;30(8):1321-8.
3. O'Brien M, Paz-Ares L, Marreaud S, Dafni U, Oselin K, Havel L, et al. Pembrolizumab versus placebo as adjuvant therapy for completely resected stage IB–IIIA non-small-cell lung cancer (PEARLS/KEYNOTE-091): an interim analysis of a randomised, triple-blind, phase 3 trial. The Lancet Oncology. 2022;23(10):1274-86.
4. Cancer Research UK. Lung cancer statistics [Accessed on 16/Apr/24]. 2023.
5. The Royal College of Surgeons of England (RCS England). National Lung Cancer Audit: State of the Nation Report 2023 (Data Tables). 2023.
6. International Agency for Research on Cancer (IARC). International Cancer Benchmarking Partnership (ICBP), Cancer Survival in High-Income Countries (SURVMARK-2) [Accessed on 17/Apr/24]. 2024.
7. American Cancer Society. Lung Cancer Survival Rates | 5-Year Survival Rates for Lung Cancer [Accessed on 17/Apr/24]. 2024.
8. Chevallier M, Borgeaud M, Addeo A, Friedlaender A. Oncogenic driver mutations in non-small cell lung cancer: Past, present and future. World journal of clinical oncology. 2021;12(4):217-37.
9. Ravdin PM, Davis G. Prognosis of patients with resected non-small cell lung cancer: impact of clinical and pathologic variables. Lung cancer (Amsterdam, Netherlands). 2006;52(2):207-12.
10. Travis WD, Rekhtman N. Pathological diagnosis and classification of lung cancer in small biopsies and cytology: strategic management of tissue for molecular testing. Seminars in respiratory and critical care medicine. 2011;32(1):22-31.
11. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Annals of surgical oncology. 2010;17(6):1471-4.
12. UyBico SJ, Wu CC, Suh RD, Le NH, Brown K, Krishnam MS. Lung cancer staging essentials: the new TNM staging system and potential imaging pitfalls. Radiographics : a review publication of the Radiological Society of North America, Inc. 2010;30(5):1163-81.
13. National Institute for Health and Care Excellence (NICE). Lung cancer in adults - Quality Standard 17 2012 [Available from: https://www.nice.org.uk/guidance/qs17/resources/lung-cancer-in-adults-pdf-2098490350021.

14. Choi YL, Soda M, Yamashita Y, Ueno T, Takashima J, Nakajima T, et al. EML4-ALK mutations in lung cancer that confer resistance to ALK inhibitors. The New England journal of medicine. 2010;363(18):1734-9.
15. Ou SH, Bartlett CH, Mino-Kenudson M, Cui J, Iafrate AJ. Crizotinib for the treatment of ALK-rearranged non-small cell lung cancer: a success story to usher in the second decade of molecular targeted therapy in oncology. The oncologist. 2012;17(11):1351-75.
16. Roche. ALINA Advisory Board - Discussion of the Clinical Data and Health Technology Assessment (HTA) Submission for Adjuvant Alectinib for ALK+ Stage IB–IIIA NSCLC [Data on File]. 2024.
17. Le T, Gerber DE. ALK alterations and inhibition in lung cancer. Seminars in cancer biology. 2017;42:81-8.
18. Schneider JL, Lin JJ, Shaw AT. ALK-positive lung cancer: a moving target. Nature cancer. 2023;4(3):330-43.
19. National Disease Registration Service (NDRS). Core – Molecular and biomarkers [Accessed on 30/Apr/24]. 2022.
20. Johung KL, Yeh N, Desai NB, Williams TM, Lautenschlaeger T, Arvold ND, et al. Extended Survival and Prognostic Factors for Patients With ALK-Rearranged Non-Small-Cell Lung Cancer and Brain Metastasis. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2016;34(2):123-9.
21. Tian HX, Zhang XC, Yang JJ, Guo WB, Chen ZH, Wang Z, et al. Clinical characteristics and sequence complexity of anaplastic lymphoma kinase gene fusions in Chinese lung cancer patients. Lung cancer (Amsterdam, Netherlands). 2017;114:90-5.
22. ALK Positive UK. About ALK-positive lung cancer [Accessed on 10/May/24]. 2023.
23. Guérin A, Sasane M, Zhang J, Culver KW, Dea K, Nitulescu R, et al. Brain metastases in patients with ALK+ non-small cell lung cancer: clinical symptoms, treatment patterns and economic burden. Journal of Medical Economics. 2015;18(4):312-22.
24. Roy Castle Lung Cancer Foundation. Lung cancer and brain metastases [Accessed on 10/May/24].
25. Driver & Vehicle Licensing Agency (DVLA). Assessing fitness to drive – a guide for medical professionals. 2024.
26. Steindl A, Yadavalli S, Gruber KA, Seiwald M, Gatterbauer B, Dieckmann K, et al. Neurological symptom burden impacts survival prognosis in patients with newly diagnosed non-small cell lung cancer brain metastases. Cancer. 2020;126(19):4341-52.
27. National Lung Cancer Audit (NLCA). State of the Nation Report 2024. 2024.
28. Martin J, Ginsberg RJ, Venkatraman ES, Bains MS, Downey RJ, Korst RJ, et al. Long-term results of combined-modality therapy in resectable non-small-cell lung cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2002;20(8):1989-95.

29. Sugimura H, Nichols FC, Yang P, Allen MS, Cassivi SD, Deschamps C, et al. Survival after recurrent nonsmall-cell lung cancer after complete pulmonary resection. The Annals of thoracic surgery. 2007;83(2):409-17; discussioin 17-8.
30. NSCLC Meta-analysis Collaborative Group. Preoperative chemotherapy for non-small-cell lung cancer: a systematic review and meta-analysis of individual participant data. Lancet (London, England). 2014;383(9928):1561-71.
31. Williams BA, Sugimura H, Endo C, Nichols FC, Cassivi SD, Allen MS, et al. Predicting postrecurrence survival among completely resected nonsmall-cell lung cancer patients. The Annals of thoracic surgery. 2006;81(3):1021-7.
32. Lim JU. Update on Adjuvant Treatment in Resectable Non-Small Cell Lung Cancer and Potential Biomarkers Predicting Postoperative Relapse. Tuberculosis and respiratory diseases. 2023;86(1):14-22.
33. National Institute for Health and Care Excellence (NICE). Treatment for lung cancer [Accessed on 17/Apr/24]. 2019.
34. Tsuboi M, Herbst RS, John T, Kato T, Majem M, Grohé C, et al. Overall Survival with Osimertinib in Resected EGFR-Mutated NSCLC. The New England journal of medicine. 2023;389(2):137-47.
35. Tang WF, Ye HY, Tang X, Su JW, Xu KM, Zhong WZ, et al. Adjuvant immunotherapy in early-stage resectable non-small cell lung cancer: A new milestone. Frontiers in oncology. 2023;13:1063183.
36. Rivera MP, Mehta AC, Wahidi MM. Establishing the diagnosis of lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 Suppl):e142S-e65S.
37. Vansteenkiste J, Crinò L, Dooms C, Douillard JY, Faivre-Finn C, Lim E, et al. 2nd ESMO Consensus Conference on Lung Cancer: early-stage non-small-cell lung cancer consensus on diagnosis, treatment and follow-up. Ann Oncol. 2014;25(8):1462-74.
38. Bowes K, Jovanoski N, Brown AE, Di Maio D, Belleli R, Chadda S, et al. Treatment patterns and survival of patients with locoregional recurrence in early-stage NSCLC: a literature review of real-world evidence. Medical oncology (Northwood, London, England). 2022;40(1):4.
39. Kelsey CR, Marks LB, Hollis D, Hubbs JL, Ready NE, D'Amico TA, et al. Local recurrence after surgery for early stage lung cancer: an 11-year experience with 975 patients. Cancer. 2009;115(22):5218-27.
40. Pignon JP, Tribodet H, Scagliotti GV, Douillard JY, Shepherd FA, Stephens RJ, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2008;26(21):3552-9.
41. Boyd JA, Hubbs JL, Kim DW, Hollis D, Marks LB, Kelsey CR. Timing of local and distant failure in resected lung cancer: implications for reported rates of local failure. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer. 2010;5(2):211-4.

42. Andreas S, Chouaid C, Danson S, Siakpere O, Benjamin L, Ehness R, et al. Economic burden of resected (stage IB-IIIA) non-small cell lung cancer in France, Germany and the United Kingdom: A retrospective observational study (LuCaBIS). Lung cancer (Amsterdam, Netherlands). 2018;124:298-309.
43. J. Remon J-CSaSP, on behalf of the ESMO Guidelines Committee,. eUpdate – Early and Locally Advanced Non-Small-Cell Lung Cancer (NSCLC) Treatment Recommendations. 2021.
44. National Comprehensive Cancer Network (NCCN) Guidelines. Treatment by Cancer Type [Accessed on 18/Apr/24]. 2024.
45. National Institute for Health and Care Excellence (NICE). Lung cancer: diagnosis and management - NICE guideline [NG122]. 2024.
46. Postmus PE, Kerr KM, Oudkerk M, Senan S, Waller DA, Vansteenkiste J, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. Annals of Oncology. 2017;28:iv1-iv21.
47. Burdett S, Pignon JP, Tierney J, Tribodet H, Stewart L, Le Pechoux C, et al. Adjuvant chemotherapy for resected early-stage non-small cell lung cancer. The Cochrane database of systematic reviews. 2015;2015(3):Cd011430.
48. West H, Hu X, Zhang S, Song Y, Chirovsky D, Gao C, et al. Treatment Patterns and Outcomes in Resected Early-stage Non-small Cell Lung Cancer: An Analysis of the SEER-Medicare Data. Clinical lung cancer. 2023;24(3):260-8.
49. Artal Cortés Á, Calera Urquizu L, Hernando Cubero J. Adjuvant chemotherapy in non-small cell lung cancer: state-of-the-art. Translational lung cancer research. 2015;4(2):191-7.
50. Bezjak A, Lee CW, Ding K, Brundage M, Winton T, Graham B, et al. Quality-of-life outcomes for adjuvant chemotherapy in early-stage non-small-cell lung cancer: results from a randomized trial, JBR.10. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2008;26(31):5052-9.
51. Park S, Kim IR, Baek KK, Lee SJ, Chang WJ, Maeng CH, et al. Prospective analysis of quality of life in elderly patients treated with adjuvant chemotherapy for non-small-cell lung cancer. Ann Oncol. 2013;24(6):1630-9.
52. Felip E, Altorki N, Zhou C, Csőszi T, Vynnychenko I, Goloborodko O, et al. Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB-IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial. Lancet (London, England). 2021;398(10308):1344-57.
53. Wu YL, Tsuboi M, He J, John T, Grohe C, Majem M, et al. Osimertinib in Resected EGFR-Mutated Non-Small-Cell Lung Cancer. The New England journal of medicine. 2020;383(18):1711-23.
54. National Institute for Health and Care Excellence (NICE). Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection [TA761]. 2022.

55. Friedlaender A, Banna G, Patel S, Addeo A. Diagnosis and Treatment of ALK Aberrations in Metastatic NSCLC. Current treatment options in oncology. 2019;20(10):79.
56. Roche. Draft Alectinib Summary of Product Characteristics (SmPC) [Data on File]. 2024.
57. Peters S, Camidge DR, Shaw AT, Gadgeel S, Ahn JS, Kim DW, et al. Alectinib versus Crizotinib in Untreated ALK-Positive Non-Small-Cell Lung Cancer. The New England journal of medicine. 2017;377(9):829-38.
58. Shaw AT, Kim DW, Nakagawa K, Seto T, Crinó L, Ahn MJ, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. The New England journal of medicine. 2013;368(25):2385-94.
59. Novello S MJ, Oh I, et al. Primary results from the phase III ALUR study of alectinib vs. chemotherapy in previously treated ALK+ non−small-cell lung cancer (NSCLC). Ann Oncol. 2017;28(Suppl 5):v605-49.
60. Roche. Final CSR Study − MO29750 (ALUR) − Randomized, Multicenter, Phase III, Open-Label Study of Alectinib versus Pemetrexed or Docetaxel in Anaplastic Lymphoma Kinase-Positive Advanced Non-Small Cell Lung Cancer Patients Previously treated with Platinum Based Chemotherapy and Crizotinib [Data on File]. 2019.
61. Mok T, Camidge DR, Gadgeel SM, Rosell R, Dziadziuszko R, Kim DW, et al. Updated overall survival and final progression-free survival data for patients with treatment-naive advanced ALK-positive non-small-cell lung cancer in the ALEX study. Ann Oncol. 2020;31(8):1056-64.
62. Gadgeel S, Peters S, Mok T, Shaw AT, Kim DW, Ou SI, et al. Alectinib versus crizotinib in treatment-naive anaplastic lymphoma kinase-positive (ALK+) non-small-cell lung cancer: CNS efficacy results from the ALEX study. Ann Oncol. 2018;29(11):2214-22.
63. Roche. Primary CSR Study − BO28984 (ALEX) − Randomized, Multicenter, Phase III, Open-Label Study of Alectinib versus Crizotinib in Treatment-Naïve Anaplastic Lymphoma Kinase-Positive Advanced Non-Small Cell Lung Cancer [Data on File]. 2017.
64. Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. The Lancet Oncology. 2012;13(3):239-46.
65. Roche. Primary CSR Clinical Report: Study BO40336 (ALINA): A Phase III, open-label, randomised study to evaluate the efficacy and safety of adjuvant alectinib versus adjuvant platinum-based chemotherapy in patients with completely resected Stage IB to Stage IIIA ALK+ NSCLC [Data on File]. 2023.
66. Wu Y-L, Dziadziuszko R, Ahn Jin S, Barlesi F, Nishio M, Lee Dae H, et al. Alectinib in Resected ALK-Positive Non–Small-Cell Lung Cancer. New England Journal of Medicine. 2024;390(14):1265-76.

67. Brookmeyer R, Crowley J. A Confidence Interval for the Median Survival Time. Biometrics. 1982;38(1):29-41.
68. Brunelli A, Socci L, Refai M, Salati M, Xiumé F, Sabbatini A. Quality of life before and after major lung resection for lung cancer: a prospective follow-up analysis. The Annals of thoracic surgery. 2007;84(2):410-6.
69. Myrdal G, Gustafsson G, Lambe M, Hörte LG, Ståhle E. Outcome after lung cancer surgery. Factors predicting early mortality and major morbidity. European Journal of Cardio-Thoracic Surgery. 2001;20(4):694-9.
70. Ostroff JS, Krebs P, Coups EJ, Burkhalter JE, Feinstein MB, Steingart RM, et al. Health-related quality of life among early-stage, non-small cell, lung cancer survivors. Lung cancer (Amsterdam, Netherlands). 2011;71(1):103-8.
71. Maruish M. E. User's Manual for the SF-36v2 Health Survey (3rd edition). Quality Metric Incorporated. 2011.
72. Roche. Adjuvant/Neoadjuvant Treatment Of Early Non-Small Cell Lung Cancer (NSCLC): Systematic Literature Review (SLR) To Identify Economic Evaluations [Data on File]. 2023.
73. Chouaid C, Agulnik J, Goker E, Herder GJ, Lester JF, Vansteenkiste J, 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. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer. 2013;8(8):997-1003.
74. National Institute for Health and Care Excellence (NICE). Atezolizumab for adjuvant treatment of resected non-small-cell lung cancer [TA823]. 2022.
75. National Institute for Health and Care Excellence (NICE). NICE health technology evaluations: the manual [PMG36]. 2023.
76. Guyot P, Ades AE, Ouwens M, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Medical Research Methodology. 2012.
77. Wu YL, Yang JC, Kim DW, Lu S, Zhou J, Seto T, et al. Phase II Study of Crizotinib in East Asian Patients With ROS1-Positive Advanced Non-Small-Cell Lung Cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2018;36(14):1405-11.
78. 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 Surgery. Clinical lung cancer. 2017;18(6):e441-e8.
79. Wu YL, Lu S, Lu Y, Zhou J, Shi YK, Sriuranpong V, et al. Results of PROFILE 1029, a Phase III Comparison of First-Line Crizotinib versus Chemotherapy in East Asian Patients with ALK-Positive Advanced Non-Small Cell Lung Cancer. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer. 2018;13(10):1539-48.

80. Solomon BJ, Mok T, Kim DW, Wu YL, Nakagawa K, Mekhail T, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. The New England journal of medicine. 2014;371(23):2167-77.
81. Soria JC, Tan DSW, Chiari R, Wu YL, Paz-Ares L, Wolf J, et al. First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study. Lancet (London, England). 2017;389(10072):917-29.
82. 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.
83. Hida T, Nokihara H, Kondo M, Kim Y, Azuma K, Seto T, et al. Alectinib versus crizotinib in patients with ALK-positive non-small-cell lung cancer (J-ALEX): an open-label, randomised phase 3 trial. Lancet. 2017:29-39.
84. Li Z, Zhao J. Clinical efficacy and safety of crizotinib and alectinib in ALK-positive non-small cell lung cancer treatment and predictive value of CEA and CA125 for treatment efficacy. American Journal of Translational Research. 2021:13108-16.
85. Zhou C, Lu Y, Kim S, Baisamut T, Zhou J, Zhang Y, et al. LBA11 Alectinib (ALC) vs crizotinib (CRZ) in Asian patients (pts) with treatment-naïve advanced ALK+ non-small cell lung cancer (NSCLC): 5-year update from the phase III ALESIA study. Annals of Oncology. 2022.
86. Solomon BJ, Bauer TM, Mok TSK, 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. The Lancet Respiratory medicine. 2023;11(4):354-66.
87. Camidge DR, Kim HR, Ahn MJ, Yang JCH, Han JY, Hochmair MJ, 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 : official publication of the International Association for the Study of Lung Cancer. 2021;16(12):2091-108.
88. Yang J, Liu G, Lu S, He J, Burotto M, Ahn M, et al. Brigatinib versus alectinib in ALK-positive NSCLC after disease progression on crizotinib: Results of phase 3 ALTA-3 trial. Journal of Thoracic Oncology. 2023:1743-55.
89. Hotta K, Hida T, Nokihara H, Morise M, Kim Y, Azuma K, et al. Final overall survival analysis from the phase III J-ALEX study of alectinib versus crizotinib in ALK inhibitor-naïve Japanese patients with ALK-positive non-small-cell lung cancer. ESMO Open. 2022.
90. 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.

91. Yang JC, Liu G, Lu S, He J, Burotto M, Ahn MJ, et al. Brigatinib Versus Alectinib in ALK-Positive NSCLC After Disease Progression on Crizotinib: Results of Phase 3 ALTA-3 Trial. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer. 2023;18(12):1743-55.
92. Novello S, Mazières J, Oh IJ, de Castro J, Migliorino MR, Helland Å, 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. Ann Oncol. 2018;29(6):1409-16.
93. Wong ML, McMurry TL, Stukenborg GJ, Francescatti AB, Amato-Martz C, Schumacher JR, et al. Impact of age and comorbidity on treatment of non-small cell lung cancer recurrence following complete resection: A nationally representative cohort study. Lung cancer (Amsterdam, Netherlands). 2016;102:108-17.
94. National Institute for Health and Care Excellence (NICE). Pembrolizumab for adjuvant treatment of resected non-small-cell lung cancer [ID3907]. 2024.
95. Woods BS, Sideris, E., Palmer, S. J., Latimer, N., & Soares, M. F. O.,. NICE DSU technical support document 19: partitioned survival analysis for decision modelling in health care: a critical review. 2017.
96. Sonoda D, Matsuura Y, Ichinose J, Nakao M, Ninomiya H, Mun M, et al. Ultra-late recurrence of non-small cell lung cancer over 10 years after curative resection. Cancer management and research. 2019;11:6765-74.
97. Office for National Statistics (ONS). National life tables: UK [Accessed on 19/Apr/24]. 2024.
98. Janssen-Heijnen ML, van Steenbergen LN, Steyerberg E, Visser O, De Ruysscher DK, Groen HJ. Long-term excess mortality for survivors of non-small cell lung cancer in the Netherlands. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer. 2012;7(3):496-502.
99. Kennedy MP, Hall PS, Callister ME. Factors affecting hospital costs in lung cancer patients in the United Kingdom. Lung cancer (Amsterdam, Netherlands). 2016;97:8-14.
100. National Institute for Health and Care Excellence (NICE). NICE British National Formulary (BNF) [Accessed on 19/Apr/24]. 2024.
101. NHS England. 2021/22 National Cost Collection Data Publication. 2023.
102. Personal Social Services Research Unit (PSSRU). Unit Costs of Health and Social Care programme (2022 – 2027). 2023.
103. Gov.uk. Drugs and pharmaceutical electronic market information tool (eMIT). 2023.
104. The Royal College of Radiologists. Radiotherapy dose fractionation Fourth edition. 2024.
105. National Institute for Health and Care Excellence (NICE). Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy [TA428]. 2017.
106. National Institute for Health and Care Excellence (NICE). Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer [TA531]. 2018.

107. National Institute for Health and Care Excellence (NICE). Pralsetinib for treating RET fusion-positive advanced non-small-cell lung cancer [TA812]. 2022.
108. NHS Manchester University. Immuno-histochemistry and Research [Accessed on 19/Apr/24]. 2017.
109. National Institute for Health and Care Excellence (NICE). Atezolizumab monotherapy for untreated advanced non-small-cell lung cancer [TA705]. 2021.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Alectinib for adjuvant treatment of ALK-positive non-small-cell lung cancer [ID6368]

Summary of Information for Patients (SIP)

May 2024

File name	Version	Contains confidential information	Date
ID6368_Alectinib for ALK+ NSCLC_SIP	1.0	Yes	15.05.2024

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

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

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

SECTION 1: Submission summary

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

Generic name: Alectinib **Brand name:** Alecensa®

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

Alectinib, used alone, for adults with early anaplastic lymphoma kinase (*ALK*)-positive non-small cell lung cancer (NSCLC), after surgery.

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

A marketing authorisation application (MAA) was submitted to the Medicines and Healthcare products Regulatory Agency (MHRA) in Q4 2023. Committee for Medicinal Products for Human Use (CHMP) opinion was received in Q2 2024.

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

In 2023/24, Roche provided the following support to UK-based patient groups that are relevant to the use of alectinib/ *ALK*+ NSCLC. These included providing funds for the purpose of supporting patients, healthcare, scientific research or education that is independent and free from Roche influence, where Roche did not receive any direct benefit or gains. These included:

- A £10,550 grant to ALK+ UK to support their annual conference in 2023 for patients and carers;
- A £11,897 grant to ALK+ UK to support their annual conference in 2024 for patients and carers;
- A £30,000 (+ VAT if applicable) global-led sponsorship of the Global Lung Cancer Coalition (GLCC), involving members of the ALK+ UK and Roy Castle Lung Cancer Foundation.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

ALK-positive NSCLC and how many people have the condition

In the UK, lung cancer is the third most common type of cancer, making up about 13% of all new cancer cases, with about 48,500 of new cases every year (1). It is also the main cause of death from cancer, accounting for 21% of all cancer deaths from 2017−2019 (1). Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, making up 91% all lung cancer cases in England (5).

ALK-positive (*ALK*+) NSCLC refers to a subtype of lung cancer that has a specific genetic alteration involving the *ALK* gene (anaplastic lymphoma kinase). A change in this gene leads to the production of an abnormal ALK protein that promotes the growth of cancer cells. Identifying this change is crucial because it allows for the use of targeted treatments, specifically ALK inhibitors, which can block the activity of the abnormal protein and therefore help control the spread of cancer.

Burden of _ALK_+ NSCLC on patients and carers

About 30% of NSCLC patients find out they have the disease early on, while most people, about 60%, are diagnosed when it is already very advanced (2). The chances of living for five more years after diagnosis are very low for those with advanced lung cancer, about

1−5% (2). However, for those diagnosed early, the survival rates are better, between 14−70%, depending on how far the cancer has spread and the treatments used (2-5). NSCLC patients often have a persistent cough, difficulty breathing (dyspnoea), and chest pain, especially if the tumour has spread to the pleura (lining of the lungs) or nearby chest structures. Other common symptoms include fatigue, recurring infections, coughing up blood (haemoptysis), and unexplained weight loss, all of which can affect lung function and general health.

Specifically, *ALK*+ NSCLC tends to appear in younger patients, usually never-smokers or light-smokers, and are still working and supporting families. A significant concern for them is the high chance (about 50−60%) of the cancer spreading to the brain during their disease (6, 7). Brain metastases can cause severe symptoms like headaches, difficulty breathing, weakness, nausea, mood changes, seizures, coordination issues, confusion, fatigue, and problems with speech and reading. Because of these symptoms, those diagnosed with brain metastases cannot drive, as mandated by the Driver & Vehicle Licensing Agency (DVLA) (8).

ALK+ NSCLC is often diagnosed at a late stage, making it harder to cure. This late diagnosis, along with the clinical characteristics mentioned, often lead to a poor disease outcome. However, patients who are diagnosed at an earlier stage and who are in good health have a much higher chance of receiving treatment with curative intent. The well-being of patients with this type of lung cancer is also a big concern. Treatments, especially those using ALK inhibitors, need to be effective but also consider how they affect the patient's quality of life. This includes easing symptoms, maintaining health, and helping with everyday activities.

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

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

How *ALK*+ NSCLC is diagnosed

Diagnosing NSCLC is a detailed process that begins with gathering the patient's medical history and a physical examination. Doctors then use advanced imaging techniques, such as chest X-rays and computed tomography (CT) scans, to get a clearer view of the lungs. They also take tissue samples for histological examination to closely look at the cells under a microscope.

In addition to these steps, identifying the molecular characteristics of the tumour is crucial. This involves testing for specific biomarkers, like *ALK* rearrangements (9). Biomarkers are biological molecules that can indicate the presence of cancer in the body and help in understanding the tumour's behaviour and potential responses to treatment. Around 2% of NSCLC tumours have an *ALK* rearrangement (10). Knowing whether a tumour is *ALK*+ is important because it can be targeted with specific drugs known as ALK tyrosine kinase inhibitors (TKIs), which have been effective in treating this type of cancer.

In the UK, the main method for testing lung cancer tumours for ALK is immunohistochemistry (IHC) done on tumour biopsy samples. Some medical centres also

use fluorescence in situ hybridisation (FISH) and next-generation sequencing (NGS) for further confirmation. This testing might happen before surgery, especially if the patient is being considered for a specific combination of chemotherapy and immunotherapy, to check if the tumour does not have the changes in the *ALK* gene. It can also be done after the tumour has been removed (10). These tests are either done in the local medical centres or sent to specialised Genomic Laboratory Hubs as directed by the National Genomics Test Directory.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - If there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - Are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

What treatment are currently used, how they work and their side effects

Around 30% of people who are newly diagnosed with NSCLC are found to have the disease at an early stage. For these patients, if it's medically possible, removing the tumour through **surgery** is the preferred method of treatment. Despite this, many patients (41−76%) see their cancer return (11-15). In 2022, surgery was performed on 18% of NSCLC patients in England and 14% in Wales (16). However, only about 45% of these patients lived more than five years after surgery (17). This high rate of cancer recurrence is often due to the undetected spread of the disease, which emphasises the need for additional treatments after surgery.

Post-surgery management involves **active monitoring with regular CT scans** to detect any recurrence early. However, there is variation in the type and frequency of these follow-up scans as specific guidelines are not well-defined in the UK. Distinguishing between recurrences that occur near the original site (locoregional) and those that occur in distant parts of the body is crucial for tailoring further treatment, which might include more surgery, radiation, or systemic therapies. Locoregional recurrences happen in 10−50% of cases, and the survival rates remain low despite treatment (18).

After surgery, **platinum-based chemotherapy** is considered the standard care for helping to eliminate any remaining cancer cells and prevent recurrence. Although a study has previously shown that that this approach offers only a slight improvement in survival rates, increasing life expectancy by just 4% after five years, whether used alone or with surgery

and radiation (19). Despite its use, many patients still experience the cancer returning within 4.5 years (20), and high incidence of severe side such as low white blood cell count (neutropenia), anaemia, and nausea can significantly impact their quality of life nausea (21). Given these challenges and the modest benefits of platinum-based chemotherapy, there is increasing interest in more targeted therapies and immunotherapies, which are becoming more common as alternatives to traditional chemotherapy.

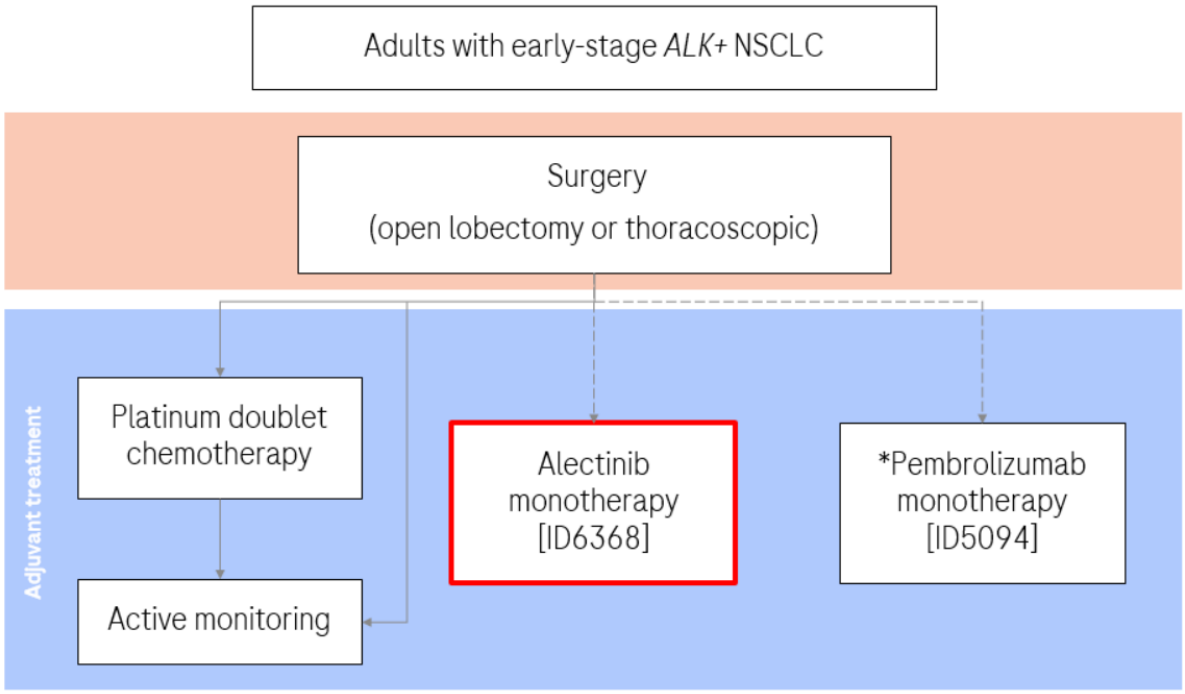
For patients with *ALK*+ NSCLC, **ALK tyrosine kinase inhibitors** (TKIs), like alectinib, have been effectively used, especially in advanced stages of the disease. TKIs are drugs that target specific enzymes involved in the growth, division, and survival of cancer cells. By blocking these enzymes, TKIs help stop cancer cells from growing and spreading.

Alectinib, known by the brand name Alecensa®, is a second next-generation ALK inhibitor that is particularly good at penetrating the central nervous system (CNS), which makes it effective in treating brain metastases, common in *ALK*+ NSCLC patients. Studies like the ALEX and ALUR have shown that alectinib not only prolonged the progression free-survival (PFS; time patients live without their disease progressing) compared to other treatments like crizotinib and traditional chemotherapy, but it also has fewer severe side effects than these other treatments (22-24).

Proposed position for alectinib in the NSCLC treatment pathway

Based on its expected marketing authorisation indication, alectinib is being positioned as an adjuvant (follow-up) treatment for adult patients with early stage *ALK*+ NSCLC, who have already undergone complete surgical removal of their tumour. The treatment pathway for alectinib is summarised below (Figure 1).

Figure 1: Proposed positioning for alectinib for early-stage *ALK*+ NSCLC patients



The red box indicates the proposed positioning of adjuvant alectinib.

** Subject to NICE appraisal.*

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

Context:

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

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

In the Phase III ALEX study, alectinib was compared to crizotinib for treating patients with advanced *ALK*+ NSCLC who had not received prior treatment (25). Alectinib showed greater effectiveness and was generally better tolerated than crizotinib. The study also focused on patient-reported outcomes to understand how these treatments affected patients' symptoms and health-related quality of life (HRQoL).

Patients received either alectinib (600 mg) or crizotinib (250 mg) twice daily until disease progression, death, or withdrawal. The study measured changes in symptoms, quality of life, and functioning from when the treatment started. It also looked at how long it took for patients' symptoms to significantly worsen, in specific symptoms such as cough, dyspnoea, chest pain, arm/shoulder pain, and fatigue, as well as a composite of three symptoms (cough, dyspnoea, chest pain).

The key findings from the ALEX study in terms of impact on patients and carers is as follows:

- The baseline patient characteristics were balanced between the groups, with HRQoL data evaluable for 100 patients on alectinib (66%) and 97 on crizotinib (64%).
- Patients treated with alectinib reported clinically meaningful improvements in lung cancer symptoms that persisted longer than those in the crizotinib group.
- Although both treatments had a similar time until symptoms worsened, the overall duration of symptom improvement was greater with alectinib than crizotinib.
- The duration of clinically meaningful improvement in HRQoL was extended with alectinib, lasting until Week 88 compared to Week 68 with crizotinib.

Overall, alectinib was associated with better patient-reported tolerability of common treatment-related symptoms compared to crizotinib in untreated, advanced *ALK*+ NSCLC. These results underscore alectinib's potential to improve the quality of life and symptom management in patients with *ALK*+ NSCLC, supporting its use as a preferred initial treatment option in this patient population.

Patient-reported outcome results from the study in the early stage *ALK*+ NSCLC population following surgery will be published in Q3 2024.

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

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

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

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

Alectinib's key features and how it works

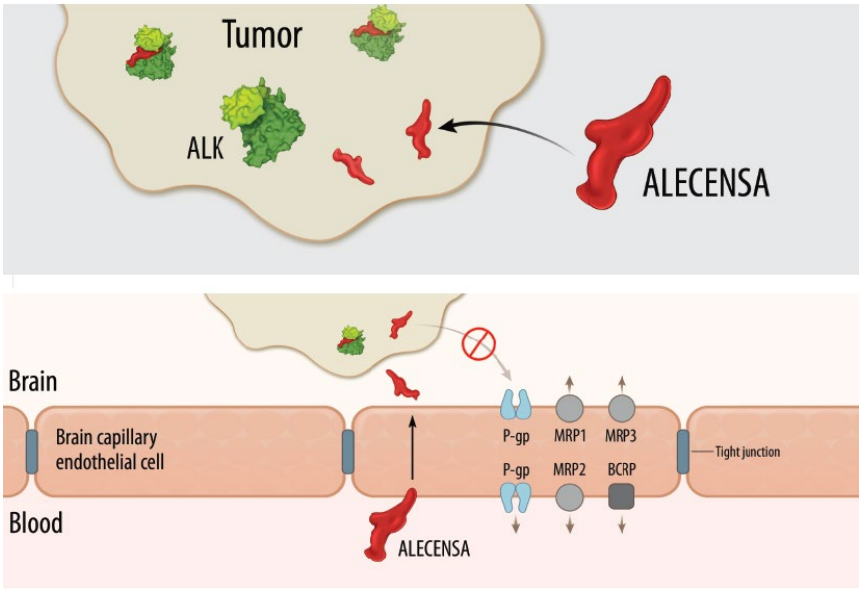
Alectinib is a targeted cancer drug that acts as a highly selective inhibitor for the ALK and RET tyrosine kinase enzymes. Previously, alectinib has been effective at blocking ALK enzyme activity, which is crucial in stopping certain cellular signalling pathways like 'STAT 3' and 'PI3K/AKT'. These pathways are involved in cancer cell growth and survival, and blocking them leads to the death of tumour cells (apoptosis).

Alectinib has also shown effectiveness both in laboratory and in animal studies against various altered forms of the ALK enzyme, including those genetic changes that make cancer cells resistant to another cancer drug, crizotinib.

Most importantly, alectinib is not affected by proteins in the blood-brain barrier (such as P-gp or BCRP) that pump drugs out of the brain. This means alectinib can enter and stay in the CNS, making it potentially effective for treating brain metastases in NSCLC patients.

See Figure 2 for an illustrated diagram to show how alectinib works.

Figure 2: How alectinib (Alecensa®) works



3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Alectinib is not used in combination with other medicines.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Before starting treatment with alectinib, it is essential to confirm that a patient has *ALK*+ NSCLC. This is done using a validated *ALK* assay, a specific test designed to detect the presence of *ALK* genetic alterations in cancer cells.

Patients will receive alectinib under the supervision of a doctor experienced in the use of anticancer treatments.

How much and how often alectinib is given

In the ALINA trial, studying alectinib vs platinum-based chemotherapy in this population, the recommended dose of alectinib was 600 mg (four 150 mg capsules), taken twice daily with food orally.

Treatment with alectinib continued until one of the following occurred: the disease recurred, the patient experienced unacceptable side effects, or the treatment reached a duration of 2 years.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

The ALINA study (NCT03456076) (26)

The ALINA study is an ongoing, global, Phase III trial to compare the effectiveness and safety of alectinib against platinum-based chemotherapy, in patients with early stage *ALK*+ NSCLC after surgery. ALINA is being conducted at 113 centres in 26 countries worldwide, including 3 centres in the UK. The study began enrolling patients on 16th August 2018, and the latest data used in this report were collected until 26th June 2023 (primary analysis).

The primary outcome measure in ALINA is on how long patients remain disease-free after treatment (disease-free survival [DFS]). It also looks at other outcomes like overall survival (OS), time to recurrence in the central nervous system or death (CNS-DFS), quality of life, and safety.

Patients who met all the necessary eligibility criteria were randomly assigned in equal numbers to receive either alectinib at a dose of 600 mg taken orally twice a day, or a specified platinum-based chemotherapy regimen according to the study protocol. A total of

257 patients were randomised in the study: 130 in the alectinib arm and 127 in the chemotherapy arm. See below for ALINA's key inclusion and exclusion criteria.

Key inclusion criteria

- Age ≥ 18
- Complete resection of histologically-confirmed, Stage IB (tumour ≥ 4 cm)−Stage IIIA NSCLC (as per the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC), 7th edition), with negative margins
- Documented *ALK*-positive disease according to an Food and Drug Administration (FDA)-approved and CE-marked test
- Eastern Cooperative Oncology Group (ECOG) Performance Status of Grade 0 or 1
- Adequate haematologic and renal function as defined per protocol

Key exclusion criteria

- Pregnant or lactating women
- Prior adjuvant radiotherapy for NSCLC
- Prior exposure to systemic anti-cancer therapy
- Prior exposure to ALK inhibitors
- Stage IIIA N2 patients that, in the investigator's opinion, should receive post-operative radiation therapy (PORT)
- Liver disease as defined per protocol
- Patients with symptomatic bradycardia
- History of organ transplant
- Known human immunodeficiency virus (HIV) positivity or acquired immunodeficiency syndrome (AIDS)-related illness

3e) Efficacy

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

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

Alectinib efficacy

Alectinib was studied in the ALINA trial (26) to assess its effectiveness and safety in treating patients with early-stage *ALK*+ NSCLC who had undergone surgery. This trial focused on determining how well alectinib performs as a standalone treatment on patient outcomes and how it is metabolised by the body.

The ALINA study successfully met its primary outcome at an interim analysis, indicating that alectinib significantly improved DFS compared to chemotherapy. The results showed a hazard ratio (HR) of 0.24 (95% Confidence Interval [CI], 0.13–0.43), which translates to a 76% reduction in the risk of disease recurrence or death when using alectinib over chemotherapy. This improvement was seen across various specific groups in the study.

As for secondary outcomes, the OS data were still immature due to a low number of events (6 deaths: 2 in the alectinib group and 4 in the chemotherapy group), meaning longer follow-up is needed to better understand its effects. Additionally, the time to CNS recurrence or death was notably longer in the alectinib group, suggesting a meaningful clinical advantage in delaying CNS involvement compared to chemotherapy (HR: 0.22, 95% CI, 0.08–0.58). The next planned update will be descriptive, providing an overview and analysis of the data collected up to that point without statistical testing.

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

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

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

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

Quality of life impact of alectinib

Patients in the ALINA study (26) had to complete a 'SF-36v2 Health Survey', a widely used standardised tool for measuring HRQoL. The survey applies norm-based scoring to its 8 health domains and 2 component summary scores (Mental Component Summary [MCS] and Physical Component Summary [PCS]), setting an average score of 50 with a standard deviation of 10. Scores above 50 indicate better health, while scores below 45 suggest a lower HRQoL.

In the ALINA study, patients treated with alectinib demonstrated stable or improved HRQoL across six of the eight SF-36v2 health domains, as well as in both the MCS and PCS, from Week 12 to Week 96. These improvements met or exceeded the minimal important difference (MID), indicating significant benefits in terms of bodily pain, mental health, social functioning, vitality, and both role emotional and physical domains. Conversely, in the chemotherapy arm, HRQoL scores were generally lower during treatment but showed notable improvements during the off-treatment period, with scores in bodily pain, mental health, vitality, and component summaries reaching or exceeding the normative value of 50. This suggests that while chemotherapy impacts HRQoL negatively during treatment, patients tend to recover once treatment concludes, showing improved well-being in the follow-up period.

3g) Safety of the medicine and side effects

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

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Alectinib safety

The ALINA study (26) found that at the time of the primary analysis, alectinib was well-tolerated with a manageable toxicity profile. The observed safety data align with the previously known risks associated with alectinib, indicating no unexpected safety issues.

- Alectinib, administered at 600 mg twice daily, had a comparable rate of adverse events (AEs) to chemotherapy, with 98.4% of alectinib patients and 93.3% of chemotherapy patients experiencing at least one AE, despite alectinib's longer treatment duration. Most reported AEs were of low severity (Grade 1 or 2).
- The occurrence of more serious AEs (Grade 3−5) was similar between the alectinib (29.7%) and chemotherapy (30.8%) groups, with no Grade 5 AEs reported.
- A lower percentage of patients in the alectinib group (5.5%) discontinued treatment due to AEs compared to the chemotherapy group (12.5%).
- Two patients in the alectinib arm and five in the chemotherapy arm died during the follow-up period, with deaths in the alectinib group attributed to disease recurrence.

These results highlight alectinib's safety profile, particularly considering the extended period of drug exposure compared to chemotherapy.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

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

Alectinib is effective and well-tolerated in clinical trial

The ALINA study (26) demonstrated that alectinib significantly improved DFS compared to chemotherapy in post-surgery patients with early-stage *ALK*+ NSCLC, effectively meeting its first primary outcome. This suggests that alectinib could also help patients live longer, similar to results seen with the drug osimertinib in other NSCLC patients in early-stage adjuvant studies. Alectinib was well-tolerated, with side effects that that aligns with its known risks.

UK clinical experts have confirmed that DFS is a suitable main outcome for this study and noted that improvements in DFS could lead to longer OS. They highlighted that alectinib's benefits over chemotherapy are consistent across different stages of the disease and its safety, especially for early-stage diseases. This is important for patients who can have surgery to remove their cancer but still face a high risk of the cancer spreading and poor outcomes.

Alectinib's unique mechanism delays CNS recurrence

The ALINA trial highlighted a clinically significant delay in CNS (central nervous system) recurrence for patients treated with alectinib, showcasing the drug's effective mechanism. This delay is crucial because brain metastases are a common and debilitating complication in lung cancer, often leading to severe neurological symptoms and significantly impacting patient's quality of life. Alectinib's unique mechanism in crossing the blood-brain barrier and effectively targeting cancer cells within the CNS highlights its potential as a vital treatment option for preventing the progression of the disease into the brain. Overall, the clinically meaningful results from the ALINA trial suggest that alectinib could significantly improve the treatment landscape for *ALK*+ NSCLC patients in the UK, influencing and potentially changing clinical practices nationwide.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

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

As with all other treatments for NSCLC, alectinib might not work for all patients. Unfortunately, there is no way to predict whether a patient will respond to the treatment at the time their doctor decides to treat them with alectinib.

3i) Value and economic considerations

Introduction for patients:

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

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

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

How the model reflects the condition

- The economic case presented in this submission is based on an analysis assessing the use of adjuvant alectinib compared to adjuvant platinum based chemotherapy for adult patients with Stage IB (tumours ≥4cm) to IIIA anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) following complete tumour resection.
- The approach taken to model costs and health benefits is done by splitting patients into 8 different health states: disease-free survival, non-metastatic recurrence (treatment and no treatment), metastatic recurrence (first-line: treatment and no treatment), metastatic recurrence (second-line: treatment and no treatment) and death. This is a common approach used to model the lifetime benefits and costs of treatments used to treat different types of cancer.
- The data used to predict how long patients exposed with each treatment would remain in each health state, which informs the amount of costs and health gains they would accrue, is based on the alectinib clinical trial data and literature published.

Modelling how much a treatment extends life

- The ALINA trial aimed to study the effect of alectinib on patient outcomes against current standard of care treatment, platinum-based chemotherapy, for patients with early stage ALK+ NSCLC, after surgery. The results of the study showed that alectinib significantly reduces disease recurrence or death compared with chemotherapy, including when the disease spreads to sites such as the brain, which is a common risk amongst ALK+ NSCLC patients.

- Disease-free survival (DFS), healthcare related quality of life and adverse events are used in the economic model. Given the relatively short median follow-up period in the ALINA trial, and the fact that a large proportion of events had not occurred by the end of the available follow-up period, extrapolation techniques were used to model DFS over a (lifetime) time horizon of 40 years.

Modelling how much a treatment improves quality of life

- In ALINA trial, patient-reported outcomes (PRO) data was collected from patients using the SF-36v2 Health Survey, which yields 2 component summary scores (i.e., physical and mental) and 8 health domains (i.e., physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health) that provide a generic assessment of HRQoL.
- In addition, in order to inform economic modelling, health-status utility scores were collected using the EQ-5D-5L Questionnaire.

Modelling how the costs of treatment differ with the new treatment and cost-effectiveness results

- The total costs of alectinib are expected to be greater than platinum- based chemotherapy driven mainly by increased treatment costs.
- In addition to the clinical benefits of alectinib to patients, the ICER (Incremental Cost Effectiveness Ratio) compared to platinum-based chemotherapy was well below the conventional NICE thresholds of £20,000–£30,000 per QALY (Quality Adjusted Life Year).
- Decision making ICERs considered by the committee may be different due to differences in preferred modelling assumptions and confidential commercial discounts in the modelling.
- The medicine will lead to less days in hospital for patients as the medicine is taken orally compared to platinum- based chemotherapy which is administered in hospital.

Uncertainty

- Due to limited data availability and short-term trial follow-up, there is some uncertainty regarding the efficacy estimates included within the economic model. These are common obstacles in clinical trials.

3j) Innovation

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

Innovation in patient care

- Alectinib offers a potentially curative benefit, making it a novel option for patients with *ALK*+ NSCLC that could change the current standard of care practice.
- In the ALINA study, alectinib significantly improved disease-free survival compared to traditional chemotherapy. Alectinib was well-tolerated with no new safety concerns.
- Alectinib's unique mechanism allows it to cross the blood-brain barrier and has shown effectiveness in delaying CNS metastases, which is a common complication in NSCLC, thereby improving both prognosis and quality of life for patients.
- Overall, alectinib represents a paradigm shift in treatment approaches, providing new hope and options for patients and healthcare providers in an area with high unmet needs.

3k) Equalities

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

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

No equality issues have been identified.

SECTION 4: Further information, glossary and references

4a) Further information

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

Patient groups and charities:

- ALK Positive Lung Cancer UK
- Roy Castle Lung Cancer Foundation
- Global Lung Cancer Coalition (GLCC)

Further information on NICE and the role of patients:

- Public involvement at NICE
- NICE's guides and templates for patient involvement in HTAs
- EUPATI guidance on patient involvement in NICE
- EFPIA – working together with patient groups
- National Health Council Value Initiative
- INAHTA
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe

4b) Glossary of terms

Acronym	Definition
AIDS	Acquired immunodeficiency syndrome
AJCC	American Joint Committee on Cancer
ALK	Anaplastic lymphoma kinase
BCRP	Breast cancer resistance protein
CHMP	Committee for Medicinal Products for Human Use
CNS	Central nervous system
DFS	Disease-free survival
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
FISH	Fluorescence in situ hybridisation
HIV	Human immunodeficiency virus
HTA	Health Technology Assessment
IHC	Immunohistochemistry
INV	Investigator-assessed
LRR	Local/regional recurrence
MAA	Marketing authorisation application
MCS	Mental Component Summary
MHRA	Medicines and Healthcare products Regulatory Agency
MID	Minimal important difference
NGS	Next-generation sequencing
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NSCLC	Non-small cell lung cancer
PFS	Progression-free survival
QALY	Quality-adjusted life year
RET	Rearranged during transfection
UICC	Union for International Cancer Control

4c) References

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

1. Cancer Research UK. Lung cancer statistics [Accessed on 16/Apr/24]. 2023.
2. International Agency for Research on Cancer (IARC). International Cancer Benchmarking Partnership (ICBP), Cancer Survival in High-Income Countries (SURVMARK-2) [Accessed on 17/Apr/24]. 2024.
3. American Cancer Society. Lung Cancer Survival Rates | 5-Year Survival Rates for Lung Cancer [Accessed on 17/Apr/24]. 2024.
4. Chevallier M, Borgeaud M, Addeo A, Friedlaender A. Oncogenic driver mutations in non-small cell lung cancer: Past, present and future. World journal of clinical oncology. 2021;12(4):217-37.
5. Ravdin PM, Davis G. Prognosis of patients with resected non-small cell lung cancer: impact of clinical and pathologic variables. Lung cancer (Amsterdam, Netherlands). 2006;52(2):207-12.
6. Johung KL, Yeh N, Desai NB, Williams TM, Lautenschlaeger T, Arvold ND, et al. Extended Survival and Prognostic Factors for Patients With ALK-Rearranged Non-Small-Cell Lung Cancer and Brain Metastasis. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2016;34(2):123-9.
7. Tian HX, Zhang XC, Yang JJ, Guo WB, Chen ZH, Wang Z, et al. Clinical characteristics and sequence complexity of anaplastic lymphoma kinase gene fusions in Chinese lung cancer patients. Lung cancer (Amsterdam, Netherlands). 2017;114:90-5.
8. Driver & Vehicle Licensing Agency (DVLA). Assessing fitness to drive – a guide for medical professionals. 2024.
9. National Institute for Health and Care Excellence (NICE). Lung cancer in adults - Quality Standard 17 2012 [Available from: https://www.nice.org.uk/guidance/qs17/resources/lung-cancer-in-adults-pdf-2098490350021.
10. Roche. ALINA Advisory Board - Discussion of the Clinical Data and Health Technology Assessment (HTA) Submission for Adjuvant Alectinib for ALK+ Stage IB–IIIA NSCLC [Data on File]. 2024.
11. Martin J, Ginsberg RJ, Venkatraman ES, Bains MS, Downey RJ, Korst RJ, et al. Long-term results of combined-modality therapy in resectable non-small-cell lung cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2002;20(8):1989-95.
12. Sugimura H, Nichols FC, Yang P, Allen MS, Cassivi SD, Deschamps C, et al. Survival after recurrent nonsmall-cell lung cancer after complete pulmonary resection. The Annals of thoracic surgery. 2007;83(2):409-17; discussioin 17-8.
13. NSCLC Meta-analysis Collaborative Group. Preoperative chemotherapy for non-small-cell lung cancer: a systematic review and meta-analysis of individual participant data. Lancet (London, England). 2014;383(9928):1561-71.
14. Williams BA, Sugimura H, Endo C, Nichols FC, Cassivi SD, Allen MS, et al. Predicting postrecurrence survival among completely resected nonsmall-cell lung cancer patients. The Annals of thoracic surgery. 2006;81(3):1021-7.
15. Lim JU. Update on Adjuvant Treatment in Resectable Non-Small Cell Lung Cancer and Potential Biomarkers Predicting Postoperative Relapse. Tuberculosis and respiratory diseases. 2023;86(1):14-22.
16. National Lung Cancer Audit (NLCA). State of the Nation Report 2024. 2024.

17. National Institute for Health and Care Excellence (NICE). Treatment for lung cancer [Accessed on 17/Apr/24]. 2019.
18. Bowes K, Jovanoski N, Brown AE, Di Maio D, Belleli R, Chadda S, et al. Treatment patterns and survival of patients with locoregional recurrence in early-stage NSCLC: a literature review of real-world evidence. Medical oncology (Northwood, London, England). 2022;40(1):4.
19. Burdett S, Pignon JP, Tierney J, Tribodet H, Stewart L, Le Pechoux C, et al. Adjuvant chemotherapy for resected early-stage non-small cell lung cancer. The Cochrane database of systematic reviews. 2015;2015(3):Cd011430.
20. West H, Hu X, Zhang S, Song Y, Chirovsky D, Gao C, et al. Treatment Patterns and Outcomes in Resected Early-stage Non-small Cell Lung Cancer: An Analysis of the SEER-Medicare Data. Clinical lung cancer. 2023;24(3):260-8.
21. Artal Cortés Á, Calera Urquizu L, Hernando Cubero J. Adjuvant chemotherapy in non-small cell lung cancer: state-of-the-art. Translational lung cancer research. 2015;4(2):191-7.
22. Novello S MJ, Oh I, et al. Primary results from the phase III ALUR study of alectinib vs. chemotherapy in previously treated ALK+ non−small-cell lung cancer (NSCLC). Ann Oncol. 2017;28(Suppl 5):v605-49.
23. Peters S, Camidge DR, Shaw AT, Gadgeel S, Ahn JS, Kim DW, et al. Alectinib versus Crizotinib in Untreated ALK-Positive Non-Small-Cell Lung Cancer. The New England journal of medicine. 2017;377(9):829-38.
24. Roche. Final CSR Study − MO29750 (ALUR) − Randomized, Multicenter, Phase III, Open-Label Study of Alectinib versus Pemetrexed or Docetaxel in Anaplastic Lymphoma Kinase-Positive Advanced Non-Small Cell Lung Cancer Patients Previously treated with Platinum Based Chemotherapy and Crizotinib [Data on File]. 2019.
25. Pérol M, Pavlakis N, Levchenko E, Platania M, Oliveira J, Novello S, et al. Patient-reported outcomes from the randomized phase III ALEX study of alectinib versus crizotinib in patients with ALK-positive non-small-cell lung cancer. Lung cancer (Amsterdam, Netherlands). 2019;138:79-87.
26. Roche. Primary CSR Clinical Report: Study BO40336 (ALINA): A Phase III, open-label, randomised study to evaluate the efficacy and safety of adjuvant alectinib versus adjuvant platinum-based chemotherapy in patients with completely resected Stage IB to Stage IIIA ALK+ NSCLC [Data on File]. 2023.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Alectinib for adjuvant treatment of ALK-positive non-small-cell lung cancer [ID6368]

Company Response to Clarification Questions

June 2024

File name	Version	Contains confidential information	Date
ID6368 alectinib clarification questions to PM for company [Redacted]_Roche response_final_20.06.2024	1.0	Yes	20th June 2024

Section A: Clarification on effectiveness data

ALINA trial

A1. Priority question. The EAG notes differences between the results of the disease-free survival (DFS) analysis using investigator-assessed DFS compared to DFS as assessed by blinded independent central review (BICR) provided as an appendix to the clinical study report (CSR), particularly for the chemotherapy treatment arm ([redacted] for alectinib and [redacted] for chemotherapy in the BICR assessment in the intention to treat [ITT] population). The EAG considers the BICR assessment to be a more robust measure of DFS compared to the investigator-assessed DFS. Please can the Company:

a) **Comment on the differences observed between investigator-assessed and BICR-assessed DFS results, including any potential explanation for differences in DFS status across the two methods;**

Differences observed between the investigator and Blinded Independent Central Review (BICR) assessment are multifactorial.

1. The investigator and BICR central readers accessed different levels of information when determining the cancer recurrence. The investigator's assessment of cancer recurrence was based on the totality of the evidence, including radiological images, tumour markers, physical exam findings, laboratory results, biopsy results, and other possible opinions from the multidisciplinary team (MDT). In addition, the investigator could continuously assess the relapsed cancer with subsequent treatment and further diagnostic workups, especially for equivocal lesions that appeared initially on radiological images. For the BICR assessment, the central readers did not have access to various clinical information mentioned above, but largely determined the recurrence based on the radiological images and biopsy results if patients performed. For the majority of the patients, radiological images were the only evidence used for BICR assessment. Therefore, BICR accessed less clinical

evidence when determining the cancer recurrence compared with the investigators.

2. BICR analysis was performed retrospectively, with the collection of images and storage for subsequent reading implemented in protocol v7 (16 December 2021). There were several patients whose images were not collected and read by BICR, these patients without any BICR data were censored at the date of randomisation plus 1 day.

A number of meta-analysis have been performed to demonstrate high correlation between investigator (INV) and BICR assessments (1, 2). Despite the differences observed in the ALINA trial, the concordance rates were high in the Stage II-IIA subpopulation and in the Intent-To-Treat (ITT) population. The results from the Disease-Free Survival (DFS) analyses comparing treatment arms were consistent between the INV and BICR assessments in both the Stage II-IIIA subpopulation (stratified hazard ratio [HR]: 0.24 vs. [redacted], respectively) and ITT population (stratified HR: 0.24 vs. [redacted], respectively). Therefore, the Company does not believe the differences in INV and BICR assessments have significantly impacted the interpretation of the results.

b) Provide a version of Figure 5 of the Company Submission (CS; Kaplan-Meier plot in the ITT population) where DFS curves for alectinib and chemotherapy arms as assessed by BICR are presented instead of investigator-assessed DFS;

Figure 1: Kaplan-Meier plot of DFS, ITT population - assessed by BICR

c) Perform a scenario analysis in the economic model using DFS data as assessed by BICR in the ITT population of ALINA to test the impact on the results, with a clear description of curve selection, extrapolation and adjustments performed for this scenario.

Using DFS data assessed by BICR in the ITT population of ALINA, the exponential model now appears to be the best fit based on AIC/BIC criteria, as shown in Table 1 and illustrated in Figure 2. Results of the scenario analysis presented in Table 2 demonstrates that alectinib remains cost-effective. For each scenario, the results from the updated base case have also been included, as per the updated Company Submission, Section B.3.10.1, page 114.

Table 1: AIC/BIC using DFS data as assessed by BICR in the ITT population of ALINA

Distribution	AIC (rank)	BIC (rank)
Exponential	623.9 9 (1)	631.0 (1)
Weibull	624.8 (4)	635.4 (4)
Log-Normal	627.1 (7)	637.7 (6)
Gen. Gamma	626.7 (6)	640.8 (7)
Log-Logistic	624.6 (2)	635.2 (2)
Gompertz	625.4 (5)	636.1 (5)
Gamma	624.7 (3)	635.3 (3)

Figure 2: DFS extrapolation using chosen parametric survival model using BICR in the ITT population of ALINA

Table 2: Scenario analysis using DFS data as assessed by BICR in the ITT population of ALINA

	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/LYG)	ICER (£/QALY)
Updated base case	Alectinib	[redacted]	12.40	9.90	-	-	-	-	-
	Platinum- based chemotherapy	[redacted]	8.51	6.60	[redacted]	3.89	3.30	[redacted]	[redacted]
Scenario	Alectinib	[redacted]	12.64	10.10	-	-	-	-	-
	Platinum- based chemotherapy	[redacted]	9.40	7.36	[redacted]	3.24	2.75	[redacted]	[redacted]

A2. Priority question. Given that 20.3% of patients randomised to alectinib had ongoing treatment at the June 2023 data-cut, please provide the following:

a) A breakdown of how many of the 15 disease recurrence events with alectinib in the ITT population occurred in patients that had completed treatment vs had ongoing treatment with alectinib at this time-point;

Of the 15 patients with disease recurrence events in the alectinib arm, [redacted] patients discontinued due to death, [redacted] patients completed 24 months (731 days) of alectinib treatment, [redacted] are still ongoing treatment.

b) Details about the duration of treatment for those that had not yet completed alectinib treatment (e.g. mean, median, standard deviation and min/max values).

Please note that the duration of treatment was calculated in days by subtracting the date of last exposure from the date of first exposure + 1 day. Per protocol, patients are treated with alectinib for 24 months (approximately 731 days, months = days x 30.44).

Table 3: Details about the duration of treatment (in days) for patients in the ITT population that had not yet completed alectinib treatment

	N	Mean	Standard deviation	Median	Minimum value	Maximum value
Treatment duration in patients with disease recurrence events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment duration in all patients in the alectinib arm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

A3. Priority question. Please provide a BICR version of the analysis of central nervous system (CNS) recurrence or death outcome presented in Section B.2.6.3.1 of the CS, including summary data and a Kaplan-Meier plot as is

already presented for the investigator-assessed outcome in Table 14 and Figure 7 of the CS.

The data requested has not been analysed as this endpoint was not planned in the protocol. In addition, given the high levels of consistency seen and demonstrated between INV and BICR DFS, CNS-BICR is expected to be broadly concordant too.

Additionally, CNS recurrences have not been included in the economic analysis. The clinically meaningful benefit of alectinib vs chemotherapy seen in the ALINA study with respect to CNS disease-free survival (hazard ratio for CNS disease recurrence or death, 0.22; 95% CI, 0.08 to 0.58) would only improve the cost-effectiveness of alectinib if added to the economic analysis.

A4. The EAG notes slight differences in the numbers of patients said to have subsequent anti-cancer treatments in Tables 25 and 26 of the CS, which may suggest that some patients may have had a subsequent anti-cancer treatment without having experienced a recurrence. Please can the Company:

a) Confirm whether it is correct that some patients in ALINA had a subsequent anti-cancer treatment without a recurrence having occurred;

   The Company can confirm that some patients in ALINA study had a subsequent anti-cancer treatment without a recurrence having occurred ([redacted] patients in the alectinib arm and [redacted] patients in the chemotherapy arm). The post recurrent subsequent therapy output shown in CS, Table 26 only includes patients that have experienced disease recurrence. It is therefore, restricted to patients who had a DFS and a subsequent anti-cancer therapy after that DFS event. In contrast, the subsequent follow-up anti-cancer systemic therapy data (CS, Table 25) includes any patients that received a non-study anti-cancer systemic treatment irrespective of whether they had disease progression. This data has not been published.

b) State how many patients this applied to in the alectinib and chemotherapy treatment arms, along with a breakdown of the treatments provided and rationale for each patient this applied to;

[redacted] patients from the alectinib arm received subsequent anti-cancer treatment without having experienced a recurrence. From all patients with a subsequent anti-cancer systemic therapy (CS, Table 25), [redacted] patients in the alectinib arm had a DFS event and received subsequent anti-cancer therapy after. While for the chemotherapy arm, [redacted] had a DFS event, and received subsequent anti-cancer treatment. Please note that the difference in patient numbers receiving systemic therapy in the chemotherapy arm in Tables 25 and 26 from the Company Submission is because the patients started subsequent anti-cancer treatment before the occurrence of the DFS event.

For the [redacted] patients in the alectinib arm who did not have recurrence, the breakdown of treatments can be found below:

- [redacted]
- [redacted]
- [redacted]

The rationale for each patient is not available, as the electronic Case Report Form (eCRF) was not designed to collect this information.

c) Discuss the potential impact of this on the results of ALINA.

The impact of these differences are expected to be limited, as before patients have disease recurrence, they are in disease-free status. In the ALINA trial, only a limited number of patients received other anti-cancer therapy before recurrence ([redacted] patients), therefore the overall impact on the results is minimal.

A5. Feedback from the EAG's clinical experts was that the population of ALINA may be slightly younger than would be expected for this setting compared to UK clinical practice, with a median age of 70 years being suggested based on real-world UK data for a similar population (adjuvant osimertinib in EGFR+ patients) being cited by one

clinical expert as potentially more reflective of the UK population.[1] Please can the Company:

a) Discuss how generalisable it considers the mean age in the ALINA trial to be to UK clinical practice, citing any additional studies that may support a mean age of [redacted] years in the population covered by this appraisal;

Clinical expert opinion highlighted that the age of the population with *ALK*+ NSCLC in their centres is reflective of the ALINA trial population age (median 54 years old in the alectinib arm and median 57 years old in the chemotherapy arm) (3).

Feedback from one of the investigators of the trial in the UK stated that when screening patients, all the potential participants identified were <60 years old. At that same centre, data on [redacted] patients resulted in an average of [redacted] years old, across first-line treatment with an ALK tyrosine kinase inhibitor (TKI) of advanced *ALK*+ NSCLC. In another centre, patients in the metastatic setting are <65 years old and the clinician assumes in the adjuvant setting this will be similar.

A survey collected by the ALK+ UK lung cancer patient organisation on brain scans, showed an average age of survey respondents of 54 years old, the youngest being 21 and the oldest being 77 years old (n=86) (4). In 2019, the results of a multicentre retrospective analysis across 23 NHS England trusts were presented looking at treatment patterns/outcomes in ALK+ NSCLC. The median age of the 132 patients included was 53 years old (5). A multicentre retrospective observational real-world study of 81 pre-treated ALK+ metastatic NSCLC patients from 13 NHS trusts across London and South East England noted a median age of 52 years old (6). The study aimed to assess lorlatinib efficacy and toxicity profile in a real-world observational UK urban population.

The *ALK*+ UK patient organisation contains data on [redacted] ALK-positive lung cancer patients throughout the UK. The median age at diagnosis reported by patients was [redacted] years.

Providing the real-world data presented above, the Company believes that the median age presented in the ALINA study is reflective of the UK population.

b) Perform a scenario analysis where the input for baseline age in the economic model is 70 years rather than 54.90 years (Table 44 of the CS).

The results of the scenario analysis using a baseline age of 70 years rather than 54.90 years is shown in Table 4 below. The ICER increases by [redacted]; however, alectinib remains cost effective.

Table 4: Scenario analysis with 70 years as the baseline age in the economic model (with PAS price for alectinib)

	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/LYG)	ICER (£/QALY)
Updated base case	Alectinib	[redacted]	12.40	9.90	-	-	-	-	-
	Platinum-based chemotherapy	[redacted]	8.51	6.60	[redacted]	3.89	3.30	[redacted]	[redacted]
Scenario	Alectinib	[redacted]	9.00	7.21	-	-	-	-	-
	Platinum-based chemotherapy	[redacted]	7.14	5.53	[redacted]	1.86	1.68	[redacted]	[redacted]

A6. Please can the Company provide details of how many patients in each arm of the ALINA trial received the following:

a) Neoadjuvant radiotherapy alone;

[redacted] received neoadjuvant radiotherapy alone.

b) Neoadjuvant chemoradiation treatment (if permitted in ALINA);

[redacted] received neoadjuvant chemoradiation treatment (not permitted).

c) Neoadjuvant chemoimmunotherapy (if permitted in ALINA);

[redacted] received neoadjuvant chemoimmunotherapy (not permitted).

d) Chemoradiation as a subsequent therapy;

This data is not available and cannot be provided. The eCRF was not designed to collect chemoradiation as a whole; instead, chemotherapy and radiotherapy were collected separately.

e) Radiotherapy alone as a subsequent therapy.

Follow-up radiotherapy was completed for [redacted] patients in the alectinib arm and [redacted] patients in the chemotherapy arm. However, please note data is not available on whether radiotherapy was received alone or not. The eCRF was not designed to collect radiotherapy alone and therefore, the Company cannot guarantee that these patients had radiotherapy alone.

A7. Please clarify the difference between 'eCRF' and 'IxRS' for 'Initial diagnosis staging per AJCC 7th edition' in Table 5 of the CS and confirm which of these should be considered to be most accurate, given the numbers in each stage differ slightly between the two versions?

The most accurate numbers regarding 'Initial diagnosis staging per AJCC 7th edition' should be taken from the eCRF.

An interactive voice or web-based response system (IxRS) was used for performing and managing central randomisation and drug allocation. In addition, relevant instructions were provided to each study site by the IxRS provider. For efficacy

analysis, participants were analysed according to the treatment assigned at randomisation by IxRS. Safety analysis were completed according to the treatment patients actually received, regardless of the initial treatment assignment by the IxRS (e.g. a patient will be included in the alectinib arm in safety analyses if the patient receives any amount of alectinib). eCRF was used to collect and capture all the other patient information throughout the study, as required per protocol.

A8. Please provide the numbers analysed for each group and time-point in Tables 16 and 17 of the CS for SF-36 outcome data.

Tables 16 and 17 from the CS have been updated below with *n* numbers for each cell (Table 5 and Table 6).

Table 5: [redacted] (ITT patients)

Assessment scores (mean [SD])	Alectinib			Chemotherapy		
	Baseline	Week 12	Week 96	Baseline	Week 12	DFV7
Bodily pain	47.76 [redacted]	[redacted]	[redacted]	48.12 [redacted]	[redacted]	[redacted]
General health	46.74 [redacted]	[redacted]	[redacted]	44.90 [redacted]	[redacted]	[redacted]
Mental health	46.09 [redacted]	[redacted]	[redacted]	45.15 [redacted]	[redacted]	[redacted]
Physical functioning	47.28 [redacted]	[redacted]	[redacted]	46.72 [redacted]	[redacted]	[redacted]
Role emotional	41.95 [redacted]	[redacted]	[redacted]	41.66 [redacted]	[redacted]	[redacted]
Role physical	40.91 [redacted]	[redacted]	[redacted]	40.08 [redacted]	[redacted]	[redacted]
Social functioning	44.08 [redacted]	[redacted]	[redacted]	41.85 [redacted]	[redacted]	[redacted]
Vitality	50.97 [redacted]	[redacted]	[redacted]	49.57 [redacted]	[redacted]	[redacted]
MCS	45.69 [redacted]	[redacted]	[redacted]	44.23 [redacted]	[redacted]	[redacted]
PCS	46.65 [redacted]	[redacted]	[redacted]	46.21 [redacted]	[redacted]	[redacted]

*SF-36v2 = Short Form 36-Item Health Survey, version 2; ITT = intent-to-treat; MCS = Mental Component Summary score; PCS = Physical Component Summary score; DFV7 = Disease Follow-Up visit 7. The scales including Physical Functioning, Role Physical, and Bodily Pain contribute most to the PCS. The scales including Mental Health, Role Emotional, and Social Functioning contribute most to the MCS. *Due to differences in treatment administration schedules, the Disease Follow-Up Visit 7 should not be compared to the Week 96 visit.*

Table 6: Minimal important difference (MID)

Domain	MID	Change from baseline			
		Alectinib		Chemotherapy	
		Week 12	Week 96	Week 12	DFV7*
Bodily pain	3	[redacted]	[redacted]	[redacted]	[redacted]
General health	2	[redacted]	[redacted]	[redacted]	[redacted]
Mental health	3	[redacted]	[redacted]	[redacted]	[redacted]
Physical functioning	3	[redacted]	[redacted]	[redacted]	[redacted]
Role emotional	4	[redacted]	[redacted]	[redacted]	[redacted]
Role physical	3	[redacted]	[redacted]	[redacted]	[redacted]
Social functioning	3	[redacted]	[redacted]	[redacted]	[redacted]
Vitality	2	[redacted]	[redacted]	[redacted]	[redacted]
MCS	3	[redacted]	[redacted]	[redacted]	[redacted]
PCS	2	[redacted]	[redacted]	[redacted]	[redacted]

*MID = minimal important difference; SF-36v2 = Short Form 36-Item Health Survey, version 2; ITT = intent-to-treat; MCS = Mental Component Summary score; PCS = Physical Component Summary score; DFV7 = Disease Follow-Up visit 7. The scales including Physical Functioning, Role Physical, and Bodily Pain contribute most to the PCS. The scales including Mental Health, Role Emotional, and Social Functioning contribute most to the MCS. *Due to differences in treatment administration schedules, the Disease Follow-Up Visit 7 should not be compared to the Week 96 visit.*

A9. Please provide a breakdown of the EQ-5D-5L results obtained in ALINA, similar to how this has been presented for SF-36 in Table 16 of the CS, with time-points and domains updated as required and numbers analysed clearly presented.

Table 7: EQ-5D-5L version: Summary of EQ-5D-5L mean utility and visual analogous score (VAS) scores at baseline, Week 12, Week 96 (alectinib) and Disease Follow-Up Visit 7* (chemotherapy, mean [SD]) (ITT patients)

Assessment scores (mean [SD])	Alectinib			Chemotherapy		
	Baseline	Week 12	Week 96	Baseline	Week 12	DFV7
Utility score	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VAS score	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

A10. Please provide further details about the 'product dose omission issue' and 'product dose omission in error' included in Table 21 of the CS for alectinib - what did these involve, were they rectified and what is the potential impact on the results of the ALINA trial?

"Product dose omission issue' and 'product dose omission in error' were used to describe one or more missed doses of study treatment, and are not in themselves adverse events (AEs). Both of these are product administration errors and issues, but coded differently. These terms are considered 'special situations' as described in BO40336 Protocol v7, Section 5.3.5.12, and were required to be collected in the eCRF as per protocol. These were sporadic omissions of study treatment and no pattern has been observed.

If a planned dose of alectinib is missed, patients can make up that dose unless the next dose is due within 6 hours. If vomiting occurs after taking a dose of alectinib, patients should take the next dose at the scheduled time. Patients should not take two doses at the same time to make up for a missed dose. Overall, the Company believes there was no impact on ALINA study results because of the favourable benefit-risk.

A11. With regards to the type of surgery performed in the ALINA trial as presented in Table 6 of the CS, please provide details of the proportion of patients in each treatment

arm that received minimally invasive vs non-minimally invasive surgery for any of the four types of surgical procedure that this applies to.

Data on the ways of operation (minimally invasive vs non-minimally invasive) was not collected during the ALINA trial, and therefore will not be available.

A12. Please clarify how many patients were excluded from ALINA for the following reasons:

a) Patients with stage IIIa N2 disease that, in the investigator's opinion, should receive postoperative radiation therapy;

[redacted] with Stage IIIa N2 disease, who were deemed by the Investigator to receive postoperative radiation therapy, were enrolled in the ALINA study.

b) Patients with N3 disease identified at/after surgery.

[redacted] with N3 disease were enrolled in the ALINA study.

Comparison against active monitoring

A13. Priority question. For the scenario against active monitoring, the efficacy of active monitoring was assumed to match that of platinum-based chemotherapy (with treatment costs set as zero and the follow-up healthcare resource also the same as chemotherapy). Please confirm whether adverse events on active monitoring were assumed to be the same as chemotherapy or whether these were excluded for active monitoring.

Adverse events on active monitoring were assumed to be the same as chemotherapy given that the cost of adverse events are minimal. AE costs were removed from the active monitoring arm and explored in scenario analyses as shown in Table 8. The results show that the ICER increases by [redacted], however alectinib remains cost effective.

Table 8: Scenario analysis with adverse events set to zero for active monitoring (with PAS price for alectinib)

	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/LYG)	ICER (£/QALY)
Base case	Alectinib	[redacted]	12.40	9.90	-	-	-	-	-
	Platinum- based chemotherapy	[redacted]	8.51	6.60	[redacted]	3.89	3.30	[redacted]	[redacted]
Scenario	Alectinib	[redacted]	12.40	9.90	-	-	-	--	-
	Platinum- based chemotherapy	[redacted]	8.51	6.60	[redacted]	3.89	3.30	[redacted]	[redacted]

A14. In the CS, the Company states that limited studies to inform the effectiveness of active monitoring are available, meaning an assumption that its efficacy is the same as platinum-based chemotherapy was made for this comparison. Please provide further details on any available evidence that was considered and how/why the decision to assume equivalence to platinum-based chemotherapy was made. For example, was a formal feasibility assessment performed in terms of whether any indirect treatment comparisons could be performed and what were the conclusions of this?

Although no formal feasibility assessment was performed on active monitoring, as mentioned in the Company Submission, UK clinicians consulted by the Company would only consider active monitoring for less than 10% of patients, for whom the risks of adjuvant treatment outweigh the benefits. Some clinicians indicated they would not advocate for active monitoring due to high risk of disease recurrence. Despite this small pool of patient population, the Company has taken a conservative approach, by assuming the efficacy of active monitoring to be the same as platinum-based chemotherapy. In turn, the clinical benefit of active monitoring is overestimated in the scenario analysis. Nevertheless, alectinib was still found to be highly cost effective when compared to platinum-based chemotherapy (and in turn, active monitoring). These findings underscore that alectinib represents a substantial improvement over current treatment options and represents a cost effective treatment option for *ALK*+ NSCLC patients within the NHS.

Systematic literature review

A15. Please provide a list of studies excluded from the clinical systematic literature review (SLR), with a brief rationale for exclusion for each study.

The list of studies excluded from the clinical SLR can be found in Table 54 from the Appendix in this response document.

Section B: Clarification on cost-effectiveness data

For any scenarios requested in Section B, the EAG requests that updates are made to the PAS price version of the CEM only, to avoid potential discrepancies between the PAS and list price versions of the CEM. Please ensure that all scenarios are implemented as user selectable options in the CEM so that they can be combined. Furthermore, if the Company chooses to update its base case results, please ensure that cost-effectiveness results, sensitivity and scenario analyses incorporating the revised base case assumptions are provided with the response along with a log of changes made to the Company base case.

Questions B7, B9, B14, B16, B17, B19, B25, B36, B37, B43 and B45 request additional details currently missing from the CS. The EAG requests that, as well as providing the information in the clarification response, the Company provides an updated Company Submission (Document B) with the additional information incorporated using tracked changes.

Based on changes requested by the EAG, the ICER has increased from [redacted] to [redacted]. Despite the base case ICER increasing, alectinib remains cost-effective and well below the willing-to-pay threshold (WTP) threshold of £20,000-£30,000 per QALY. The list of updated assumptions that have affected the base case ICER are listed in Table 11.

Table 9: Original base-case results (with PAS price for alectinib)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/LYG)	ICER (£/QALY)
Alectinib	[redacted]	12.42	9.79	-	-	-	-	-
Platinum-based chemotherapy	[redacted]	8.82	6.61	[redacted]	3.90	3.18	[redacted]	[redacted]

Table 10: Updated base-case results (with PAS price for alectinib)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/LYG)	ICER (£/QALY)
Alectinib	[redacted]	12.40	9.90	-	-	-	-	-
Platinum-based chemotherapy	[redacted]	8.51	6.60	[redacted]	3.89	3.30	[redacted]	[redacted]

Table 11: list of changes to assumptions in the base case

Question	Variable	Previous values	New values
B16	Updated distributions for rechallenge disallowed	Please see Table 37	
B22	Age adjustment of utilities updated	Please refer to "CQ Change log" in the CEM	
B29	Emit prices	Cisplatin: small vial (£26.72), large vial (£50.22) Carboplatin small vial (£20.20) large vial (£232.64) Pemetrexed small vial (£160), large vial (£800) Vinorelbine: small vial (£329.50), large vial (£1,539.80) Gemcitabine: small vial (£162) large vial (£162)	Cisplatin: small vial (£27.98), large vial (£29.27) Carboplatin small vial (9.28) large vial (£71.44) Pemetrexed small vial (£24.53), large vial (£159.35) Vinorelbine: small vial (£75.16), large vial (£172.56). Gemcitabine: small vial (£18.17) large vial (£45.96)
B31	Admin cost for alectinib and all oral therapies on a monthly basis	Please refer to "CQ Change log" in the CEM	
B34	Cost of administration for oral therapies	£9.00	£10.00
B35	First and subsequent administration cost for chemotherapy	£475.94	First-£475.94 Subsequent-£368 44
B36	Cost of surgery	£160.62	£588.30
B37	Cost of radiotherapy	£233.94	£244.23
B39	Updated AEs in non-metastatic and metastatic health states	Please refer to "safety" sheet in the CEM	
B44	Updated healthcare resource use	Community nurse visit (£75) Clinical nurse specialist (£85) GP surgery visit (£41)	Community nurse visit (£82) Clinical nurse specialist (£94) GP surgery visit (£50.50)
B50	PSSRU end of life cost	£4,598	£19,934

B51a	Administration costs have not been applied for alectinib as an adjuvant treatment	Please refer to “CQ Change log” in the CEM
B51b	error in the calculation of treatment acquisition costs for alectinib based on tunnel states	Please refer to “CQ Change log” in the CEM
B51c	The cure assumption is applied one cycle too early in the model traces	Please refer to “CQ Change log” in the CEM
B52	Half cycle correction in markov trace	Please refer to “CQ Change log” in the CEM

General questions

B1. Priority question. Please confirm if the efficacy data presented in the Canadian CEM technical report provided in the reference pack (‘ID6368 alectinib eNSCLC_ALINA_CEM_Technical_Report_v1.2 25052024KM [CON]’) are equivalent to the efficacy data used in the economic model.

As mentioned on the EAG call, please disregard the Canadian technical report as it was shared in error. All information in both the company submission and the CEM is specific to the UK. All relevant references are included in the company submission. The efficacy data presented in the CEM report is the same as the efficacy data used in the economic model. However, the efficacy data for patients post-recurrence is not completely the same as the treatment options differ (e.g. chemotherapy as treatment for non-metastatic recurrence). The literature sources used for each health state is outlined in Section B.3.2.4 and summarised in Table 27 of the Company Submission.

B2. The EAG notes that the CEM does not explore differences in CNS recurrence between patients treated with adjuvant alectinib and chemotherapy. Please comment on any related benefits of alectinib, which have therefore not been captured in the cost-effectiveness analysis.

Although the CEM does not explore differences in CNS recurrence between patients treated with adjuvant alectinib and chemotherapy, the structure of the ALINA CEM was clinically validated by seven UK clinical experts during an advisory board in

February 2024 (3). The clinical experts stated that the structure currently used by the CEM appropriately captures the disease and treatment pathways of adjuvant *ALK*+ NSCLC.

The ALINA trial indicates that more patients treated with adjuvant chemotherapy experienced CNS recurrence compared to those treated with the adjuvant ALK inhibitor. Additionally, patients with CNS recurrence tend to have a worse prognosis than those with non-CNS recurrence, as evidenced by the advanced-stage *ALK*+ NSCLC clinical SLR. Therefore, the inclusion of CNS recurrence would reduce the ICER in favour of alectinib. The exclusion of CNS recurrence from the economic analysis can therefore be seen as a conservative approach with respect to the cost-effectiveness of alectinib.

Systematic literature review

B3. Priority question. The EAG notes that the SLR of evidence on outcomes for locally advanced or metastatic *ALK*+ NSCLC, which was used to identify inputs to parametrise transition probabilities in the recurrence health states, was last updated in September 2023. Please provide justification for why this has not been subsequently updated.

The SLR was conducted in September 2023, eight months prior to the Company Submission. According to NICE guidelines, SLRs should be conducted within six months of the Company Submission deadline. Since we do not anticipate any additional studies being conducted within the remaining two months, there is a low risk that relevant studies have been missed within this timeframe.

B4. Priority question. In order to identify transition probabilities for the non-metastatic recurrence health state, the aforementioned SLR was supplemented by a targeted literature review (TLR) conducted in 2021, which identified prospective and retrospective studies:

a) Please clarify whether this TLR has been subsequently updated;

The TLR has not been updated.

b) If not, please rerun the searches to ensure that any subsequently published literature has been captured.

It is important to note that the TLR was not intended for this submission. Instead, the SLR was performed to inform the efficacy of treatments after recurrence. The TLR results were employed pragmatically due to the absence of relevant studies in the SLR.

Updating the TLR would be a time-consuming process, potentially taking several months. It is believed to be highly unlikely that any new relevant literature would be found in an updated search. Therefore, the Company proposes to run a scenario analysis to vary the input used for radiotherapy efficacy. This approach was discussed with the EAG during the clarification meeting, who agreed this is a reasonable alternative.

The radiotherapy efficacy values in the CEM were varied by +/-20% and used to run a scenario analysis, which are presented in Table 12 and Table 13. These changes had a minimal impact on the ICER.

Table 12: Scenario analysis varying the input used for radiotherapy efficacy (+20%)

	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/LYG)	ICER (£/QALY)
Updated base case	Alectinib	[redacted]	12.40	9.90	-	-	-	-	-
	Platinum- based chemotherapy	[redacted]	8.51	6.60	[redacted]	3.89	3.30	[redacted]	[redacted]
Scenario	Alectinib	[redacted]	12.49	9.97	-	-	-	-	-
	Platinum- based chemotherapy	[redacted]	8.58	6.65	[redacted]	3.91	3.31	[redacted]	[redacted]

Table 13: Scenario analysis varying the input used for radiotherapy efficacy (-20%)

	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/LYG)	ICER (£/QALY)
Updated base case	Alectinib	[redacted]	12.40	9.90	-	-	-	-	-
	Platinum- based chemotherapy	[redacted]	8.51	6.60	[redacted]	3.89	3.30	[redacted]	[redacted]
Scenario	Alectinib	[redacted]	12.34	9.86	-	-	-	-	-
	Platinum- based chemotherapy	[redacted]	8.46	6.56	[redacted]	3.88	3.29	[redacted]	[redacted]

B5. Priority question. The EAG notes that transition probabilities in the metastatic recurrence health states were informed only by the SLR, which was restricted to RCTs in the *ALK*+ patient population (although some observational studies, and studies not restricted to *ALK*+ patients were used to parametrise the non-metastatic recurrence health state transition probabilities). Please clarify whether any searches were conducted to identify appropriate sources for model inputs for the metastatic recurrence health states with other study designs (for example, observational studies), or relevant to different mutation statuses, in line with the TLR informing the non-metastatic recurrence health state.

No additional searches were specifically conducted to identify sources beyond RCTs for the metastatic recurrence health states. While the SLR could have been less restrictive in certain areas, such as population and year of publication, specific decisions were made to impose these restrictions when the SLR was carried out. This approach was adopted to ensure the search would effectively identify relevant and high-quality literature, while being manageable in scope. One of these aspects was the study design, where the search focused on identifying evidence from published RCTs, given that other study designs possess inherent limitations, which could compromise the validity and reliability of the findings.

Efficacy

B6. Priority question. The model structure used in the CEM implicitly assumes that patients will receive at most one line of treatment in the non-metastatic recurrence setting, and two lines of treatment in the metastatic recurrence setting. Please provide further justification for why further lines of treatment were not considered.

During the conceptualisation of the ALINA CEM, the company decided that the treatment of non-metastatic recurrence and metastatic recurrence would be modelled separately given differences in the clinical outcomes, safety and costs associated with the different treatment settings. Careful consideration was taken to ensure that the CEM appropriately captured the treatment pathways of patients diagnosed with early-stage *ALK*+ NSCLC after experiencing a DFS event.

While the CEM could have modelled subsequent lines of metastatic treatment, the company decided that it may not be appropriate given that the pragmatic search showed that relatively few people proceed to third- and fourth-line treatment after progression on second-line treatment (7).

In order to validate these assumptions, the model structure of the CEM was presented to UK clinical experts in February 2024. The clinical experts stated that the structure that the team had proposed to use appropriately captures the disease and treatment pathways of early-stage *ALK*+ NSCLC (3).

Moreover, the results from a SLR that identified previously conducted economic evaluations in the space of early-stage NSCLC concluded that restricting the modelling of metastatic treatment to the first two lines was deemed appropriate by NICE in the past and peer-reviewed journals (8-11). Therefore, it was decided that restricting the modelling of metastatic treatment to the first two lines was appropriate.

B7. Priority question. For all health states, it was assumed that a constant proportion of patients leaving the state move into the death state:

a) Please provide a justification for this assumption;

The CEM has had to assume that a time-invariant proportion of patients experiencing an event (i.e., disease-free or progression-free) would transition to the death health state from all non-death health states, excluding the 2L metastatic treatment health state.

Two SLRs were conducted to identify evidence on this matter, which could have allowed for relaxing this assumption. However, the SLRs did not find any relevant evidence as demonstrated in the clinical SLRs.

b) For each health state, please provide the evidence informing the proportion of patients moving into the death state (i.e. the literature or trial data informing the input values, and details of any manipulations of raw data to derive the parameter values), and update the CS to reflect this;

The proportion of patients moving into the death state is informed by the ALINA trial. Patients can move from disease-free, non-metastatic recurrence, metastatic recurrence heath states to the death health state.

Table 14 presents the number of patients who experienced each type of event from ALINA for the alectinib arm, chemotherapy arm, and pooled across arms. The CEM informs the proportion of patients who experience each type of event based on the arm specific data. It uses this approach as the TAEs indicated that the ability of alectinib to slow down or prevent recurrence, specifically recurrence affecting the central nervous system, could lead to a higher proportion of patients being detected with non-metastatic versus metastatic recurrence as their earliest contributing event.

Table 14: Type of DRS events (ALINA, CCOD 26/Jun/23)

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%)

The CEA informs the type of earliest contributing disease-free survival events with Sections 5.1.2.2 and 5.1.4.2 of the ALINA CSR (12).

Patients who have non-metastatic or metastatic recurrence (first-line) can experience further disease progression or death while they are progression-free. The CEM allows this to differ by treatment option and attempted to use the same sources to do this that inform the PFS.

However, as summarised in Table 15, only one study includes information on the type of progression event a patient experiences (progression or death). Thus, the CEM 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 15: Types of PFS events

Non-metastatic recurrence					
PFS event	**Chemoradiotherapy**				
Total events	**14**				
Death	NR				
Progression	NR				
Reference	(Nakamichi, *et al.*, 2017)				
Metastatic recurrence (first-line)					
PFS event	**Alectinib**	**Crizotinib**	**Brigatinib**	**Lorlatinib**	**Pooled**
Total events	**81**	**92**	**73**	**49**	**-**
Death	9 (11.1%)	NR	NR	NR	-
Progression	72 (88.9%)	NR	NR	NR	-
Reference	ALEX (ITT, Intervention Arm, Clinical Cutoff: 30.11.2018)*	Solomon, *et al.*, 2023	Camidge, *et al.*, 2021	Solomon, *et al.*, 2023	-

*NR= not reported; *Refer to Table 12 of the updated ALEX CSR.*

c) The EAG notes the CEM includes the implicit assumption that 0% of transitions out of the disease-free state will lead to the death state in the alectinib arm (not accounting for adjustment for general population mortality). Please provide a scenario in which the same assumption is also applied in the chemotherapy arm;

The results of the scenario analysis applying the implicit assumption that 0% of transitions out of the disease-free state for both alectinib and chemotherapy arm is shown in Table 16 below. This has a minimal impact on the results and the ICER only increases by [redacted]

Table 16: Scenario analysis applying the implicit assumption that 0% of transitions out of the disease-free state for both alectinib and chemotherapy arm (with PAS price for alectinib)

	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/LYG)	ICER (£/QALY)
Base case	Alectinib	[redacted]	12.40	9.90	-	-	-	-	-
	Platinum-based chemotherapy	[redacted]	8.51	6.60	[redacted]	3.89	3.30	[redacted]	[redacted]
Scenario	Alectinib	[redacted]	12.43	9.92	-	-	-	--	-
	Platinum-based chemotherapy	[redacted]	8.51	6.60	[redacted]	3.93	3.33	[redacted]	[redacted]

d) The EAG also notes that the CEM was parameterised such that 100% of patients leaving the non-metastatic recurrence, off treatment health state will proceed to the death state rather than the metastatic recurrence, off treatment health state. Please provide a justification for this assumption. Please also provide a scenario in which a proportion of patients proceed from the non-metastatic recurrence, off treatment health state to the metastatic recurrence, off treatment health state, rather than the death health state.

The SLR did not identify any studies that study the PFS or OS of patients who do not receive any treatment. 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 (Wong, *et al.*, 2016). As this study only presents OS and not PFS for these patients, the CEM 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

Furthermore, this scenario cannot be executed correctly and should not be run improperly by applying the suggested proportion. This is because, for these patients, only information on their overall survival (OS) is available, and the estimates in the efficacy sheet are used to project their OS. Running the scenario as requested by the EAG would require changing the estimates for 'No treatment' in the efficacy sheet to those that project progression-free survival (PFS). However, since Wong *et al.* (2016) do not provide results on PFS, this scenario cannot be run.

B8. Priority question. The probability of transition from the disease free to death health state is bounded below by age- and sex-adjusted general population mortality risk. However, the other transition probabilities out of the disease-free health state do not account for this adjustment, resulting in a calculated DFS which is artificially lower than the input DFS. Please provide a scenario in which the transition probabilities from the disease-free health state to the non-

metastatic recurrence and metastatic recurrence health states are proportionally adjusted to account for the background mortality risk.

At the request of the EAG, the CEM now includes an option that allows the model to use this alternative approach. The results of the scenario analysis, presented in Table 17 below, indicate that the ICER decreases by [redacted]

Table 17: Scenario analysis using the transition probabilities from the disease-free health state to the non-metastatic recurrence and metastatic recurrence health states which are proportionally adjusted to account for the background mortality risk (with PAS price for alectinib)

	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/LYG)	ICER (£/QALY)
Updated base case	Alectinib	[redacted]	12.40	9.90	-	-	-	-	-
	Platinum- based chemotherapy	[redacted]	8.51	6.60	[redacted]	3.89	3.30	[redacted]	[redacted]
Scenario	Alectinib	[redacted]	12.82	10.26	-	-	-	--	-
	Platinum- based chemotherapy	[redacted]	8.60	6.68	[redacted]	4.22	3.59	[redacted]	[redacted]

B9. Priority question. Based on the CS, it is unclear whether the proportional hazards (PH) was assumed to hold for observed DFS in the ALINA trial for the alectinib and chemotherapy arms:

a) **Please clarify if the PH assumption was assumed to hold, and update section B.3.3.1 of the CS accordingly;**

The PH assumption was assumed to hold as demonstrated by the Schoenfield test; this has been updated in the Company Submission, Section B.3.3.1.1.

b) **Please either confirm that the log-cumulative hazard plot (Figure 4) and Schoenfeld residuals plot (Figure 5) of the Canadian CEM technical report correspond to the same data used in the economic model, or provide these plots for the data used in the economic model. Please also add these to the CS;**

As mentioned previously, the Canadian technical report should be ignored. The log-cumulative hazard plot (CS, Figure 4) and Schoenfeld residuals plot (CS, Figure 5) of the Canadian CEM technical report correspond to the same data used in the economic model. These plots have been added to Section 3.3.1.1.1 and the Company Submission has been updated.

c) **If the PH assumption was assumed to hold, please justify the choice of the log-logistic distribution to extrapolate the DFS curves;**

Log-logistic distribution was used to extrapolate the DFS curves in the base case. This decision was based on visual fit, AIC and BIC goodness-of-fit statistics and UK clinical expert opinion. The AIC/BIC scores indicate a log-logistic distribution appears to provide the best fit to the observed data.

d) **If the PH assumption was not assumed to hold, please justify the choice of joint models for extrapolating the DFS curves.**

The PH assumption was assumed to hold.

B10. Priority question. The EAG notes that the visual fit of the DFS extrapolations for alectinib are relatively poor. Therefore, please provide scenarios in which DFS extrapolations for alectinib and chemotherapy are fitted independently using the standard parametric distributions listed in NICE Decision Support Unit Technical Support Document 14 (NICE DSU TSD14), and provide plots and goodness of fit statistics for each choice of extrapolation.

Based on AIC/BIC as shown in Table 18 and Table 19, the best fitting models are Exponential/Gompertz for alectinib, and log-logistic for chemotherapy. However despite AIC and BIC scores, it is not appropriate to use the Gompertz distribution for alectinib as it leads to worse DFS compared to chemotherapy which is not clinically plausible.

Table 18: AIC/BIC scores for independent standard parametric distributions for alectinib

Distribution	AIC (rank)	BIC (rank)
Exponential	197.9 (2)	200.8 (1)
Weibull	198.5 (3)	204.2 (3)
Log-Normal	200.8 (7)	206.5 (6)
Gen. Gamma	200.2 (6)	208.8 (7)
Log-Logistic	198.8 (5)	204.6 (5)
Gompertz	197.2 (1)	202.9 (2)
Gamma	198.7 (4)	204.5 (4)

Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC).

Table 19: AIC/BIC scores for independent standard parametric distributions for chemotherapy

Distribution	AIC (rank)	BIC (rank)
Exponential	514.2 (6)	517.1 (3)
Weibull	513.3 (5)	519.0 (5)
Log-Normal	509.8 (1)	515.4 (1)
Gen. Gamma	511.7 (3)	520.2 (6)
Log-Logistic	510.9 (2)	516.6 (2)
Gompertz	515.8 (7)	521.5 (7)
Gamma	512.5 (4)	518.2 (4)

Using the best-fitting curves that do not intersect, this would be the log-normal for the chemotherapy arm and exponential for the alectinib arm, as shown in Figure 3 below.

As demonstrated in the scenario analysis in Table 20, using these two distributions reduces the ICER by [redacted], further demonstrating that alectinib is cost effective.

Figure 3: Disease-free survival extrapolations using the log-normal distribution for the alectinib arm and exponential distribution for chemotherapy arm

ALE; Alectinib. CHT; chemotherapy. KM; Kaplan Meier. DFS; Disease-free survival.

Table 20: Scenario analysis in which DFS extrapolations for alectinib and chemotherapy are fitted independently using log-normal and exponential distributions (with PAS price for alectinib)

	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/LYG)	ICER (£/QALY)
Updated base case	Alectinib	[redacted]	12.40	9.90	-	-	-	-	-
	Platinum- based chemotherapy	[redacted]	8.51	6.60	[redacted]	3.89	3.30	[redacted]	[redacted]
Scenario	Alectinib	[redacted]	12.64	10.11	-	-	-	--	-
	Platinum- based chemotherapy	[redacted]	8.36	6.47	[redacted]	4.29	3.63	[redacted]	[redacted]

It is not appropriate to use different distributions to model DFS for the different arms, as this could lead to crossovers in DFS. Furthermore as the proportional hazards assumption holds, it is not recommended to fit DFS extrapolations independently. Given that proportional hazards hold, the log-logistic is the most appropriate distribution to use for both alectinib and chemotherapy arm. a scenario analysis using the log-normal distribution for both arms is explored in Table 21. Using the log-normal distribution increase the ICER to [redacted].

Figure 4: Disease-free survival extrapolations using the log-normal distribution for the alectinib arm and chemotherapy arm

ALE; Alectinib. CHT; chemotherapy. KM; Kaplan Meier. DFS; Disease-free survival.

Table 21: Scenario analysis in which DFS extrapolations for alectinib and chemotherapy are fitted independently using log-normal distribution (with PAS price for alectinib)

	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/LYG)	ICER (£/QALY)
Updated base case	Alectinib	[redacted]	12.40	9.90	-	-	-	-	-
	Platinum- based chemotherapy	[redacted]	8.51	6.60	[redacted]	3.89	3.30	[redacted]	[redacted]
Scenario	Alectinib	[redacted]	12.64	10.11	-	-	-	--	-
	Platinum- based chemotherapy	[redacted]	9.05	7.06	[redacted]	3.59	3.05	[redacted]	[redacted]

B11. Priority question. The economic model includes the assumption that all transition probabilities between the recurrence and death health states are time-invariant. Little justification is provided for this assumption, given that all of the data sources used to parametrise transition probabilities include Kaplan-Meier survival curves. For all transition probabilities, please could the following be provided:

a) Plots of the Kaplan-Meier data overlaid with extrapolations based on standard parametric distributions listed in NICE DSU TSD14 (the EAG notes that the plots provided in the Canadian CEM technical report, if relevant to this submission, are too low-quality to be interpretable);

A systematic literature review (SLR) was conducted on the efficacy and safety of interventions for ALK-positive NSCLC to identify evidence that could inform the progression-free survival (PFS) and overall survival (OS) of patients who receive or do not receive treatment after relapse. This is necessary because ALINA does not systematically collect data on disease progression after the first recurrence.

Since the Company does not have access to the individual patient data (IPD) from the studies identified by the SLRs, approximated datasets were generated by digitizing the Kaplan-Meier (KM) estimates of PFS and OS which were converted to IPD (Guyot, Ades, Ouwens, & Welton, 2012). Similar to the disease-free survival (DFS) analysis, the results from parametric survival analyses are used to produce the output needed to project outcomes over time.

Although several analyses were conducted, where the outcomes of interest follow various distributions, the CEM uses the results from analyses that assume the outcomes follow an exponential distribution to model PFS and OS. This restricts the transition probabilities to being time-invariant. However, the CEM applies the aforementioned mortality adjustment if it results in a higher proportion of patients transitioning to death.

An advantage of this restriction is that it simplifies the CEM. With a continuous flow of patients into the non-metastatic and metastatic recurrence health states, the analysis would have required several tunnel states to allow for time-variant

transitions. A limitation of this restriction is that, if it is not appropriate from a statistical or clinical standpoint, it can lead to incorrect modelling of the time 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 (Jovanoski & Ying, 2023). This approach was accepted by NICE for the TA823 appraisal (13). Nevertheless, the Kaplan-Meier data overlaid with extrapolations based on standard parametric distributions for each health state is provided below.

Non-metastatic recurrence

The Kaplan-Meier data overlaid with extrapolations based on standard parametric distributions for radiotherapy, chemotherapy and no treatment in the non-metastatic recurrence disease state is presented in Figure 5, Figure 6 and Figure 7, respectively. It was assumed that the efficacy of patients who receive surgery is similar to that of patients who receive radiotherapy therefore the data will be the same as Figure 5. For patients who receive alectinib for non-metastatic recurrence, it was assumed that the efficacy and safety of is similar to that of patients who receive alectinib for advanced NSCLC. Therefore, the current data that is included in the model on the efficacy and safety of alectinib as first-line metastatic treatment was used to inform this treatment option.

Figure 5: Kaplan-Meier data overlaid with extrapolations for radiotherapy in the non- metastatic recurrence health state

Figure 6: Kaplan-Meier data overlaid with extrapolations for chemotherapy in the non- metastatic recurrence health state

Figure 7: Kaplan-Meier data overlaid with extrapolations for no treatment in the non- metastatic recurrence health state

Metastatic recurrence (1L)

The Kaplan-Meier data overlaid with extrapolations based on standard parametric distributions for alectinib, brigatinib, lorlatinib and no treatment in metastatic recurrence (1L) disease state is presented in Figure 8, Figure 9, Figure 10, and Figure 11, respectively. It is assumed that the efficacy for chemotherapy is the same as chemotherapy used in metastatic recurrence (1L).

Figure 8: Kaplan-Meier data overlaid with extrapolations for alectinib in the metastatic recurrence (1L) health state

Figure 9: Kaplan-Meier data overlaid with extrapolations for brigatinib in the metastatic recurrence (1L) health state

Figure 10: Kaplan-Meier data overlaid with extrapolations for lorlatinib in the metastatic recurrence (1L) health state

Figure 11: Kaplan-Meier data overlaid with extrapolations for no treatment in the metastatic recurrence (1L) health state

Metastatic recurrence (2L)

The Kaplan-Meier data overlaid with extrapolations based on standard parametric distributions for alectinib and chemotherapy in metastatic recurrence (2L) disease state is presented in Figure 12 and Figure 13. In the absence of data on this matter, an assumption was made that the efficacy, safety and treatment discontinuation of second-line lorlatinib is similar to second-line alectinib.

Figure 12: Kaplan-Meier data overlaid with extrapolations for alectinib in the metastatic recurrence (2L) health state

Figure 13: Kaplan-Meier data overlaid with extrapolations for chemotherapy in the metastatic recurrence (2L) health state

b) AIC and BIC values for each fitted extrapolation.

Non-metastatic recurrence

Table 22: AIC/BIC scores for radiotherapy in the non- metastatic recurrence health state

Distribution	AIC (rank)	BIC (rank)
Exponential	400.8 (5)	402.8 (4)
Weibull	402.8 (6)	406.8 (6)
Log-Normal	389.7 (2)	393.8 (2)
Gen. Gamma	384.6 (1)	390.6 (1)
Log-Logistic	390.9 (3)	394.9 (3)
Gompertz	399.5 (4)	403.6 (5)
Gamma		

Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC).

Table 23: AIC/BIC scores for chemotherapy in the non- metastatic recurrence health state

Distribution	AIC (rank)	BIC (rank)
Exponential	787.1 (4)	790.3 (4)
Weibull	787.3 (5)	793.8 (5)
Log-Normal	777.8 (1)	784.2 (1)
Gen. Gamma	779.8 (2)	789.5 (3)
Log-Logistic	781.1 (3)	787.6 (2)
Gompertz	789.1 (6)	795.6 (6)
Gamma		

Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC).

Table 24: AIC/BIC scores for no treatment in the non- metastatic recurrence health state

Distribution	AIC (rank)	BIC (rank)
Exponential	1167.8 (5)	1171.2 (5)
Weibull	1124.5 (4)	1131.2 (4)
Log-Normal	1085.4 (1)	1092.1 (1)
Gen. Gamma		
Log-Logistic	1094.9 (2)	1101.6 (2)
Gompertz	1102.5 (3)	1109.1 (3)
Gamma		

Metastatic recurrence (1L)

Table 25: AIC/BIC scores for alectinib in the metastatic recurrence (1L) health state

Distribution	AIC (rank)	BIC (rank)
Exponential	459.1 (6)	462.1 (6)
Weibull	448.9 (5)	455.0 (5)
Log-Normal	439.6 (2)	445.7 (1)
Gen. Gamma	438.8 (1)	447.8 (2)
Log-Logistic	444.0 (4)	450.0 (4)
Gompertz	442.0 (3)	448.0 (3)
Gamma		

Table 26: AIC/BIC scores for brigatinib in the metastatic recurrence (1L) health state

Distribution	AIC (rank)	BIC (rank)
Exponential	727.9 (4)	730.8 (2)
Weibull	729.1 (6)	734.9 (6)
Log-Normal	722.3 (1)	728.2 (1)
Gen. Gamma	722.3 (1)	731.0 (1)
Log-Logistic	727.7 (3)	732.6 (4)
Gompertz	727.9 (4)	733.7 (5)
Gamma		

Table 27: AIC/BIC scores for lorlatinib in the metastatic recurrence (1L) health state

Distribution	AIC (rank)	BIC (rank)
Exponential	511.3 (5)	514.3 (5)
Weibull	505.5 (4)	511.5 (4)
Log-Normal	497.6 (2)	503.6 (2)
Gen. Gamma		
Log-Logistic	502.5 (3)	508.5 (3)
Gompertz	494.5 (1)	500.5 (1)
Gamma		

Table 28: AIC/BIC scores for no treatment in the metastatic recurrence (1L) health state

Distribution	AIC (rank)	BIC (rank)
Exponential	2093.4 (6)	2097.3 (6)
Weibull	2016.9 (5)	2024.8 (5)
Log-Normal	1964.6 (2)	1972.5 (1)
Gen. Gamma	1964.3 (1)	1976.2 (3)

Log-Logistic	1968.1 (3)	1975.9 (2)
Gompertz	1972.6 (4)	1980.5 (4)
Gamma	198.7 (4)	204.5 (4)

Metastatic recurrence (2L)

Table 29: AIC/BIC scores for alectinib in the metastatic recurrence (2L) health state

Distribution	AIC (rank)	BIC (rank)
Exponential	202.6 (5)	205.0 (1)
Weibull	201.2 (3)	206.0 (4)
Log-Normal	201.0 (2)	205.8 (3)
Gen. Gamma	202.8 (6)	209.9 (6)
Log-Logistic	201.0 (1)	205.7 (2)
Gompertz	201.5 (4)	206.3 (5)
Gamma		

Table 30: AIC/BIC scores for chemotherapy in the metastatic recurrence (2L) health state

Distribution	AIC (rank)	BIC (rank)
Exponential	103.9 (6)	105.5 (4)
Weibull	102.3 (5)	105.7 (5)
Log-Normal	100.1 (2)	103.5 (2)
Gen. Gamma	100.8 (3)	105.8 (6)
Log-Logistic	101.2 (4)	104.6 (3)
Gompertz	99.3 (1)	102.7 (1)
Gamma		

Please also include a user-adjustable option in the CEM to use survival data for recurrence health states extrapolated using any standard parametric distribution, not just the exponential distribution.

A user-adjustable option in the CEM for this request has not been provided as the CEM does not allow post-DFS transition probabilities to be time-variant. Additionally, the modelled PFS/OS appears to align well with the observed PFS/OS.

B12. Priority question. The EAG's clinical experts stated that progression-free survival (PFS) from the ALEX trial might be more reflective of outcomes for patients treated with alectinib in the non-metastatic recurrence health state than the ALINA trial. Therefore, please provide a scenario in which the transition

probabilities from the non-metastatic recurrence health state for patients treated with alectinib are informed by the ALEX trial rather than the ALINA trial.

A scenario analysis in which the transition probabilities from the non-metastatic recurrence health state for patients treated with alectinib are informed by the ALEX trial rather than the ALINA trial are presented in Table 32. As demonstrated below, this change has a minimal impact on the ICER [redacted]). The inputs to inform transition probabilities from the non-metastatic recurrence health state for patients treated with alectinib from the ALEX and ALINA trial are presented in Table 31.

Table 31: Inputs to inform transition probabilities from the non-metastatic recurrence health state for patients treated with alectinib

Source	Inputs to inform Transitions
ALINA	0.033
ALEX	0.022

Table 32: Scenario analysis in which the transition probabilities from the non-metastatic recurrence health state for patients treated with alectinib are informed by the ALEX trial (with PAS price for alectinib)

	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/LYG)	ICER (£/QALY)
Base case	Alectinib	[redacted]	12.40	9.90	-	-	-	-	-
	Platinum- based chemotherapy	[redacted]	8.51	6.60	[redacted]	3.89	3.30	[redacted]	[redacted]
Scenario	Alectinib	[redacted]	12.43	9.92	-	-	-	--	-
	Platinum- based chemotherapy	[redacted]	8.61	6.67	[redacted]	3.82	3.25	[redacted]	[redacted]

B13. Priority question. The EAG's clinical advisors suggested that chemoradiation is a key treatment option for patients with non-metastatic recurrence, which is not represented in the CEM, and which would be expected to have improved efficacy compared to either treatment alone:

a) **Please clarify whether the market shares for each treatment option provided by clinical experts at the advisory board account for combination therapies;**

The market shares for each treatment option provided by clinical experts at the advisory board does not account for combination therapies. The clinicians did not highlight that chemoradiation is a key treatment option for patients with non-metastatic recurrence.

b) **Please provide a scenario in the CEM in which chemoradiation is included as a distinct treatment option for patients with non-metastatic recurrence.**

A scenario analysis in which chemoradiation is included as a distinct treatment option has not been conducted because the UK clinicians did not identify chemoradiation as a treatment option during the advisory board in February 2024.

B14. Priority question. The EAG notes that the TLR used to identify sources for transition probabilities for the non-metastatic recurrence health state identified five studies reporting progression-free survival for patients treated with radiotherapy (Nakamichi *et al.* 2017, Kim *et al.* 2017, Agolli *et al.* 2015, Terada *et al.* 2020, Wu *et al.* 2017); however, only two of these (Wu *et al.* 2017 and Nakamichi *et al.* 2017) are mentioned in the CS:

a) **Please provide justification for the decision to exclude Kim *et al.* 2017, Agolli *et al.* 2015, and Terada *et al.* 2020 from consideration as a source for transition probabilities, and update section B.3.2.4.1 of the CS accordingly;**

The studies by Kim *et al.* 2017, Agolli *et al.* 2015, and Terada *et al.* 2020 were excluded as sources for transition probabilities due to their small sample sizes and specific limitations. Agolli *et al.* 2015 included only 28 patients (14), Terada

et al. 2020 included 46 patients (15), and while Kim *et al.* 2017 had a slightly larger overall sample, only 15 patients received radiotherapy, and the study did not focus on non-metastatic recurrence (16). In contrast, Wu *et al.* 2017 and Nakamichi *et al.* 2017 were selected because they had larger sample sizes (n=152 and n=56, respectively) (17, 18), providing more robust data on progression-free survival. The Company wanted to include studies with > 50 patients as larger sample sizes reduce bias and enhance the reliability of transition probabilities, which is crucial for accurate modelling.

b) The EAG considers that, although the cohort examined in Wu *et al.* 2017 does not exclude patients receiving chemotherapy alongside radiotherapy, the characteristics of the patient cohort are more representative of UK clinical practice. Therefore, please present a scenario in which transition probabilities for patients receiving radiotherapy in the non-metastatic recurrence health state are based on Wu *et al.* 2017.

To estimate the transition probabilities for treatments modelled in the CEM, when individual patient data (IPD) is not accessible, an appropriate study is identified that provides Kaplan-Meier (KM) curves for the relevant endpoint for patients treated with the specified treatment. The KM curve is digitised, and the digitised KM data is then used to create approximated IPD.

A limitation of Wu *et al.* 2017 is that it only presents KM curves for overall survival (OS). This study cannot be used to estimate the probability of experiencing a progression-free event for patients treated with radiotherapy after experiencing non-metastatic recurrence and therefore a scenario analysis cannot be run.

B15. Priority question. The EAG's clinical experts suggested that there is insufficient evidence to assume a difference in the proportion of patients who are considered cured in the long term, depending on whether patients receive adjuvant chemotherapy or alectinib. Furthermore, the experts also suggested that most patients who are disease-free for 5 years could be considered cured, and would not receive further treatment or follow-up:

a) Please provide scenarios in which the proportion of disease-free patients considered cured 10 years after initiating treatment is the same regardless of the adjuvant treatment received, exploring a range of values for this cure fraction;

A range of cure fraction rates applied at 10 years in both treatment arms were explored in scenario analyses, the results are presented in Table 33, Table 34, and Table 35. Regardless of the cure fraction rate used, alectinib remains cost-effective.

Table 33: Scenario analysis in which 92% of disease-free patients considered cured 10 years after initiating treatment is the same regardless of the adjuvant treatment received (with PAS price for alectinib)

	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/LYG)	ICER (£/QALY)
Updated base case	Alectinib	[redacted]	12.40	9.90	-	-	-	-	-
	Platinum- based chemotherapy	[redacted]	8.51	6.60	[redacted]	3.89	3.30	[redacted]	[redacted]
Scenario	Alectinib	[redacted]	12.38	9.88	-	-	-	--	-
	Platinum- based chemotherapy	[redacted]	8.51	6.60	[redacted]	3.87	3.28	[redacted]	[redacted]

Table 34: Scenario analysis in which 85% of disease-free patients considered cured 10 years after initiating treatment is the same regardless of the adjuvant treatment received (with PAS price for alectinib)

	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/LYG)	ICER (£/QALY)
Updated base case	Alectinib	[redacted]	12.40	9.90	-	-	-	-	-
	Platinum- based chemotherapy	[redacted]	8.51	6.60	[redacted]	3.89	3.30	[redacted]	[redacted]
Scenario	Alectinib	[redacted]	12.30	9.81	-	-	-	--	-
	Platinum- based chemotherapy	[redacted]	8.47	6.57	[redacted]	3.83	3.25	[redacted]	[redacted]

Table 35: Scenario analysis in which 75% of disease-free patients considered cured 10 years after initiating treatment is the same regardless of the adjuvant treatment received (with PAS price for alectinib)

	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/LYG)	ICER (£/QALY)
Updated base case	Alectinib	[redacted]	12.40	9.90	-	-	-	-	-
	Platinum- based chemotherapy	[redacted]	8.51	6.60	[redacted]	3.89	3.30	[redacted]	[redacted]
Scenario	Alectinib	[redacted]	12.19	9.72	-	-	-	--	-
	Platinum- based chemotherapy	[redacted]	8.42	6.52	[redacted]	3.78	3.20	[redacted]	[redacted]

b) Please provide a scenario in which the time point at which the cure assumption is applied is 5 years rather than 10 years.

A scenario in which the time point at which cure assumption is applied is 5 years rather than 10 years is presented in Table 36 and demonstrates that the ICER decreases by [redacted].

Table 36: Scenario analysis where cure assumption is applied at 5 years (with PAS price for alectinib)

	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/LYG)	ICER (£/QALY)
Updated base case	Alectinib	[redacted]	12.40	9.90	-	-	-	-	-
	Platinum- based chemotherapy	[redacted]	8.51	6.60	[redacted]	3.89	3.30	[redacted]	[redacted]
Scenario	Alectinib	[redacted]	13.79	11.09	-	-	-	--	-
	Platinum- based chemotherapy	[redacted]	9.67	7.59	[redacted]	4.12	3.51	[redacted]	[redacted]

B16. Priority question. The EAG notes that, in both the CS and the CEM, the market shares for subsequent treatments for patients who received adjuvant treatment with alectinib are the same for the 'rechallenge allowed' and 'rechallenge disallowed' time periods (see Table 41 in Document B of the CS, and the Treatment Description sheet in the CEM). Please correct the market shares for the 'rechallenge disallowed' time period to account for exclusion of alectinib in both the CS and the CEM.

The market shares for subsequent treatments in the "rechallenge disallowed" time periods have been updated in the CEM. Table 41 in the company submission has been updated to reflect these changes. The previous and new values are listed are in Table 37.

Table 37: Market shares for subsequent treatments in the "rechallenge disallowed" time periods (previous and new values)

		Inputs	Option 1	Option 2	Option 3	Option 4
Previous values	**Non-metastatic recurrence**	Treatment option	Radiotherapy	Surgery	Alectinib	Chemotherapy (cisplatin + pemetrexed)
		Alectinib arm (Re-challenge disallowed)	38%	17%	20%	25%
	Metastatic recurrence (1L)	Treatment option	Alectinib	Chemotherapy	Brigatinib	Loratinib
		Alectinib arm (Re-challenge disallowed)	23%	13%	26%	38%
	Metastatic recurrence (2L)	Treatment option	Alectinib	Loralatinib	Chemotherapy	
		Alectinib arm (Re-challenge disallowed)	16%	49%	35%	-
New values		**Inputs**	**Option 1**	**Option 2**	**Option 3**	**Option 4**
	Non-metastatic recurrence	Treatment option	Radiotherapy	Surgery	Alectinib	Chemotherapy (cisplatin + pemetrexed)
		Alectinib arm (Re-challenge disallowed)	47.50%	21.30%	0%	31.30%
	Metastatic recurrence (1L)	Treatment option	Alectinib	Chemotherapy	Brigatinib	Loratinib
		Alectinib arm (Re-challenge disallowed)	0%	17%	34%	49%
	Metastatic recurrence (2L)	Treatment option	Alectinib	Loralatinib	Chemotherapy	
		Alectinib arm (Re-challenge disallowed)	0%	58.35%	41.70%	-

B17. The EAG notes that the PROFILE 1007 trial, which was identified as a source for PFS data in the ALK inhibitor naive patient population in the SLR, was not considered as a source for transition probabilities for patients receiving chemotherapy in the non-metastatic recurrence health state. Please clarify the reason for this, and update section B.3.2.4.1 of the CS accordingly.

The Company would have preferred to inform the PFS of patients who receive chemotherapy for non-metastatic recurrence with evidence from a study focussing on this population. However, the *ALK*+ aNSCLC clinical SLR did not identify any studies that assessed the efficacy of chemotherapy for patients with locoregional recurrence or de novo locally advanced *ALK*+ NSCLC.

Thus, the team decided to inform the PFS of patients who receive chemotherapy for non-metastatic recurrence with evidence from a study that assesses the efficacy of 1L chemotherapy in patients with advanced-stage *ALK*+ NSCLC. As the Profile 1007 study compares crizotinib with chemotherapy in patients with locally advanced or metastatic *ALK*+ lung cancer who had received one prior platinum-based regimen (i.e. 2L treatment), the team did not consider the use of this study. Section B.3.2.4.1 of the CS has been updated.

B18. The EAG notes that a standardised mortality ratio (SMR) of 1.25 is applied to age- and sex-adjusted general population mortality to model background mortality in the CEM. However, this is not mentioned in the Company Submission:

a) Please provide details of the source of the SMR applied, and a justification for the application of an SMR; please also update the CS to include this information;

   The model adjusts the probability of death of these patients with a standardised mortality ratio of 1.25 (25% more cases of death than the general population) to account for excess mortality faced by these lung cancer survivors. This estimate was based on Janssen-Heijnen *et al.* (2012) who reported a 10-year conditional relative survival of 69–82% with a sample of Stage I–III patients (dependent on stage and age at diagnosis) (19) and in line with appraisal TA823 (13).

Section B.3.3.1.3, mortality adjustment, page 97 in the Company Submission has been updated to include the justification for applying an SMR and source used.

b) Please provide a scenario in which the SMR is not applied.

The results of the scenario analysis in which the SMR is not applied is shown in Table 38 below. As shown in Table 38, the ICER reduces by [redacted] when the SMR is set to one.

Table 38: Scenario analysis where SMR is not applied (with PAS price for alectinib)

	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/LYG)	ICER (£/QALY)
Base case	Alectinib	[redacted]	12.40	9.90	-	-	-	-	-
	Platinum-based chemotherapy	[redacted]	8.51	6.60	[redacted]	3.89	3.30	[redacted]	[redacted]
Scenario	Alectinib	[redacted]	12.78	10.19	-	-	-	--	-
	Platinum-based chemotherapy	[redacted]	8.65	6.70	[redacted]	4.14	3.48	[redacted]	[redacted]

B19. The CEM includes an option to include a treatment waning effect as a scenario. Please provide details of how this has been implemented, and any assumptions which have been made. Please also update the CS to include this information.

The CEM allows for the treatment effect of the adjuvant alectinib to decrease over time and eventually cease. When this process begins, the CEM assumes that the clinical outcomes for patients in the drug arm are informed by the chemotherapy arm. This adjustment is not applied in the base case. While longer-term follow-up data from ALINA would be needed to determine the appropriateness of this adjustment, current results suggest it may not be suitable. Disease-free survival in Figure 14 does not appear to be converging across arms, despite most patients on alectinib completing 24 months of treatment. Section B.3.3.1.3, Treatment Waning Effect, page 95-96 in the company submission has been updated.

Figure 14: Projected investigator-assessed DFS with log-logistic parametric survival model and cure, mortality and treatment effect adjustments (ALINA, CCOD 26/Jun/23)

B20. The EAG acknowledges that the overall survival (OS) data from the ALINA trial are inappropriate for direct use in the economic model due to lack of maturity; however, these data may be used to validate the OS results derived from the economic model. Please present a side-by-side comparison of the OS data from ALINA and the

calculated OS results from the economic model, and comment on any differences between the observed and calculated results.

A comparison of the OS data from the ALINA trial and modelled OS can be found in Figure 15. OS from the ALINA trial are immature (i.e. 2.3% event–patient ratio). Given the extremely low-to-event patient ratio, this cannot this data be used directly in the CEM and cannot be used to validate the OS results from the CEM. This would lead to inaccurate decisions being made on whether the modelled OS is valid.

Figure 15: Overall survival- alectinib and chemotherapy arm

Health-related quality of life

B21. Priority question: For the general population utility values, the NICE methods guide recommends using the Health Survey for England (HSE) 2014 dataset, as recommended by the DSU (Hernández Alava *et al.* 2022). Please update the general population utility values used for age adjustment in the model to use the HSE 2014 dataset.

The general population utility values in the CEM have been updated using the HSE 2014 dataset.

B22. Priority question. The EAG notes that age adjustment of utilities has been applied incorrectly in the CEM; rather than multiplying health state utility values

by general population utility at the age of interest divided by general population utility at the baseline age, the utility value has been bounded above by general population utility at the age of interest. Please correct this in the CEM.

The Company took the approach of using time-invariant health state utility values (HSUV), and then switching to the use of general population utility values when they become lower (age, sex adjusted) than the HSUV. This ensures that the CEM does not implicitly assume that patients with NSCLC have a higher utility value than individuals from the general population. The approach used is just one of several methods that could be used to model utilities and has been used in previous CEMs that have been published in peer-reviewed journals (20). The CEM has been updated to include an option that allows the analysis to use the suggested EAG approach.

B23. Priority question: The EAG notes that minimal detail is provided in the CS on the regression analysis performed to obtain utility values used in the economic model:

a) Was the regression analysis pre-specified?

The EQ-5D-5L questionnaire was administered to patients in the ALINA study in order to generate utility values for use in economic modelling. Patients completed the questionnaire at baseline, every 3 weeks up to week 12, and then every 12 weeks until disease recurrence, withdrawal of consent, death, or week 96, whichever came first. A linear mixed effects model, using a normal random subject effect, was pre-specified to assess the health state utility values over time after randomization into the study.

b) How was the model structure and final included variables decided upon?

When discussing the model structure and variables included, the company carefully considered the design of the cost-effectiveness model and the health states that were modelled within it. However, due to the specific administration schedule of the EQ-5D-5L in the ALINA study; it was only possible to use study-based data to inform the disease-free health state. Given the significant differences in treatment administration schedules between the alectinib and chemotherapy arms, it was decided to estimate utilities not only by treatment

arm but also by whether patients were on or off treatment in both arms. This distinction was particularly relevant for the chemotherapy arm, where patients stopped treatment after 12 weeks.

It is important to note that the estimated off-treatment utility for alectinib, which had a planned treatment duration of 2 years, was based on limited data. Specifically, the data relied on patients' safety follow-up visits after the end of treatment. An interaction effect between treatment and on/off status was included to account for the assumption that patients receiving chemotherapy might experience lower utilities while on treatment and potentially have more potential to recover when coming off treatment. Additionally, baseline utility was accounted for by including it as a covariate in the model. Age was initially considered as a covariate as well, but its effect became non-significant when baseline utility was included in the model.

c) Details of the regression model outputs, including regression coefficients for the model fitted using data derived using UK tariffs, associated p values for each model coefficient, and evidence of goodness of fit (for example, R^2 values and residuals plots).

The details of the regression model including estimates of the fixed-effects parameters based on data derived using UK tariffs, as well as the corresponding standard errors and t-value, can be found in Table 39 and Table 40. However, please note that p-values can be challenging to interpret in mixed effects models fitted using the lme4 package in R. As a result, the output of p-values was omitted. Figure 16 show the standardised residuals vs fitted values by treatment arm, and the fitted vs observed values by treatment arm.

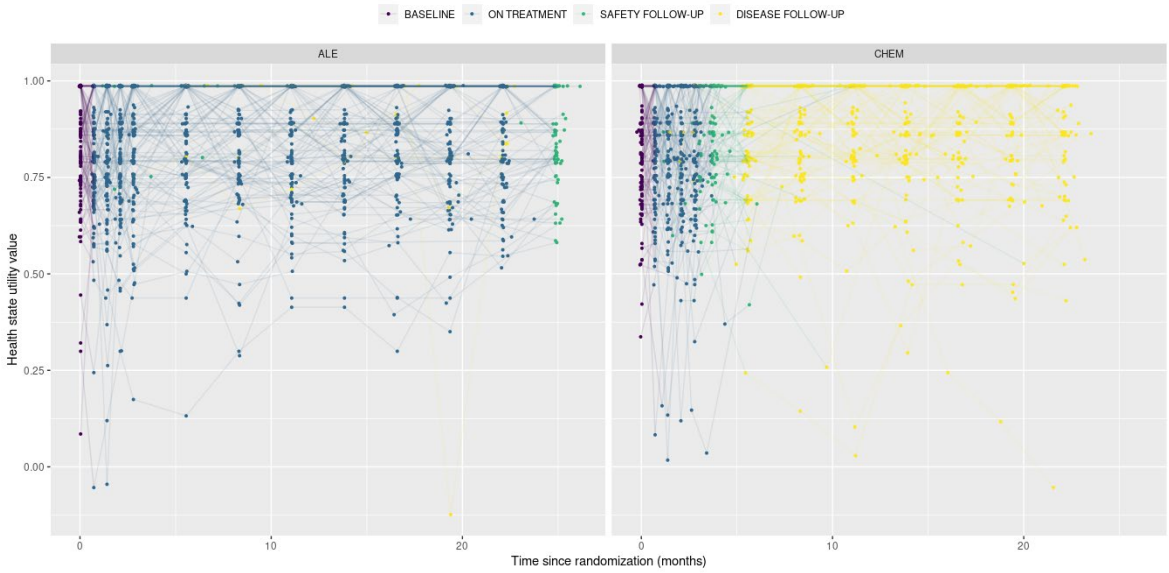
Table 39: Health state utility values – Summary (ALINA, CCOD 26/Jun/23)

Health state	Estimate	Std. error (Bootstrapped)
Alectinib – On-treatment	0.828	0.01
Alectinib – Off-treatment	0.863	0.014
Chemotherapy – On-treatment	0.811	0.011
Chemotherapy – Off-treatment	0.858	0.011

Table 40: Health state utility values – Mixed-effects model (ALINA, CCOD 26/Jun/23)

Fixed effects	Estimate	Std. error	t value
Intercept	0.487	0.04201	11.59
Baseline utility	0.3912	0.0494	7.918
Alectinib	0.01735	0.01487	1.167
Off-treatment	0.04729	0.005986	7.9
Alectinib*Off-treatment	-0.01194	0.01216	-0.982

Figure 16: Graphical display of ALINA utilities using UK tariffs



B24. Priority question: Please clarify why adverse events (AEs) were not included in the regression analysis to obtain the impact of AEs as opposed to using separate treatment specific utility values?

There are several approaches that could have been used to model health state utilities in the CEM. The chosen approach was based on the need to apply separate health state utility values to patients treated with adjuvant alectinib and adjuvant chemotherapy, as well as to patients on and off treatment, due to differences in treatment schedules between the therapies.

The estimated health state utility values for the 'on treatment' group (for both arms) are expected to already account for any disutility caused by adverse events. The inclusion of adverse events as covariates in the analysis might have introduced issues such as multicollinearity, which could prevent accurate estimation of the required

health state utility values. Thus, the current regression model was deemed appropriate.

B25. Priority question. Table 33 of the CS states that the utility value applied for recurrence is 0.77. However, in the economic model the value appears only to be applied for non-metastatic recurrence, with a value of 0.70 applied for metastatic recurrence:

a) Please update Table 33 to include all relevant data used in the economic model for utility values;

Table 33 in the Company Submission has been updated to include the utility values for both non-metastatic recurrence and metastatic recurrence. This did not affect the base case results, as the utility value of 0.70 was already included in the CEM.

b) The EAG notes that the value of 0.70 is derived from the Chouaid *et al.* regression coefficients (intercept of 0.77 plus Stage IV coefficient of -0.07). It is noted in the CS that the Company's clinical advisors considered the value of 0.77 too high for this health and it was tested in scenario analysis. The EAG notes that in the Company's ad board document, it is noted that clinicians considered 0.70 to be too high for patients with metastatic disease recurrence. Based on the clinical advice received, please clarify why more appropriate sources were not searched for and used?

A burden of illness systematic literature review (SLR) examining utilities after recurrence was conducted which identified the Chouaid *et al.* study, identified, however no further appropriate sources were. A scenario analysis using a utility value of 0.60 for the metastatic recurrence health states was conducted and presented in Table 41. This value of 0.60 is deemed to be overly conservative and in fact the Company believes the true utility value in this health state is higher. However, this artificially low value was used in the scenario analysis to demonstrate the lack of impact this parameter has on the overall cost-effectiveness. The ICER reduced by [redacted] and alectinib remained cost-effective.

Table 41: Scenario analysis using 0.60 as the utility value for metastatic disease recurrence

	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/LYG)	ICER (£/QALY)
Updated Base case	Alectinib	[redacted]	12.40	9.90	-	-	-	-	-
	Platinum- based chemotherapy	[redacted]	8.51	6.60	[redacted]	3.89	3.30	[redacted]	[redacted]
Scenario	Alectinib	[redacted]	12.50	9.76	-	-	-	--	-
	Platinum- based chemotherapy	[redacted]	8.51	6.34	[redacted]	3.89	3.42	[redacted]	[redacted]

B26. In the SLR conducted for HRQoL studies (Appendix H), only studies based on early-stage NSCLC were included, with advanced/metastatic studies noted as an exclusion criteria. Please clarify why these studies were excluded from the review, despite the knowledge that utility values for the metastatic/recurred disease health states would be needed for the economic model?

The SLR conducted for HRQoL studies specifically focused on early-stage NSCLC. Another SLR (burden of illness of locally advanced and metastatic NSCLC) was run to inform the HRQoL of patients with locally advanced and metastatic NSCLC. Overall, 29 studies were included in this SLR. Out of these, 23 studies reported data for Research Question 1, focusing on treatment patterns in ALK+ advanced NSCLC patients. Additionally, 6 studies provided data for Research Question 2, addressing clinical effectiveness in early-stage NSCLC patients. In the Company Submission, the study by Chouaid *et al.*, as identified in the burden of illness SLR, was referenced for the utility values for metastatic/recurred disease health states used in the economic model.

To be transparent, the full burden of illness SLR report has been provided as a separate document.

B27. Table 32 in the “Measurement and valuation of health effects” section of the CS reports frequency and monthly probability of AEs. However, these are not used in relation to HRQoL. Please clarify why disutilities for AEs were not applied in the model.

For patients in the DFS health state, separate health state utility values were estimated for those on and off treatment, differentiated by treatment arm. Since the health state utility values for the 'on treatment' group should already account for the disutility associated with any adverse events they may have experienced, not directly modelling this impact should not substantially affect the model's results. The same approach applies to the post-DFS health state utility values. The safety profile for all arms is tolerable and therefore the omission of not directly modelling AE disutility is not likely to meaningfully impact cost-effectiveness.

B28. Please comment on any potential bias that may be implemented in the model by not accounting for any disutility associated with subsequent treatments included in the model.

If the CEM had accounted for the disutility of adverse events, it would have double-counted the disutility associated with treatment.

Drug acquisition and administration costs

B29. Priority question. The EAG notes that many of the costs of subsequent treatments have been sourced via the BNF when lower prices are available in the drugs and pharmaceutical electronic market information tool (eMIT). Therefore, please update the CEM using eMIT prices for the following treatments: cisplatin, carboplatin, pemetrexed, vinorelbine and gemcitabine.

The CEM has been updated using eMIT prices. Costs used in the initial submission and updated costs that have been submitted as part of this response are presented side-by-side in Table 42. Table 35, in the company submission has also been updated. This update increases the base case ICER by [redacted].

Table 42: Drug acquisition costs

	Drug	Small vial/small pack		Large vial/large pack		Source
		Vial size /pack size	List price per pack (£)	Vial size /pack size	List price per pack	
Previous values	Cisplatin	50	26.72	100	50.22	BNF 2024 (21)
	Carboplatin	50	20.2	600	232.64	BNF 2024 (21)
	Pemetrexed	100	160	500	800	BNF 2024 (21)
	Vinorelbine	10	329.5	50	1,539.80	BNF 2024 (21)
	Gemcitabine	1,000	162	1,000	162	BNF 2024 (21)
New values	Cisplatin	50	27.98	100	29.27	eMIT 2023 (22)
	Carboplatin	50	9.28	600	71.44	eMIT 2023 (22)
	Pemetrexed	100	24.52	500	159.35	eMIT 2023 (22)

	Vinorelbine	10	75.16	50	172.56	eMIT 2023 (22)
	Gemcitabine	1,000	18.17	1,000	45.96	eMIT 2023 (22)

B30. Priority question. The EAG notes that an average cost per week for alectinib is applied for each week in the cycle, instead of applying the cost of a full pack at the start of each cycle, which would better reflect how alectinib would be prescribed in practice. Therefore, the EAG considers that this will lead to incorrect discounting of the true costs and underestimate the costs of alectinib if patients progress or die. Please either update the model base case to calculate costs of alectinib based on how they will be prescribed in practice or include a scenario analysis with this implemented.

Applying cost of a full pack of alectinib at the start of a cycle was explored in scenario analysis and is presented in Table 43. The ICER increases by [redacted], however alectinib remains cost effective.

Table 43: Scenario analysis applying cost of a full pack of alectinib at the start of a cycle

	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/LYG)	ICER (£/QALY)
Updated Base case	Alectinib	[redacted]	12.40	9.90	-	-	-	-	-
	Platinum- based chemotherapy	[redacted]	8.51	6.60	[redacted]	3.89	3.30	[redacted]	[redacted]
Scenario	Alectinib	[redacted]	12.399	9.898	-	-	-	--	-
	Platinum- based chemotherapy	[redacted]	8.507	6.597	[redacted]	3.892	3.301	[redacted]	[redacted]

B31. Priority question. The economic model applies an administration cost for alectinib and all other oral therapies, associated with pharmacy dispensing. The EAG notes that in the economic model this cost is applied on a weekly basis, despite products usually being prescribed as a monthly supply. For example, the draft Summary of Product Characteristics (SmPC) for alectinib states that a pack size is 224, which would equate to 28 days' worth. Please amend this error in the economic model for all oral therapies.

The CEM has been updated to apply a monthly administration cost for alectinib and all other oral therapies. This change reduces the ICER, in favour of alectinib.

B32. The EAG notes that the relative dose intensity (RDI) of alectinib is not included in the economic model. Please clarify why this has been excluded and include a scenario with this implemented.

Relative dose intensity (RDI) of alectinib has not been included in the model given the high dose intensity (i.e. median dose intensity of 99.4%; refer to Table 11 of CSR). If RDI was modelled, this would impact the results in favour of alectinib as the total cost of treatment would decrease for the alectinib arm. Thus, the exclusion of relative dose intensity can be seen as a conservative approach.

B33. Please clarify why vial sharing is assumed for intravenous (IV) therapies and therefore no wastage is included? Please include a scenario in the model where vial sharing is not permitted.

The CEM initially did not include an option to relax the assumption of perfect vial sharing for patients treated with IV-administered chemotherapy. This was because adding this complexity was deemed unnecessary, as most patients with *ALK*+ NSCLC are treated with orally administered ALK inhibitors. The CEM has now been updated to include an option that allows for relaxing the assumption of perfect vial sharing for patients treated with IV-administered chemotherapy.

Assuming that there is no vial sharing of IV administered chemotherapy had a small impact on the ICER in favour of adjuvant alectinib as shown in Table 44 below.

Table 44: Scenario analysis where vial sharing is not permitted (with PAS price for alectinib)

	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/LYG)	ICER (£/QALY)
Updated base case	Alectinib	[redacted]	12.40	9.90	-	-	-	-	-
	Platinum-based chemotherapy	[redacted]	8.51	6.60	[redacted]	3.89	3.30	[redacted]	[redacted]
Scenario	Alectinib	[redacted]	12.40	9.90	-	-	-	--	-
	Platinum-based chemotherapy	[redacted]	8.51	6.60	[redacted]	3.89	3.30	[redacted]	[redacted]

B34. The EAG notes that the cost of administration for oral treatments is based on Personal Social Services Research Unit (PSSRU) 2022. PSSRU 2023 is the most recent version available. Therefore, please update the cost of administration based on PSSRU 2023.

Based on PSSRU 2023, the cost of administration for oral treatments is £10 rather than £9. This update has been reflected in the CEM. Table 36 and Table 44 in the Company Submission has also been updated. This change had a minimal impact to the ICER.

B35. The CS notes that the administration cost for IV therapies included in the model is assumed to be equal to £475.94 from NHS Reference Costs "Deliver subsequent elements of a chemotherapy cycle (SB15Z):

a) The EAG notes that the cost used by the Company represents SB14Z "Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance" and not SB15Z noted by the Company. Please clarify the correct cost and source intended to be used;

   The administration cost for IV therapies included in the model is SB14Z "Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance" rather than SB15Z. This code has been corrected in the Company Submission.

b) In addition, please clarify why separate costs were not applied for first attendance and subsequent delivery, as these are available in NHS Reference Costs?

   Separate costs were not applied for first attendance and subsequent delivery as this functionality did not exist in the previous iteration of the model. A conservative approach was used by taking the highest administration cost (SB14Z). However, this has now been updated in the model, please see Question 35c.

   At the request of the EAG, the CEM now allows administration cost of the initial cycle of IV chemotherapy to be different to the subsequent cycles of IV

chemotherapy for treatment options in the non-metastatic recurrence and metastatic recurrence health states..

Assuming a difference in the costs of the initial cycle and subsequent cycles of IV chemotherapy had a small impact on the ICER in favour of adjuvant alectinib – see response to B35c for further details.

c) Please provide an option in the model to implement separate costs for first and subsequent administrations for IV chemotherapy treatments and provide results of this scenario.

The CEM has been updated to include separate costs for first and subsequent treatments for IV chemotherapy. A scenario analysis has not been conducted as this change is now incorporated in the base case, which has been updated accordingly. As a result, Table 36 in the company submission has also been revised. This change increased the ICER by [redacted], thus having a minimal impact on the ICER.

Subsequent treatment costs

B36. The Company Submission provides no description of the type or cost of surgery used for recurrence. However, the cost included in the economic model for surgical resection is £160.62, which references NHS reference costs 2021-2022, general surgery service, code 100. This cost refers to outpatient attendance for general surgery. The EAG considers this cost to grossly underestimate the cost associated with surgery for NSCLC recurrence and is inappropriate to use in the economic model:

a) Please clarify why this cost was used;

The Company agrees that this is not an appropriate cost to use. The cost has been updated in Table 38 in the Company Submission as per Q36b below.

b) Please source a more appropriate NHS reference cost which is reflective of the type of surgery performed and update the economic model. Please also update the CS with details of the costs used.

A more appropriate NHS reference cost has been sourced, “DZO2K- Complex Thoracic Procedures, 19 years and over, with CC Score 0-2” the cost of surgery in the base case has been updated from £160.62 to £588.30. This was validated with a clinician. The CEM and Table 38, page 110 in the Company Submission has been updated. Overall, this has a minimal impact (increases ICER by [redacted]).

B37. The Company Submission provides no description of the type or costs of radiotherapy used in the model (Conformal 3-dimensional radiotherapy). The economic model states 20 treatment cycles are used in “Treatment regimes” cell F79 whereas in cells F118-121 alternative data is presented and used in the calculation of radiotherapy treatment costs:

a) Please provide a description of how the type of radiotherapy and the total treatment dose of 66 was informed. Please also update the CS with this information.

The type of radiotherapy and the total treatment dose is informed by radiotherapy dose fractionation, fourth edition (23). The most conservative approach was taken for radiotherapy resulting in 66gy in 33 fractions over 6.5 weeks as per the Royal College of Radiologist’s guidance on fractionation. Cell F29 in the “treatment regimens” sheet has been updated in the CEM to reflect this change; this had zero impact on the ICER.

b) The economic model references the cost of radiotherapy as £236.94, reference “NHS reference costs 2021-2022, RAD”. Although the Company did not provide detail, the EAG notes that this cost refers to the total HRG cost for radiotherapy. The EAG do not consider this to be an appropriate cost to use to inform the cost of individual fractions of radiotherapy or its preparation. Please either update the base case economic model or provide a scenario analysis in which a more specific NHS Reference Cost is used to reflect the type of radiotherapy used in the model.

After consultation with a clinician, the cost of radiotherapy in the base case has been updated from £235.94 to £244.23. This update uses the weighted average cost of the following cost codes: SC22Z (Deliver a Fraction of Treatment on a

Megavoltage Machine), SC31Z (Deliver a Fraction of Adaptive Radiotherapy on a Megavoltage Machine), and SC52Z (Preparation for Complex Conformal Radiotherapy, with Technical Support). This update has a minimal impact on the ICER (ICER increased by [redacted]).

B38. The EAG notes that maximum treatment duration for subsequent treatments following recurrence are based on the median time on treatment from the studies used to inform transition probabilities. Please include a scenario in which treatment duration is based on PFS rather than median time on treatment.

Scenario analysis based on treatment duration derived from progression-free survival (PFS) rather than median treatment duration is shown in Table 45. This change decreases the ICER by [redacted], demonstrating a significant impact and making alectinib even more cost-effective.

Table 45: Scenario analysis based on treatment duration derived from progression-free survival (PFS) rather than median treatment duration

	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/LYG)	ICER (£/QALY)
Updated base case	Alectinib	[redacted]	12.40	9.90	-	-	-	-	-
	Platinum- based chemotherapy	[redacted]	8.51	6.60	[redacted]	3.89	3.30	[redacted]	[redacted]
Scenario	Alectinib	[redacted]	12.40	9.90	-	-	-	--	-
	Platinum- based chemotherapy	[redacted]	8.51	6.60	[redacted]	3.89	3.30	[redacted]	[redacted]

Adverse event costs

The EAG notes that limited discussion is provided in the CS regarding adverse event costs associated with both adjuvant and subsequent treatments and has identified a number of issues associated with these, described further below.

B39. In Table 32 of the CS, it can be seen that a number of treatment emergent AEs were observed. However, the CS states that only AEs that occurred with a difference in incidence rate of at least 2% between treatment arms were included in the economic model, of which the Company includes six AEs. Please clarify why appendicitis, which was reported in Table 32 to have been experienced by one patient only (in the alectinib arm), was included in the economic model and other AEs which were experienced by only one or two patients in one treatment arm were not included (e.g. alanine aminotransferase increased, aspartate aminotransferase increased)?

The adverse events included in the model are consistent with Table 27 in the CSR. Table 32 of the CS represents the occurrence of Grade 3–5 treatment emergent AEs during adjuvant treatment. Table 27 of the CSR is related to the AEs that occurred with a difference in incidence rate of at least 2% between treatment arms. In the case of appendicitis, in the safety-evaluable population, this occurred in 4 patients in the alectinib arm (3.1%) and in 0 patients in the chemotherapy arm, hence why it was included in the model.

B40. The EAG notes the following discrepancies between the number of patients with grade 3 to 5 adverse events included in Table 32 of the CS compared to the clinical study report for ALINA. Please clarify which is correct and update in the economic model if required:

a) One grade 3 to 5 appendicitis event for alectinib reported in Table 32 of the CS whereas [redacted] grade 3 to 5 appendicitis events for alectinib are described in the CSR;

b) Zero grade 3 to 5 ‘blood creatinine phosphokinase increased’ events reported for chemotherapy in Table 32 of the CS whereas [redacted] was reported in the CSR for this treatment arm.

The discrepancies between CS, Table 32 and the CSR are due to the fact that Table 32 in the CS is on the occurrence of Grade 3-5 AEs *related to study treatment* in the safety-evaluable patients (see page 239 of the CSR). “Appendicities” (n=4) in the alectinib arm and “Blood Creatine Phosphokinase Increased” (n=1) in the chemotherapy arm are part of “All Grade 3-5 AEs” in the safety-evaluable population (see page 241 of the CSR).

B41. The cost used for both neutropenia and nausea are referenced to be sourced from TA812. While the EAG was able to identify this cost in TA812, the source reported in TA812 is that this has been taken from TA531 and inflated. Therefore, the Company has not accounted for the fact that TA812 uses a different cost year to the current appraisal. The EAG also notes that clinical experts to the EAG stated that nausea would tend to be managed with supportive medication such as anti-emetics. If the Company still consider the costs used in their model to be the most appropriate, please use the cost from the original source (Brown 2013 referenced in TA531) and inflate to the current cost year appropriately.

This cost for neutropenia and nausea has been inflated and updated in the “safety” sheet in the CEM. It is assumed that the cost of nausea includes the cost of supportive medicines such as anti-emetics.

B42. Please provide further clarification as to why a cost is included for neutropenia but not neutrophil/white blood cell decreased?

The cost for neutrophil count decreased was set to £0, which is in line with TA428 (24) and TA531 (25) NICE appraisals.

B43. The EAG notes that no detail is provided in the CS on the cost of AEs experienced for treatments used in recurrence health states. The EAG identified a number of discrepancies with these costs:

a) Based on the CEM technical report provided to the EAG, it appears that costs for AEs for recurrence states are based on Canadian data. In addition, regardless of if the costs are in Canadian dollars, the costs in the recurrence health states are significantly higher than those included in the disease-free health state. Please update the economic model and CS with appropriate costs and provide justification for the costs used;

As mentioned previously in this response, the Canadian technical report should be ignored. The AE costs in the non-metastatic and metastatic health states have been updated in the "safety" sheet of the model. The changes have had a minimal impact on the ICER ([redacted]). Table 42, page 120 in the Company Submission has been updated to reflect these updates.

b) Please clarify why all AEs in the metastatic health states are assumed to have an associated cost, when the same is not true for those experienced in the disease-free health state?

As mentioned in 43a, the AE costs in the non-metastatic and metastatic health states have been updated. AEs that occurred with a difference in incidence rate of at least 2% between treatment arms were included in the model in line with the disease-free health state.

Disease management costs

B44. Priority question. The EAG notes that a more recent version of PSSRU (2023) is available to that used in the Company's submission (2022). Please update any costs for health care resource use included in the model from PSSRU to be sourced from the most recent version.

The healthcare costs in the CEM have been updated to align with PSSRU 2023; Table 46 outlines the healthcare resource updates, including the previous and new values, and specifies where change was made in the model. These changes had a minimal impact to the ICER (+£20). Section B.3.5.1.3, Table 38, page 116 in the Company Submission has been updated.

Table 46: Healthcare resource costs that has been updated according to PSSRU 2023

Healthcare resource use	Previous value	New value	Change in the model
Community nurse visit	£75	£82	"Direct cost tab" Cell F56
Clinical nurse specialist	£85	£94	"Direct cost tab" Cell F60

GP surgery visit	£41	£50.50	"Direct cost tab" Cell 62

B45. Priority question. The CS provides details on the number of CT scans included for the disease-free health states only:

a) Please update the CS to include details of CT scans used in all health states

Table 40, page 117 in the Company Submission has been updated to include details of CT scans used in all health states.

b) In the economic model, patients with metastatic recurrence on 2nd line treatment are assumed to have zero CT scans. The Company's ad board document states that all experts suggested that patients would receive CT scans every 3 months in the metastatic setting. Please clarify why the advice of the clinical advisors was not implemented in the model and provide a scenario analysis in which CT scans are implemented for patients on 2nd line metastatic recurrence.

The cost of CT scans for patients in the 2L metastatic health state was initially excluded; however, this has now been updated in the CEM. Scenario analyses presented in Table 47 demonstrates that this has a minimal impact on the ICER (ICER reduces by [redacted]).

Table 47: Scenario analysis using the cost of CT scans in the 2L metastatic health state

	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/LYG)	ICER (£/QALY)
Updated base case	Alectinib	[redacted]	12.40	9.90	-	-	-	-	-
	Platinum- based chemotherapy	[redacted]	8.51	6.60	[redacted]	3.89	3.30	[redacted]	[redacted]
Scenario	Alectinib	[redacted]	12.40	9.90	-	-	-	--	-
	Platinum- based chemotherapy	[redacted]	8.51	6.60	[redacted]	3.89	3.30	[redacted]	[redacted]

B46. For patients in the 1st line metastatic recurrence health state, the economic model assumes that patients on treatment have one MRI scan per year whereas those off treatment have two MRIs per year. However, the Company's ad board report states that clinical experts suggested that patients with metastatic disease would receive MRI scans once every six months. Please clarify this difference and implement a scenario in which all patients in 1st line metastatic recurrence receive two MRI scans per year.

This was incorrectly incorporated in the model, and a scenario using two MRI scans in the 1L metastatic recurrence has been provided in Table 48 below. This scenario has a minimal impact on the ICER.

Table 48: Scenario analysis using 2 MRI scans in the 1L metastatic recurrence (with PAS price for alectinib)

	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/LYG)	ICER (£/QALY)
Updated base case	Alectinib	[redacted]	12.40	9.90	-	-	-	-	-
	Platinum- based chemotherapy	[redacted]	8.51	6.60	[redacted]	3.89	3.30	[redacted]	[redacted]
Scenario	Alectinib	[redacted]	12.40	9.90	-	-	-	--	-
	Platinum- based chemotherapy	[redacted]	8.51	6.60	[redacted]	3.89	3.30	[redacted]	[redacted]

B47. The EAG notes that in the Company's advisory board notes, clinical experts all agreed that 1.18 community nurse visits per year was higher than they would expect to see in clinical practice. The EAG's clinical experts also noted that this is not a resource they would routinely see provided on an annual basis. Please include a scenario in which alternative values are used for community nurse visits in the economic model.

A scenario using an arbitrary value of 0.5 community visits are presented in Table 49 below. This scenario has a minimal impact on the ICER.

Table 49: Scenario analysis using 0.5 community nurse visits per year

	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/LYG)	ICER (£/QALY)
Updated base case	Alectinib	[redacted]	12.40	9.90	-	-	-	-	-
	Platinum- based chemotherapy	[redacted]	8.51	6.60	[redacted]	3.89	3.30	[redacted]	[redacted]
Scenario	Alectinib	[redacted]	12.40	9.90	-	-	-	-	-
	Platinum- based chemotherapy	[redacted]	8.51	6.60	[redacted]	3.89	3.30	[redacted]	[redacted]

B48. Clinical advisors to the EAG noted that patients would be required to attend an outpatient appointment every time a CT scan was required. This was also noted by one of the clinical experts in the Company's ad board meeting. Please include a scenario in which additional outpatient visits are included for each CT scan.

Scenario analyses in which patients would be required to attend an outpatient appointment every time a CT scan was required are presented in Table 50. In this scenario, the ICER decreases by [redacted] and alectinib remains cost effective.

Table 50: Scenario analysis in which additional outpatient visits are included for each CT scan

	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/LYG)	ICER (£/QALY)
Updated base case	Alectinib	[redacted]	12.40	9.90	-	-	-	-	-
	Platinum- based chemotherapy	[redacted]	8.51	6.60	[redacted]	3.89	3.30	[redacted]	[redacted]
Scenario	Alectinib	[redacted]	12.40	9.90	-	-	-	--	-
	Platinum- based chemotherapy	[redacted]	8.51	6.60	[redacted]	3.89	3.30	[redacted]	[redacted]

B49. The EAG's clinical experts noted that all patients receiving alectinib and any chemotherapy treatment would require blood tests prior to each cycle of treatment as part of routine monitoring. Please include a scenario in which this is implemented.

Scenario analyses where all patients receiving alectinib and any chemotherapy treatment would require blood tests prior to each cycle of treatment as part of routine monitoring is presented in Table 51. This scenario has a minimal impact on the ICER.

Table 51: Scenario analysis in which additional outpatient visits are included for each CT scan (with PAS price for alectinib)

	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/LYG)	ICER (£/QALY)
Updated base case	Alectinib	[redacted]	12.40	9.90	-	-	-	-	-
	Platinum- based chemotherapy	[redacted]	8.51	6.60	[redacted]	3.89	3.30	[redacted]	[redacted]
Scenario	Alectinib	[redacted]	12.64	10.11	-	-	-	--	-
	Platinum- based chemotherapy	[redacted]	9.05	7.12	[redacted]	3.59	2.99	[redacted]	[redacted]

Other costs

B50. End-of-life care costs for cancer are available from the latest PSSRU Unit Costs of Health and Social Care 2023 Manual (Table 7.2.2). Please explore the PSSRU cancer end of life care cost in a scenario.

The cost for end-of-life cancer care, according to PSSRU 2023, is £19,934 (26). As this is a more appropriate cost, Table 43, page 121 in the Company Submission has been updated.

The results of the scenario analysis utilising the previous cost of £4,598 for end of life care are presented in Table 52 below. As shown in Table 52, the ICER increases by [redacted] however alectinib remains cost effective.

Table 52: Scenario analysis using the original end of life care cost (£4,598) from TA705 appraisal (with PAS price for alectinib)

	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/LYG)	ICER (£/QALY)
Base case	Alectinib	[redacted]	12.40	9.90	-	-	-	-	-
	Platinum- based chemotherapy	[redacted]	8.51	6.60	[redacted]	3.89	3.30	[redacted]	[redacted]
Scenario	Alectinib	[redacted]	12.40	9.90	-	-	-	--	-
	Platinum- based chemotherapy	[redacted]	8.51	6.60	[redacted]	3.89	3.30	[redacted]	[redacted]

Model implementation

B51. Priority question. Please correct the following errors in the CEM:

a) **Administration costs have not been applied for alectinib as an adjuvant treatment, due to an error in the 'Adjuvant Tx Schedule' sheet (cell G46 downwards);**

The formula has been corrected in the "Adjuvant Tx Schedule" sheet in the CEM.

b) **There is an error in the calculation of treatment acquisition costs for alectinib based on tunnel states; for example, in the 'TxT LR - ALE Arm' sheet from DW1006 downwards and IU1006 downwards, the formula only accounts for the first six cycles of treatment;**

The formula has been corrected in the "TxT LR - ALE Arm'" and "TxT LR - CHT" Arm sheet in the CEM.

c) **The cure assumption is applied one cycle too early in the model traces;**

The following variables have been changed from equalling 120 to 121 months, as month 121 equates to year 10 in the Markov trace (i.e. year in cycle 1 starts at 0.1, and month in cycle 1 starts at month 0):

- cure_assumption_dfs_t_1
- cure_assumption_dfs_t_2
- cure_assumption_dfs_t_1_ct
- cure_assumption_dfs_t_2_ct

d) **Sampling of Dirichlet-distributed variables in the PSA has been implemented incorrectly, leading to proportions which do not sum to 100%;**

The distribution of dirchlet-distributed variables in the 'PSA Parameters' sheet does not sum to 100%. The 'PSA Parameters' sheet generates the values of these inputs when the PSA is performed, but these are not the live values used by the CEM.

The live inputs that use the values generated in the 'PSA Parameters' sheet include an adjustment that ensures that the dirchlet-distributed variables sum to 100%. This adjustment has been included in past CEMs submitted to NICE**.** Therefore, this is not an error and has not been implemented in the CEM.

e) The scenarios relating to the proportion of patients experiencing cure have been implemented incorrectly in the automated scenario analysis (the cure fractions have not been varied for both potential cure timepoints simultaneously);

The analysis cannot be performed in the 'Scenario Analyses' sheet of the CEM. It needs to be conducted in the 'BDSA' sheet, as they require the values of the two variables to be varied simultaneously.

The following steps will need to be followed:

- In cell E36, set the variable as cure_assumption_dfs_p_1;

- In cell E37, set the variable as cure_assumption_dfs_p_2;

- In cells E49 to N49, set the values of cure_assumption_dfs_p_1

- In cells D50 to D59, set the values of cure_assumption_dfs_p_2

This process will need to be repeated for cure_assumption_dfs_p_1_ct and cure_assumption_dfs_p_2_ct

f) The PAS price version of the CEM includes links to an external document.

The Company has identified one external link in the “life tables” sheet, this has now been removed. The Company has not identified any further links to external documents or references.

B52. The EAG notes that a half-cycle correction was not implemented in the CEM; the justification given by the Company is that the addition of half-cycle corrections would ‘significantly increase the size of the model’, and would ‘have a minimal impact to the results’ (Table 28, Document B, CS). The EAG does not consider that this is sufficient

justification for excluding a half-cycle correction. Therefore, please add the option to include a half-cycle correction as a scenario.

As discussed with the EAG, half cycle adjustments have been updated in the Markov trace only.

B53. The EAG notes that the PSA does not account for correlation between parameters in the regression models used to derive health state utility values. Please clarify why this was not implemented, and explain any measures that have been taken to avoid inconsistencies in sampled values.

The values in cells F14:F17 of the 'Utility' inputs sheet are estimated utilities calculated with the parameters from a mixed-effects model, which are used by inputs u_ale_tx, u_ale_otx, u_cht_tx and u_ch_otx. As the values in these cells are not the actual parameters from the statistical model, the CEM varies these values when the PSA is performed based on a pre-specified distribution. This approach has been used in past HTA appraisals and accepted by NICE (8-11).

The values in cells F25:F29 of the 'Utility' inputs sheet are parameters from a statistical model (see Chouaid *et al.* (2013)), which are used by inputs u_other_int, u_other_stgIV, u_other_1lpd, u_other_2lpf and u_other_2lpd. It should be clarified that the CEM only uses inputs u_other_int and u_other_stgIV to inform the health state utility values of patients after non-metastatic and metastatic recurrence. The CEM does not account for correlation between the parameters from this statistical model when the PSA is performed as Chouaid *et al.* (2013) do not provide data on the covariance structure.

This could potentially lead to the CEM using inconsistent values when the PSA is performed for inputs u_other_int and u_other_stgIV (i.e. the u_other_stgIV input could be positive which would not be clinically plausible). However, one can see that this does not appear to be a problem after reviewing the samples values of these inputs in the 'Simulation' sheet (i.e. all u_other_stgIV values are less than 0).

Section C: Textual clarification and additional points

C1. Please could the following documents be provided:

a) Excel spreadsheet noting individual clinicians' responses noted in the 'Adjuvant Alectinib Advisory Board Report';

b) Pre-read documents provided to clinicians in advance of the advisory board.

Please find these provided as separate documents.

C2. Please provide a RIS file(s) to enable the references used in the Company Submission and appendices to be imported into a reference library.

A RIS file was provided in the original Company Submission package (as a zip file alongside the reference pack). Please find this attached again as a separate .text file.

C3. Please provide the following references as full PDFs, as currently only an abstract has been provided:

a) Brookmeyer R, Crowley J. A Confidence Interval for the Median Survival Time. Biometrics. 1982;38(1):29-41

b) Solomon BJ, Bauer TM, Mok TSK, 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. The Lancet Respiratory medicine. 2023;11(4):354-66.

c) UyBico SJ, Wu CC, Suh RD, Le NH, Brown K, Krishnam MS. Lung cancer staging essentials: the new TNM staging system and potential imaging pitfalls. Radiographics : a review publication of the Radiological Society of North America, Inc. 2010;30(5):1163-81.

Please find these references as full PDFs provided as separate documents.

Additional question received on 11th June 2024:

Please provide the SLR report associated with the review of the clinical literature described in Appendix D of the submission. The EAG notes that the

"ID6368 alectinib SLR report (v2)" document already provided does not appear to be the same SLR as used for this appraisal given the PICO characteristics differ to those outlined in Appendix D. Please ensure this includes details on methods of the SLR such as data extraction.

The PICO table outlined in Appendix D was taken from the SLR protocol. However, upon review, the Company notes that the PICO table in the main SLR report is considered more definitive. Please disregard the previous PICO table and refer to the one in the main SLR report, as shown in Table 53 below. All other information in the Appendix D was sourced from the main SLR.

Table 53: Inclusion and exclusion criteria for the clinical SLR

Criteria	Inclusion criteria	Exclusion criteria	Rationale
Population	Adults with resectable or locally- advanced early-stage NSCLC (stage I-IIIB) with any mutation type (PD-L1; EGFR; Wild-type etc.)	• Unresectable early-Stage NSCLC (stage I-IIIB) • Metastatic NSCLC or cancer other than NSCLC • Paediatric patients • Healthy volunteers	Includes population eligible for the IMpower010 and ALINA trial
Intervention	Chemotherapy regimens in the adjuvant setting that are considered standard of care (as recommended by key clinical guidelines) and/or routinely used in clinical practice, including a combination of: • Carboplatin • Cisplatin • Docetaxel • Etoposide	• Definitive concurrent chemoradiation with or without consolidation therapy • Concurrent chemoradiation • Post-operative radiotherapy alone • Failed treatments (e.g., study terminated)	• Represents current standard of care and/or routinely used and therefore applicable comparators for reimbursement • Considers those in development to prepare for potential

Criteria	Inclusion criteria	Exclusion criteria	Rationale
	• Gemcitabine • Paclitaxel • Pemetrexed • Vinorelbine Radiotherapy delivered sequentially in the adjuvant setting (as recommended by key clinical guidelines) and/or routinely used in clinical practice including a combination of: • Carboplatin • Cisplatin • Etoposide • Pemetrexed • Paclitaxel • Gemcitabine • Vinorelbine Newer agents under investigation delivered as monotherapy and/or in combination with chemotherapy (for example): • Atezolizumab • Nivolumab • Pembrolizumab		marketing authorisation

Criteria	Inclusion criteria	Exclusion criteria	Rationale
	• Alectinib		
Comparators	• Head-to-head comparisons (any that meet the criteria list above) • Best supportive care (i.e., Observation only/Placebo)	• Dose-comparison/administration studies without a Placebo/best supportive care arm • Neoadjuvant vs adjuvant setting without a Placebo/best supportive care arm	• Interested in direct (or indirect via NMA) comparisons with atezolizumab and alectinib. • Not aimed to evaluate best dosage for comparator projects or preferred setting
Outcomes	• Disease-free survival • Overall survival • Patient-reported outcomes • Treatment discontinuation due to AEs • Total AEs • Total serious AEs • Specific AEs (up to 4)	Any other outcome	Includes outcomes included in the IMpower010 and ALINA trial
Study design	RCTs (Phase IB/II–IV) (parallel and cross-over)	• Single-arm trials • RCTs with no release of results (i.e., protocols)	Most robust evidence to determine efficacy and safety

Criteria	Inclusion criteria	Exclusion criteria	Rationale
		• Non-RCTs • Observational studies (prospective/retrospective cohort studies, cross-sectional studies) • Case reports and case series	

AE–adverse event; EGFR–epidermal growth factor receptor; NMA–network meta-analysis; NSCLC–non-small cell lung cancer; PD-L1–programmed cell death ligand 1; RCT–randomised controlled trial.

Appendix

Table 54: List of key results excluded from the SLR search (n=93)

Source	Decision	Exclusion code	Title (Trial name)	Journal	Year	Volume	Issue	St. page	End pg	DOI
Structured searches	Exclude	Disease	Efficacy of (18)F-fluorodeoxyglucose positron emission tomography/computed tomography as a predictor of response in locally advanced non-small-cell carcinoma of the lung	Nuclear Medicine Communications	2016	37	2	129	138	http://dx.doi.org/10.1097/MNM.0000000000000422
Structured searches	Exclude	Disease	Accelerated hypofractionated radiotherapy with concomitant chemotherapy in locally advanced squamous cell carcinoma of lung: Evaluation of response, survival, toxicity and quality of life from a Phase II randomized study	British Journal of Radiology	2016	89	1062			http://dx.doi.org/10.1259/bjr.20150966
Structured searches	Exclude	Disease	Final results of the randomized phase III CHARTWEL-trial (ARO 97-1) comparing hyperfractionated-accelerated versus conventionally fractionated radiotherapy in non-small cell lung cancer (NSCLC)	Radiotherapy and Oncology	2011	100	1	76	85	http://dx.doi.org/10.1016/j.radonc.2011.06.031
Structured searches	Exclude	Disease	A Dose-finding Study Followed by a Phase II Randomized, Placebo-controlled Trial of Chemoradiotherapy With or Without Veliparib in Stage III Non–small-cell Lung Cancer: SWOG 1206 (8811)	Clinical Lung Cancer	2021	22	4	313	323.e1	http://dx.doi.org/10.1016/j.cllc.2021.02.009

Source	Decision	Exclusion code	Title (Trial name)	Journal	Year	Volume	Issue	St. page	End pg	DOI
Structured searches	Exclude	Disease	Randomized Phase III Study of Irinotecan Plu Cisplatin Versus Etoposide plus Cisplatin for Completely Resected High-Grade Neuroendocrine Carcinoma of the Lung: JCOG1205/1206	Journal of Clinical Oncology	2020	38	36	4292	4301	http://dx.doi.org/10.1200/JCO.20.01806
Structured searches	Exclude	Disease	Non-small cell lung cancer recurrence following surgery and perioperative chemotherapy: comparison of two chemotherapy regimens (IFCT-0702: a randomized phase 3 final results study)	Lung cancer (Amsterdam, Netherlands)	2015	2	89	139	145	
Structured searches	Exclude	Disease	Randomized Phase II Trial Comparing Bevacizumab Plus Carboplatin and Paclitaxel with Carboplatin and Paclitaxel Alone in Previously Untreated Locally Advanced or Metastatic Non-Small-Cell Lung Cancer	Journal of Clinical Oncology	2023	41	13	2305	2312	http://dx.doi.org/10.1200/JCO.22.02543
Structured searches	Exclude	Intervention	Effectiveness of intensive clinical and radiological follow-up in patients with surgically resected NSCLC. Analysis of 2661 patients from the prospective MAGRIT trial	European journal of cancer (Oxford, England : 1990)	2020		125	94	103	
Structured searches	Exclude	Outcome	Impact of preoperative chemotherapy on pulmonary function tests in resectable early-stage non-small cell lung cancer	Chest	2009	135	6	1588	1595	http://dx.doi.org/10.1378/chest.08-1430
Structured	Exclude	Outcome	Immunohistochemical validation study of 15-gene biomarker panel predictive of benefit from adjuvant chemotherapy	ESMO Open	2020	5	2			http://dx.doi.org/10.1136/e

Source	Decision	Exclusion code	Title (Trial name)	Journal	Year	Volume	Issue	St. page	End pg	DOI
searches			in resected non-small-cell lung cancer: Analysis of JBR.10							smoopen-2020-000679
Structured searches	Exclude	Review/Pub type	Preoperative chemotherapy is effective for stage III resectable non-small-cell lung cancer: Metaanalysis of 16 trials	Clinical Lung Cancer	2013	14	5	488	494	http://dx.doi.org/10.1016/j.cllc.2013.03.006
Structured searches	Exclude	Review/Pub type	Meta-analysis of adjuvant chemotherapy versus surgery alone in T2aN0 stage IB non-small cell lung cancer	Journal of Cancer Research and Therapeutics	2018	14	1	139	144	http://dx.doi.org/10.4103/jcrt.JCRT_862_17
Structured searches	Exclude	Review/Pub type	Benefit of adjuvant chemotherapy for patients with stage IB non-small cell lung cancer: A systematic review and meta-analysis	Annals of Translational Medicine	2021	9	18			http://dx.doi.org/10.21037/atm-21-4001
Structured searches	Exclude	Review/Pub type	Effectiveness of neoadjuvant chemotherapy on the survival outcomes of patients with resectable non-small-cell lung cancer: A meta-analysis of randomized controlled trials	Surgical Oncology	2021	38				http://dx.doi.org/10.1016/j.suronc.2021.101590
Structured searches	Exclude	Review/Pub type	Neoadjuvant Immune Checkpoint Inhibitors in Non-small Cell Lung Cancer	Journal of the College of Physicians and Surgeons Pakistan	2022	32	6	779	788	http://dx.doi.org/10.29271/jcpsp.2022.06.779

Source	Decision	Exclusion code	Title (Trial name)	Journal	Year	Volume	Issue	St. page	End pg	DOI
Structured searches	Exclude	Review/Pub type	Bayesian network meta-analysis of efficacy and safety of neoadjuvant therapy for non-small-cell lung cancer	Therapeutic Advances in Medical Oncology	2020	12				http://dx.doi.org/10.1177/17588359209735667
Structured searches	Exclude	Review/Pub type	Adjuvant cisplatin and vinorelbine for completely resected non-small cell lung cancer: Subgroup analysis of the lung adjuvant cisplatin evaluation	Journal of Thoracic Oncology	2010	5	2	220	228	http://dx.doi.org/10.1097/JTO.0b013e3181c814e7
Structured searches	Exclude	Review/Pub type	Efficacy and safety of adjuvant EGFR-TKIs for resected non-small cell lung cancer: a systematic review and meta-analysis based on randomized control trials	BMC Cancer	2022	22	1			http://dx.doi.org/10.1186/s12885-022-09444-0
Structured searches	Exclude	Review/Pub type	The role of EGFR-TKIs as adjuvant therapy in EGFR mutation-positive early-stage NSCLC: A meta-analysis	Thoracic Cancer	2021	12	7	1084	1095	http://dx.doi.org/10.1111/1759-7714.13874
Structured searches	Exclude	Review/Pub type	Induction chemoradiation is not superior to induction chemotherapy alone in stage IIIA lung cancer	Shah A.A., Berry M.F., Tzao C., Gandhi M., Worni M., Pietrobon R.,	2012	93	6	1807	1812	http://dx.doi.org/10.1016/j.athoracsur.2012.03.018

Source	Decision	Exclusion code	Title (Trial name)	Journal	Year	Volume	Issue	St. page	End pg	DOI
				D'Amico T.A.						
Structured searches	Exclude	Review/Pub type	Prognostic and predictive effect of TP53 mutations in patients with non-small cell lung cancer from adjuvant cisplatin-based therapy randomized trials: A LACE-bio pooled analysis	Journal of Thoracic Oncology	2016	11	6	850	861	http://dx.doi.org/10.1016/j.jtho.2016.02.002
Structured searches	Exclude	Review/Pub type	Investigation of the optimal platinum-based regimen in the postoperative adjuvant chemotherapy setting for early-stage resected non-small lung cancer: a Bayesian network meta-analysis	BMJ Open	2022	12	6			http://dx.doi.org/10.1136/bmjopen-2021-057098
Structured searches	Exclude	Review/Pub type	EGFR inhibitors as adjuvant therapy for resected non-small cell lung cancer harboring EGFR mutations	Lung Cancer	2019	136		6	14	http://dx.doi.org/10.1016/j.lungcan.2019.08.001
Structured searches	Exclude	Review/Pub type	A meta-analysis of adjuvant EGFR-TKIs for patients with resected non-small cell lung cancer	Lung Cancer	2019	137		7	13	http://dx.doi.org/10.1016/j.lungcan.2019.08.002
Structured searches	Exclude	Review/Pub type	Adjuvant EGFR-TKIs for Patients With Resected EGFR-Mutant Non-Small Cell Lung Cancer: A Meta-Analysis of 1,283 Patients	Chen R.-L., Sun L.-L., Cao Y., Chen H.-R., Zhou J.-X., Gu C.-Y.,	2021	11				http://dx.doi.org/10.3389/fonc.2021.629394

Source	Decision	Exclusion code	Title (Trial name)	Journal	Year	Volume	Issue	St. page	End pg	DOI
				Zhang Y., Wang S.-Y., Hou W., Lin L.-Z.						
Structured searches	Exclude	Review/Pub type	EGFR-TKI-based vs non-EGFR-TKI-based adjuvant therapy in resected non-small-cell lung cancer with EGFR mutations: A meta-analysis of randomized controlled trials	OncoTargets and Therapy	2018	11		6803	6810	http://dx.doi.org/10.2147/OTT.S174593
Structured searches	Exclude	Review/Pub type	Efficacy of Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors in the Adjuvant Setting for Patients with Resected Epidermal Growth Factor Receptor Mutant Non-Small Cell Lung Cancer: A Meta-Analysis with 11 Trials	Oncology Research and Treatment	2021	44	6	244	252	http://dx.doi.org/10.1159/000515230
Structured searches	Exclude	Review/Pub type	The Optimal Treatment for Stage IIIA-N2 Non-Small Cell Lung Cancer: A Network Meta-Analysis	Annals of Thoracic Surgery	2019	107	6	1866	1875	http://dx.doi.org/10.1016/j.athoracsur.2018.11.024
Structured searches	Exclude	Review/Pub type	The effect of postoperative radiotherapy on the survival of patients with resectable stage III-N2 non-small-cell lung cancer: A systematic review and meta-analysis	Neoplasma	2019	66	5	717	726	http://dx.doi.org/10.4149/neo_2018_181213N965
Structured searches	Exclude	Review/Pub type	Immunotherapy (excluding checkpoint inhibitors) for stage I to III non-small cell lung cancer treated with surgery or radiotherapy with curative intent	Cochrane Database of	2021	2021	12			http://dx.doi.org/10.1002/14651858

Source	Decision	Exclusion code	Title (Trial name)	Journal	Year	Volume	Issue	St. page	End pg	DOI
				Systematic Reviews						.CD011300.pub3
Structured searches	Exclude	Review/Pub type	Neoadjuvant Immunotherapy Improves Treatment for Early Resectable Non-Small-Cell Lung Cancer: A Systematic Review and Meta-analysis	Journal of Oncology	2022	2022				http://dx.doi.org/10.1155/2022/2085267
Structured searches	Exclude	Review/Pub type	Safety and Efficacy of Neoadjuvant Immune Checkpoint Inhibitor Therapy in Patients with Resectable Non-small-Cell Lung Cancer: A Systematic Review	Targeted Oncology	2021	16	4	425	434	http://dx.doi.org/10.1007/s11523-021-00818-1
Structured searches	Exclude	Review/Pub type	PD-L1 expression and Tumor mutation burden as Pathological response biomarkers of Neoadjuvant immunotherapy for Early-stage Non-small cell lung cancer: A systematic review and meta-analysis	Critical Reviews in Oncology/ Hematology	2022	170				http://dx.doi.org/10.1016/j.critrevonc.2022.103582
Structured searches	Exclude	Review/Pub type	Neoadjuvant EGFR-TKI Therapy for EGFR-Mutant NSCLC: A Systematic Review and Pooled Analysis of Five Prospective Clinical Trials	Frontiers in Oncology	2020	10				http://dx.doi.org/10.3389/fonc.2020.586596
Structured searches	Exclude	Review/Pub type	IMpower030: Phase III study evaluating neoadjuvant treatment of resectable stage II-IIIB non-small cell lung cancer (NSCLC) with atezolizumab (atezo) + chemotherapy	Annals of Oncology	2019	30		ii30		http://dx.doi.org/10.1093/annonc/mdz064.014

Source	Decision	Exclusion code	Title (Trial name)	Journal	Year	Volume	Issue	St. page	End pg	DOI
Structured searches	Exclude	Review/Pub type	A meta-analysis of adjuvant EGFR-TKIs for patients with EGFR mutation of resected non-small cell lung cancer	Medicine (United States)	2022	101	47	E31894		http://dx.doi.org/10.1097/MD.0000000000031894
Structured searches	Exclude	Review/Pub type	Neoadjuvant immunotherapy for advanced, resectable non–small cell lung cancer: A systematic review and meta-analysis	Cancer	2023	129	13	1969	1985	http://dx.doi.org/10.1002/cncr.34755
Structured searches	Exclude	Review/Pub type	Rational application of EGFR-TKI adjuvant therapy in patients with completely resected stage IB-IIIA EGFR-mutant NSCLC: a systematic review and meta-analysis of 11 randomized controlled trials	BMC Cancer	2023	23	1			http://dx.doi.org/10.1186/s12885-023-11194-6
Structured searches	Exclude	Review/Pub type	Efficacy and safety of adjuvant EGFR TKI alone and in combination with chemotherapy for resected EGFR mutation-positive non-small cell lung cancer: A Bayesian network meta-analysis	Critical Reviews in Oncology/ Hematology	2023	186				http://dx.doi.org/10.1016/j.critrevonc.2023.104010
Structured searches	Exclude	Study design	Prospective analysis of quality of life in elderly patients treated with adjuvant chemotherapy for non-small-cell lung cancer	Annals of Oncology	2013	24	6	1630	1639	http://dx.doi.org/10.1093/annonc/mds649
Structured searches	Exclude	Neoadjuvant	Neoadjuvant chemotherapy in locally advanced non-small cell lung cancer	The gulf journal of oncology	2007		2	55	64	

Source	Decision	Exclusion code	Title (Trial name)	Journal	Year	Volume	Issue	St. page	End pg	DOI
Structured searches	Exclude	Neoadjuvant	Combined modality treatment for locally advanced non-small cell lung cancer: Preoperative chemoradiation does not result in a poorer quality of life	Lung Cancer	2004	44	1	89	97	http://dx.doi.org/10.1016/j.lungcan.2003.10.004
Structured searches	Exclude	Neoadjuvant	Prophylactic Cranial Irradiation in Operable Stage IIIA Non-Small-Cell Lung Cancer Treated with Neoadjuvant Chemoradiotherapy: Results from a German Multicenter Randomized Trial	Journal of Clinical Oncology	2007	25	31	4987	4992	http://dx.doi.org/10.1200/JCO.2007.12.5468
Structured searches	Exclude	Neoadjuvant	Induction chemoradiation in stage IIIA/N2 non-small-cell lung cancer: A phase 3 randomised trial	The Lancet	2015	386	9998	1049	1056	http://dx.doi.org/10.1016/S0140-6736(15)60294-X
Structured searches	Exclude	Neoadjuvant	Safety and effectiveness of localized lung resection combined with neoadjuvant chemotherapy in the treatment of stage I-II non-small cell lung cancer	Oncology Letters	2017	13	4	2344	2348	http://dx.doi.org/10.3892/ol.2017.5675
Structured searches	Exclude	Neoadjuvant	Is neoadjuvant chemoradiotherapy a feasible strategy for stage IIIA-N2 non-small cell lung cancer? Mature results of the randomized IFCT-0101 phase II trial (IFCT-0101)	Lung Cancer	2010	69	1	86	93	http://dx.doi.org/10.1016/j.lungcan.2009.10.003
Structured searches	Exclude	Neoadjuvant	Phase III study of surgery versus definitive concurrent chemoradiotherapy boost in patients with resectable stage IIIA(N2) and	Eberhardt W.E.E., Pöttgen C., Gauler	2015	33	35	4194	4201	http://dx.doi.org/10.1200/J

Source	Decision	Exclusion code	Title (Trial name)	Journal	Year	Volume	Issue	St. page	End pg	DOI
			selected IIIB non-small-cell lung cancer after induction chemotherapy and concurrent chemoradiotherapy (ESPATUE)	T.C., Friedel G., Veit S., Heinrich V., Welter S., Budach W., Spengler W., Kimmich M., Fischer B., Schmidberger H., De Ruysscher D., Belka C., Cordes S., Hepp R., Lütke-Brintrup D., Lehmann N., Schuler M., Jöckel K.-H., Stamatis G., Stuschke M.						CO.2015.62.6812

Source	Decision	Exclusion code	Title (Trial name)	Journal	Year	Volume	Issue	St. page	End pg	DOI
Structured searches	Exclude	Neoadjuvant	Heart dose exposure as prognostic marker after radiotherapy for resectable stage IIIA/B non-small-cell lung cancer: secondary analysis of a randomized trial (ESPATUE)	Guberina M., Eberhardt W., Stuschke M., Gauler T., Heinzelmann F., Cheufou D., Kimmich M., Friedel G., Schmidberger H., Darwiche K., Jendrossek V., Schuler M., Stamatis G., Pöttgen C.	2017	28	5	1084	1089	http://dx.doi.org/10.1093/annonc/mdx069
Structured searches	Exclude	Neoadjuvant	Standardized uptake decrease on [18 f]-fluorodeoxyglucose positron emission tomography after neoadjuvant chemotherapy is a prognostic classifier for long-term outcome after multimodality treatment: Secondary analysis of a randomized trial for	Journal of Clinical Oncology	2016	34	21	2526	2533	http://dx.doi.org/10.1200/JCO.2015.65.5167

Source	Decision	Exclusion code	Title (Trial name)	Journal	Year	Volume	Issue	St. page	End pg	DOI
			resectable stage iiia/b non-small-cell lung cancer (ESPATUE)							
Structured searches	Exclude	Neoadjuvant	Randomized controlled trial of neoadjuvant chemotherapy with cisplatin and vinorelbine in patients with stage IIIA non-small cell lung cancer in China	Asia-Pacific Journal of Clinical Oncology	2009	5	2	87	94	http://dx.doi.org/10.1111/j.1743-7563.2009.01196.x
Structured searches	Exclude	Neoadjuvant	Effect of preoperative chemoradiation in addition to preoperative chemotherapy: a randomised trial in stage III non-small-cell lung cancer	The Lancet Oncology	2008	9	7	636	648	http://dx.doi.org/10.1016/S1470-2045(08)70156-6
Structured searches	Exclude	Neoadjuvant	Combining antiangiogenic therapy with neoadjuvant chemotherapy increases treatment efficacy in stage IIIA (N2) non-small cell lung cancer without increasing adverse effects	Oncotarget	2016	7	38	62619	62626	http://dx.doi.org/10.18632/oncotarget.11547
Structured searches	Exclude	Neoadjuvant	Neoadjuvant chemotherapy with gemcitabine-containing regimens in patients with early-stage non-small cell lung cancer (GINEST)	Journal of thoracic oncology	2008	1	3	37	45	
Structured searches	Exclude	Neoadjuvant	Assessing quality of life following neoadjuvant therapy for early stage non-small cell lung cancer (NSCLC): Results from a prospective analysis using the Lung Cancer Symptom Scale (LCSS) (GINEST)	Supportive Care in Cancer	2009	17	3	307	313	http://dx.doi.org/10.1007/s00520-008-0489-y
Structured	Exclude	Neoadjuvant	Neoadjuvant nivolumab or nivolumab plus ipilimumab in operable non-small	Cascone T., William	2021	27	3	504	514	http://dx.doi.org/1

Source	Decision	Exclusion code	Title (Trial name)	Journal	Year	Volume	Issue	St. page	End pg	DOI
searches			cell lung cancer: the phase 2 randomized NEOSTAR trial (NEOSTAR)	W.N., Weissferdt A., Leung C.H., Lin H.Y., Pataer A., Godoy M.C.B., Carter B.W., Federico L., Reuben A., Khan M.A.W., Dejima H., Francisco-Cruz A., Parra E.R., Solis L.M., Fujimoto J., Tran H.T., Kalhor N., Fossella F.V., Mott F.E., Tsao A.S., Blumenschein G., Le X.,						0.1038/s41591-020-01224-2

Source	Decision	Exclusion code	Title (Trial name)	Journal	Year	Volume	Issue	St. page	End pg	DOI
				Zhang J., Skoulidis F., Kurie J.M., Altan M., Lu C., Glisson B.S., Byers L.A., Elamin Y.Y., Mehran R.J., Rice D.C., Walsh G.L., Hofstetter W.L., Roth J.A., Antonoff M.B., Kadara H., Haymaker C., Bernatchez C., Ajami N.J., Jenq R.R., Sharma P., Allison J.P.,						

Source	Decision	Exclusion code	Title (Trial name)	Journal	Year	Volume	Issue	St. page	End pg	DOI
				Futreal A., Wargo J.A., Wistuba I.I., Swisher S.G., Lee J.J., Gibbons D.L., Vaporciyan A.A., Heymach J.V., Sepesi B.						
Structured searches	Exclude	Neoadjuvant	Surgical outcomes after neoadjuvant nivolumab or nivolumab with ipilimumab in patients with non–small cell lung cancer (NEOSTAR)	Sepesi B., Zhou N., William W.N., Lin H.Y., Leung C.H., Weissferdt A., Mitchell K.G., Pataer A., Walsh G.L., Rice D.C., Roth J.A., Mehran	2022	164	5	1327	1337	http://dx.doi.org/10.1016/j.jtcvs.2022.01.019

Source	Decision	Exclusion code	Title (Trial name)	Journal	Year	Volume	Issue	St. page	End pg	DOI
				R.J., Hofstetter W.L., Antonoff M.B., Rajaram R., Negrao M.V., Tsao A.S., Gibbons D.L., Lee J.J., Heymach J.V., Vaporciyan A.A., Swisher S.G., Cascone T.						
Conference searches	Exclude	Neoadjuvant	Impact of genomic aberrations and additional therapies on survival outcomes of patients with operable non-small cell lung cancer (NSCLC) from the NEOSTAR study (NEOSTAR)	Journal of Clinical Oncology	2021	39	15 SUPPL			http://dx.doi.org/10.1200/JCO.2021.39.15-suppl.8542
Structured searches	Exclude	Neoadjuvant	A randomised phase II trial of preoperative chemotherapy of cisplatin-docetaxel or docetaxel alone for clinical stage IB/II non-small-cell lung cancer:	British Journal of Cancer	2008	99	6	852	857	http://dx.doi.org/10.1038/sj

Source	Decision	Exclusion code	Title (Trial name)	Journal	Year	Volume	Issue	St. page	End pg	DOI
			Results of a Japan Clinical Oncology Group trial (JCOG 0204)							.bjc.6604613
Structured searches	Exclude	Neoadjuvant	Preoperative chemotherapy in patients with resectable non-small cell lung cancer: results of the MRC LU22/NVALT 2/EORTC 08012 multicentre randomised trial and update of systematic review (MRC LU22/NVALT 2/EORTC 08012)	Lancet	2007	369	9577	1929	1937	http://dx.doi.org/10.1016/S0140-6736(07)60714-4
Structured searches	Exclude	Neoadjuvant	Final results and pharmacoeconomic analysis of a trial comparing two neoadjuvant chemotherapy (CT) regimens followed by surgery in patients with resectable non-small cell lung cancer (NSCLC): A phase II randomised study by the European Lung Cancer Working Party	Lung Cancer	2012	77	3	605	610	http://dx.doi.org/10.1016/j.lungcan.2012.04.020
Structured searches	Exclude	Neoadjuvant	Randomized phase III study of surgery alone or surgery plus preoperative cisplatin and gemcitabine in stages IB to IIIA non-small-cell lung cancer (CHEST)	Journal of Clinical Oncology	2012	30	2	172	178	http://dx.doi.org/10.1200/JCO.2010.33.7089
Structured searches	Exclude	Neoadjuvant	Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer (CheckMate 816)	New England Journal of Medicine	2022	386	21	1973	1985	http://dx.doi.org/10.1056/NEJMoa2202170
Conference searches	Exclude	Neoadjuvant	Nivolumab (NIVO) + platinum-doublet chemotherapy (chemo) vs chemo as neoadjuvant treatment (tx) for resectable (IB-IIIA) non-small cell lung	Cancer Research	2021	81	13 SUPPL			http://dx.doi.org/10.1158/1538-7445.AM

Source	Decision	Exclusion code	Title (Trial name)	Journal	Year	Volume	Issue	St. page	End pg	DOI
			cancer (NSCLC) in the phase 3 CheckMate 816 trial (CheckMate 816)							2021-CT003
Conference searches	Exclude	Neoadjuvant	Surgical outcomes from the phase 3 CheckMate 816 trial: nivolumab (NIVO) + platinum-doublet chemotherapy (chemo) vs chemo alone as neoadjuvant treatment for patients with resectable nonsmall cell lung cancer (NSCLC) (CheckMate 816)	Journal of clinical oncology	2021	39				
Conference searches	Exclude	Neoadjuvant	Neoadjuvant nivolumab (NIVO) + platinum-doublet chemotherapy (chemo) versus chemo for resectable (IB–IIIA) non-small cell lung cancer (NSCLC): Association of pathological regression with event-free survival (EFS) in CheckMate 816 (CheckMate 816)	Journal of Clinical Oncology	2022	40	17 Suppl			http://dx.doi.org/10.1200/JCO.2022.40.17_suppl.LBA8511
Conference searches	Exclude	Neoadjuvant	932MO Nivolumab (NIVO) plus platinum-doublet chemotherapy (chemo) versus chemo as neoadjuvant treatment for resectable non-small cell lung cancer (NSCLC): Health-related quality of life (HRQoL) outcomes from CheckMate 816 (CheckMate 816)	Annals of Oncology	2022	33	Suppl 7	S973		https://dx.doi.org/10.1016/j.annonc.2022.07.1058
Conference searches	Exclude	Neoadjuvant	Clinical outcomes with neoadjuvant nivolumab (N) + chemotherapy (C) vs C by definitive surgery in patients (pts) with resectable NSCLC: 3-y results from the phase 3 CheckMate 816 trial (CheckMate 816)	Journal of Clinical Oncology	2023	41	16			https://ascopubs.org/doi/10.1200/JCO.2023.41.16_suppl.8521

Source	Decision	Exclusion code	Title (Trial name)	Journal	Year	Volume	Issue	St. page	End pg	DOI
Conference searches	Exclude	Neoadjuvant	84O Neoadjuvant nivolumab (N) + platinum-doublet chemotherapy (C) for resectable NSCLC: 3-y update from CheckMate 816 (CheckMate 816)	Journal of Thoracic Oncology	2023	18	4S	S89	S100	https://www.jto.org/action/showPdf?pii=S1556-0864%2823%2900338-6
Structured searches	Exclude	Neoadjuvant	A phase 3 study of induction treatment with concurrent chemoradiotherapy versus chemotherapy before surgery in patients with pathologically confirmed N2 stage IIIA nonsmall cell lung cancer (WJTOG9903)	Cancer	2012	118	24	6126	6135	http://dx.doi.org/10.1002/cncr.26689
Structured searches	Exclude	Neoadjuvant	Surgery with or without preoperative paclitaxel and carboplatin in early-stage non - small-cell lung cancer: Southwest oncology group trial S9900, an intergroup, randomized, phase III trial (S9900)	Journal of Clinical Oncology	2010	28	11	1843	1849	http://dx.doi.org/10.1200/JCO.2009.26.1685
Structured searches	Exclude	Neoadjuvant	Randomized phase II trial of pemetrexed-cisplatin plus bevacizumab or thoracic radiotherapy followed by surgery for stage IIIA (N2) nonsquamous non–small cell lung cancer (PIT-1)	Journal of Thoracic and Cardiovascular Surgery	2022	164	3	661	671.e4	http://dx.doi.org/10.1016/j.jtcvs.2021.11.079
Conference searches	Exclude	Neoadjuvant	PIT-1: Randomized phase II trail of pemetrexed-cisplatin plus bevacizumab or concurrent thoracic radiation therapy followed by surgery in stage IIIA (N2)	Journal of Clinical Oncology	2020	38	15			http://dx.doi.org/10.1200/JCO.2020.38.15-

Source	Decision	Exclusion code	Title (Trial name)	Journal	Year	Volume	Issue	St. page	End pg	DOI
			nonsquamous non-small cell lung cancer (PIT-1)							suppl.9014
Conference searches	Exclude	Neoadjuvant	Two cycles versus three cycles of neoadjuvant sintilimab plus platinum-doublet chemotherapy in patients with resectable non-small-cell lung cancer (neoSCORE): A randomized, single center, two-arm phase II trial (neoSCORE)	Journal of Clinical Oncology	2022	40	16			http://dx.doi.org/10.1200/JCO.2022.40.16_suppl.8500
Conference searches	Exclude	Neoadjuvant	LBA37 A randomized, multicentric phase II study of preoperative nivolumab plus relatlimab or nivolumab in patients with resectable non-small cell lung cancer (NEOpredict-Lung)	Annals of Oncology	2022	33		S1404		http://dx.doi.org/10.1016/j.annonc.2022.08.034
Structured searches	Exclude	Neoadjuvant	Erlotinib versus gemcitabine plus cisplatin as neoadjuvant treatment of stage IIIA-N2 EGFR-mutant non-small-cell lung cancer: final overall survival analysis of the EMERGING-CTONG 1103 randomised phase II trial (CTONG1103)	Signal Transduction and Targeted Therapy	2023	8	1			http://dx.doi.org/10.1038/s41392-022-01286-3
Conference searches	Exclude	Neoadjuvant	CTONG1103: Final overall survival analysis of the randomized phase 2 trial of erlotinib versus gemcitabine plus cisplatin as neoadjuvant treatment of stage IIIA-N2 EGFR-mutant non-small cell lung cancer (CTONG1103)	Journal of Clinical Oncology	2021	39	15 SUPPL			http://dx.doi.org/10.1200/JCO.2021.39.15-suppl.8502
Bibliographic	Exclude	Neoadjuvant	Erlotinib Versus Gemcitabine Plus Cisplatin as Neoadjuvant Treatment of Stage IIIA-N2 EGFR-Mutant Non–		2019	37	25	2235	2245	10.1200/JCO.19.00075

Source	Decision	Exclusion code	Title (Trial name)	Journal	Year	Volume	Issue	St. page	End pg	DOI
searches			Small-Cell Lung Cancer (EMERGING-CTONG 1103): A Randomized Phase II Study (CTONG1103)	Journal of clinical oncology						
Structured searches	Exclude	Neoadjuvant	Surgical resection after neoadjuvant durvalumab and radiation is feasible and safe in non–small cell lung cancer: Results from a randomized trial	Journal of Thoracic and Cardiovascular Surgery	2023	165	1	327	334	http://dx.doi.org/10.1016/j.jtcvs.2022.07.017
Bibliographic searches	Exclude	Neoadjuvant	Neoadjuvant durvalumab with or without stereotactic body radiotherapy in patients with early-stage non-small-cell lung cancer: a single-centre, randomised phase 2 trial	The lancet oncology	2021	22	6	824	835	https://doi.org/10.1016/S1470-2045(21)00149-2
Structured searches	Exclude	Neoadjuvant	Induction chemoradiotherapy (carboplatin-taxane and concurrent 50-Gy radiation) for bulky cN2, N3 non-small cell lung cancer	Journal of thoracic and cardiovascular surgery	2007	5	133	1179	1185	
Structured searches	Exclude	Neoadjuvant	Randomized Phase II Study of Preoperative Chemoradiotherapy +/- Panitumumab Followed by Consolidation Chemotherapy in Potentially Operable Locally Advanced (Stage IIIa, N2+) Non-Small Cell Lung Cancer: NRG Oncology RTOG 0839 (RTOG 0839)	Journal of thoracic oncology	2017		(no pagination)			
Structured	Exclude	Neoadjuvant	Neoadjuvant Camrelizumab Plus Platinum-Based Chemotherapy vs Chemotherapy Alone for Chinese	JAMA oncology	2023					http://dx.doi.org/10.1001/ja

Source	Decision	Exclusion code	Title (Trial name)	Journal	Year	Volume	Issue	St. page	End pg	DOI
searches			Patients With Resectable Stage IIIA or IIIB (T3N2) Non-Small Cell Lung Cancer: The TD-FOREKNOW Randomized Clinical Trial (TD-FOREKNOW)							maoncol.2023.2751
Conference searches	Exclude	Neoadjuvant	A randomized, controlled, multicenter phase II trial of camrelizumab combined with albumin-bound paclitaxel and cisplatin as neoadjuvant treatment in resectable stage IIIA and IIIB(T3N2) non-small-cell lung cancer (TD-FOREKNOW)	Annals of Oncology	2022	16	suppl_1	100102		10.1016/iotech/iotech100102
Conference searches	Exclude	Neoadjuvant	62MO A randomised, controlled, multicenter phase II trial of camrelizumab combined with albumin-bound paclitaxel and cisplatin as neoadjuvant treatment in locally advanced NSCLC (TD-FOREKNOW)	Annals of Oncology	2020	31		S1441	S1442	
Structured searches	Exclude	Neoadjuvant	Clinical analysis of preoperative induction chemotherapy with gemcitabine combined with cisplatin for locally advanced non-small cell lung cancer	Chinese-German Journal of Clinical Oncology	2012	11	5	266	270	http://dx.doi.org/10.1007/s10330-012-0985-x
Structured searches	Exclude	Perioperative	Long-term results of a randomized controlled trial evaluating preoperative chemotherapy in resectable non-small cell lung cancer	OncoTargets and Therapy	2013	6		645	650	http://dx.doi.org/10.2147/OTT.S44503
Structured	Exclude	Perioperative	A randomised trial comparing preoperative to perioperative	European Journal of Cancer	2013	49	12	2654	2664	http://dx.doi.org/10.1016/j.

Source	Decision	Exclusion code	Title (Trial name)	Journal	Year	Volume	Issue	St. page	End pg	DOI
searches			chemotherapy in early-stage non-small-cell lung cancer (IFCT 0002 trial)							ejca.2013.04.013
Structured searches	Exclude	Perioperative	Multi-centre randomized controlled study comparing adjuvant vs neo-adjuvant chemotherapy with docetaxel plus carboplatin in resectable stage IB to IIIA NSCLC: final results of CSLC0501 (CSLC0501)	Annals of Oncology	2016	27		vi407		http://dx.doi.org/10.1093/annonc/mdw381.01
Conference searches	Exclude	Perioperative	84P SHR-1316 vs placebo in combination with chemotherapy as perioperative treatment in patients with resectable stage II-III NSCLC: A randomized, double-blind, multicenter, phase Ib/III trial.	Annals of Oncology	2022	33	Suppl 7	S72		https://dx.doi.org/10.1016/annonc/annonc857
Structured searches	Exclude	Perioperative	Perioperative Pembrolizumab for Early-Stage Non-Small-Cell Lung Cancer (KEYNOTE-671)	The New England journal of medicine	2023	389	6	491	503	http://dx.doi.org/10.1056/NEJMoa2302983
Structured searches	Exclude	Perioperative	Perioperative Nivolumab and Chemotherapy in Stage III Non-Small-Cell Lung Cancer (NADIM II)	New England Journal of Medicine	2023	389	6	504	513	http://dx.doi.org/10.1056/NEJMoa2215530
Conference searches	Exclude	Perioperative	Nivolumab + chemotherapy versus chemotherapy as neoadjuvant treatment for resectable stage IIIA NSCLC: Primary endpoint results of pathological complete response (pCR) from phase II NADIM II trial (NADIM II)	Journal of Clinical Oncology	2022	40	16			http://dx.doi.org/10.1200/JCO.2022.40.16_suppl.8501

References

1. Zhang JJ, Chen H, He K, Tang S, Justice R, Keegan P, et al. Evaluation of Blinded Independent Central Review of Tumor Progression in Oncology Clinical Trials: A Meta-analysis. Therapeutic innovation & regulatory science. 2013;47(2):167-74.
2. Amit O, Mannino F, Stone AM, Bushnell W, Denne J, Helterbrand J, et al. Blinded independent central review of progression in cancer clinical trials: results from a meta-analysis. European journal of cancer (Oxford, England : 1990). 2011;47(12):1772-8.
3. Roche. ALINA Advisory Board - Discussion of the Clinical Data and Health Technology Assessment (HTA) Submission for Adjuvant Alectinib for ALK+ Stage IB–IIIA NSCLC [Data on File]. 2024.
4. Montague D. P39.04 ALK Positive UK: 42% of UK Patients do not Receive Regular Brain MRI Scans Despite Data Showing up to 70% of Patients Develop Brain Metastases. Journal of Thoracic Oncology. 2021;16(3, Supplement):S467.
5. Gomes F, Yip K, Tokaca N, Greystoke A, Escriu C, Conibear J, et al. The ALK project: a real-world national network and database. 2019.
6. Lucas T, Hassan H, Sattar A, So A, Buckley T, Hunter S, et al. 95 Lorlatinib in advanced ALK-rearranged NSCLC – real-world experience in a UK population. Lung cancer (Amsterdam, Netherlands). 2024;190:107656.
7. Carroll R, Bortolini M, Calleja A, Munro R, Kong S, Daumont MJ, et al. Trends in treatment patterns and survival outcomes in advanced non-small cell lung cancer: a Canadian population-based real-world analysis. BMC Cancer. 2022;22(1):255.
8. CADTH. CADTH Reimbursement Review - Atezolizumab (Tecentriq) 2022 [
9. NICE. Single Technology Appraisal - Atezolizumab for adjuvant treatment of resected non-small cell lung cancer [ID3852] - Committee Papers 2022 [

10. NICE. Single Technology Appraisal - Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection [ID3835] - Committee Papers 2021 [
11. INESSS. Tagrisso - Avis transmis au ministre en novembre 2022 2022 [
12. Roche. Primary CSR Clinical Report: Study BO40336 (ALINA): A Phase III, open-label, randomised study to evaluate the efficacy and safety of adjuvant alectinib versus adjuvant platinum-based chemotherapy in patients with completely resected Stage IB to Stage IIIA ALK+ NSCLC [Data on File]. 2023.
13. National Institute for Health and Care Excellence (NICE). Atezolizumab for adjuvant treatment of resected non-small-cell lung cancer [TA823]. 2022.
14. Agolli L, Valeriani M, Carnevale A, Falco T, Bracci S, De Sanctis V, et al. Role of salvage stereotactic body radiation therapy in post-surgical loco-regional recurrence in a selected population of non-small cell lung cancer patients. Anticancer research. 2015;35(3):1783-9.
15. Terada Y, Isaka M, Harada H, Konno H, Kojima H, Mizuno T, et al. Radiotherapy for local recurrence of non-small-cell lung cancer after lobectomy and lymph node dissection-can local recurrence be radically cured by radiation? Japanese journal of clinical oncology. 2020;50(4):425-33.
16. Kim E, Song C, Kim MY, Kim JS. Long-term outcomes after salvage radiotherapy for postoperative locoregionally recurrent non-small-cell lung cancer. Radiation oncology journal. 2017;35(1):55-64.
17. 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 Surgery. Clinical lung cancer. 2017;18(6):e441-e8.
18. Wu AJ, Garay E, Foster A, Hsu M, Zhang Z, Chaft JE, et al. Definitive Radiotherapy for Local Recurrence of NSCLC After Surgery. Clinical lung cancer. 2017;18(3):e161-e8.

19. Janssen-Heijnen ML, van Steenbergen LN, Steyerberg E, Visser O, De Ruysscher DK, Groen HJ. Long-term excess mortality for survivors of non-small cell lung cancer in the Netherlands. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer. 2012;7(3):496-502.
20. Das M, Ogale S, Jovanoski N, Johnson A, Nguyen C, Bhagwakar J, et al. Cost-effectiveness of adjuvant atezolizumab for patients with stage II-IIIA PD-L1+ non-small-cell lung cancer. Immunotherapy. 2023;15(8):573-81.
21. National Institute for Health and Care Excellence (NICE). NICE British National Formulary (BNF) [Accessed on 19/Apr/24]. 2024.
22. Gov.uk. Drugs and pharmaceutical electronic market information tool (eMIT). 2023.
23. The Royal College of Radiologists. Radiotherapy dose fractionation Fourth edition. 2024.
24. National Institute for Health and Care Excellence (NICE). Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy [TA428]. 2017.
25. National Institute for Health and Care Excellence (NICE). Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer [TA531]. 2018.
26. Jones KWH, Birch, S., Castelli, A., Chalkley, M., Dargan, A., Findlay, D., Forder, J., Gao, M., Hinde, S., Markham, S. Premji, S. Teo, H. Unit Costs of Health and Social Care 2023 Manual. 2023.

Please could the company be asked to provide a response to the following as soon as possible:

In the response to question B11, the company provided extrapolation plots and goodness-of-fit statistics for alternative extrapolations for the subsequent treatment survival data, but did not implement these as options in the model. Please could the company provide all fitted parameter values and corresponding covariance matrices, so the EAG can implement this scenario.

The requested statistics for alectinib can be found in the following files:

“eff_stem_IT_ALEC_PFS_INV_ALEX”

“eff_stem_IT_ALEC_OSURPSFT_ALUR”

“eff_stem_IT_CHEM_OSURPSET_ALUR”

The parameter values and corresponding covariance matrices for all other subsequent therapies is provided in the zip folder titled “statistics for subsequent therapies.” The names of the files indicate the type of therapy i.e RT refers to radiotherapy, CRT refers to chemotherapy.

The EAG has been unable to reproduce the results for scenarios presented in the responses to the following clarification questions. Please could the company provide a full step by step description of how each of these scenarios was implemented in the model to reproduce the scenario results provided.

- A13 (scenario with active monitoring as a comparator)

This scenario was implemented by following the steps outlined below:

- The costs for chemotherapy were set to zero, in cells G23-27 and K23-27 in the “direct cost” tabs.
- The adverse events were set to zero in cells G55-I55, G63-I63, G71-I71, G79-I79 in the “results table” tab.

Following these steps produces the results in Table 1, as per Table 8 in CQ response.

Table 1: Scenario analysis with adverse events set to zero for active monitoring (with PAS price for alectinib), as per table 8 in CQ response

	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/LYG)	ICER (£/QALY)
Updated base case	Alectinib	[redacted]	12.40	9.90	-	-	-	-	-
	Platinum-based chemotherapy	[redacted]	8.51	6.60	[redacted]	3.89	3.30	[redacted]	[redacted]
Scenario	Alectinib	[redacted]	12.40	9.90	-	-	-	--	-
	Platinum-based chemotherapy	[redacted]	8.51	6.60	[redacted]	3.89	3.30	[redacted]	[redacted]

- B10 (scenario with independently parametrised DFS extrapolations)

The scenario was implemented by following the steps outlined below:

- The drop down option in cell AC47 was changed to “separated by arms” in the “efficacy” tab.
- The choice of parametric distribution was changed to log-normal for the alectinib arm and exponential for chemotherapy arm.

Following these steps produces the updated results in Table 2.

Table 2: Scenario analysis in which DFS extrapolations for alectinib and chemotherapy are fitted independently using log-normal and exponential distributions (with PAS price for alectinib).

	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/LYG)	ICER (£/QALY)
Updated base case	Alectinib	[redacted]	12.40	9.90	-	-	-	-	-
	Platinum-based chemotherapy	[redacted]	8.51	6.60	[redacted]	3.89	3.30	[redacted]	[redacted]
Scenario	Alectinib	[redacted]	13.41	10.77	-	-	-	--	-
	Platinum-based chemotherapy	[redacted]	8.36	6.47	[redacted]	5.06	4.30	[redacted]	[redacted]

- B12 (scenario using PFS from the ALEX trial rather than the ALINA trial to parametrise transition probabilities for patients treated with alectinib in the non-metastatic recurrence health state)

The scenario was implemented by following the steps outlined below:

- In the “efficacy” tab, the values in cell F180 and G180 were copied and pasted into F144 and G144. The inputs used for this scenario were implemented in the table below.

Table 3: Inputs to inform transition probabilities from the non-metastatic recurrence health state for patients treated with alectinib

Source	Estimate	Variance
ALINA	3.416	0.064
ALEX	3.823	0.012

Following these steps produces the results in Table 4, as per Table 32 in CQ response.

Table 4: Scenario analysis in which the transition probabilities from the non-metastatic recurrence health state for patients treated with alectinib are informed by the ALEX trial (with PAS price for alectinib), as per Table 32 in CQ response

	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/LYG)	ICER (£/QALY)
Updated base case	Alectinib	[redacted]	12.40	9.90	-	-	-	-	-
	Platinum- based chemotherapy	[redacted]	8.51	6.60	[redacted]	3.89	3.30	[redacted]	[redacted]
Scenario	Alectinib	[redacted]	12.43	9.92	-	-	-	--	-
	Platinum- based chemotherapy	[redacted]	8.61	6.67	[redacted]	3.82	3.25	[redacted]	[redacted]

- B49 (scenario including a blood test in every cycle of treatment)

The scenario was implemented by following the steps outlined below:

- In cell N23 and 023 in the “direct costs” tab, “+ F57” was added to the cell.

Following these steps produces the updated results in Table 5.

Table 5: Scenario analysis in which blood tests are required prior to each cycle of treatment as part of routine monitoring (with PAS price for alectinib)

	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/LYG)	ICER (£/QALY)
Updated base case	Alectinib	[redacted]	12.40	9.90	-	-	-	-	-
	Platinum-based chemotherapy	[redacted]	8.51	6.60	[redacted]	3.89	3.30	[redacted]	[redacted]
Scenario	Alectinib	[redacted]	12.40	9.90	-	-	-	--	-
	Platinum-based chemotherapy	[redacted]	8.51	6.60	[redacted]	3.89	3.30	[redacted]	[redacted]

Figure 16 in the clarification question responses does not correspond with the description provided in the text; please could the company provide the correct figure.

The correct figure is presented in Figure 1 below. As stated in the CQ response, this shows the standardised residuals vs fitted values by treatment arm, and the fitted vs observed values by treatment arm.

In the clarification response, Figure 16 summarises the health state utility values for ALINA, a copy of the figure is provided in Figure 2.

Figure 1: The standardised residuals vs fitted values by treatment arm, and the fitted vs observed values by treatment arm

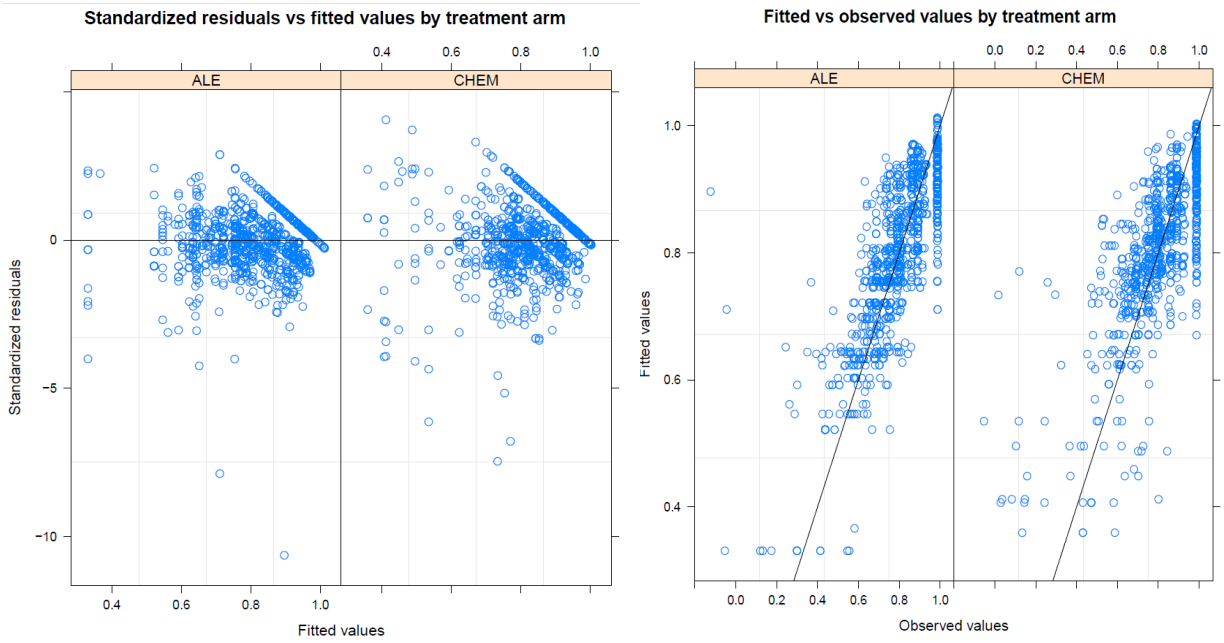
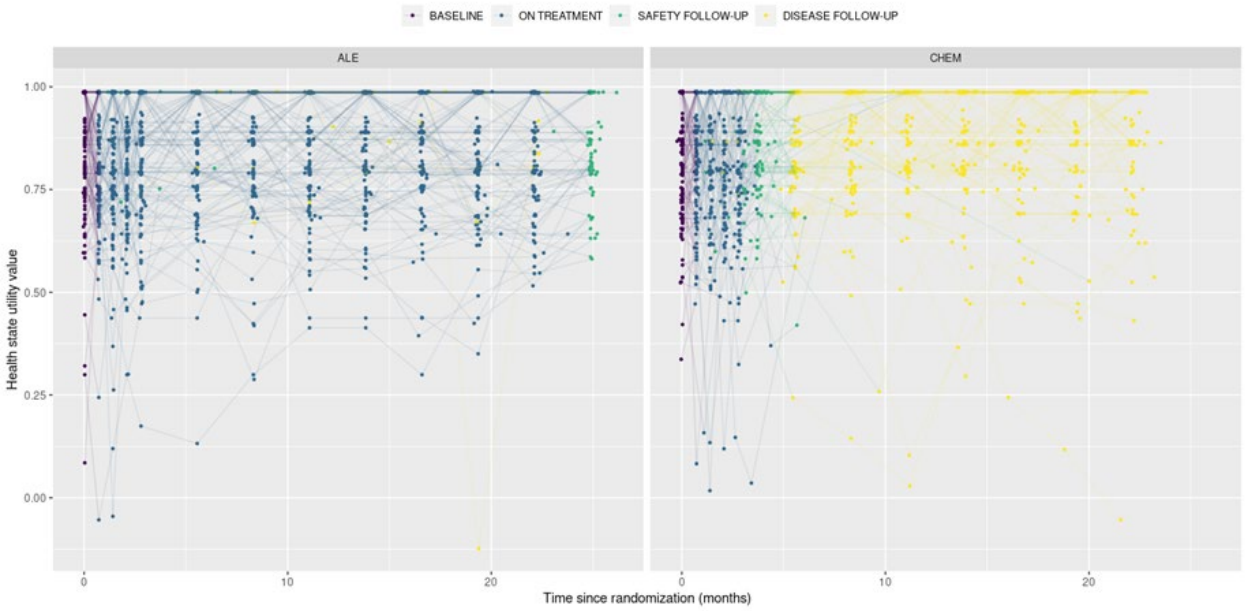


Figure 2: Graphical display of ALINA utilities using UK tariffs (As per figure 16 in clarification question response)



In the response to clarification question B36, the company proposes an updated cost of £x for surgery as a treatment for non-metastatic recurrence, based on NHS reference cost . Please could the company provide further details on how this was derived, since the EAG have been unable to identify this cost in the stated source.

The cost of surgery (£588.30) was taken from NHS reference costs 2021-2022, with the code “DZO2K Complex Thoracic Procedures, 19 years and over, with CC Score 0-2, service code 173”.

The EAG have been unable to validate the updated neutropenia and nausea costs provided by the company in response to B41. Please could the company provide further details on how these were calculated, including the inflation index used.

The inflation indices for 2021/2022 reported in PSSRU 2023 (1) were used as the figures for 2022/2023 are provisional. The values and inflation index used is provided in Table 6.

Table 6: Adverse event costs and inflation index

Adverse event	Previous cost (TA812)	New cost	Inflation index used	Source
neutropenia	625.11	668.87	1.70%	PSSRU 2023 (1)
nausea	1,059.60	1133.77	1.70%	PSSRU 2023 (1)

Please could the company confirm that its preferred updated base case includes the scenario implemented in response to B22 (alternative method for age-adjustment of utility values).

Company can confirm that the updated base case includes the scenario implemented in response to B22. This was confirmed in Table 11 of the clarification questions and implemented in cell F12 in the “utility” tab.

For the health state utility value LMM described in B23, the EAG notes that the size of the standard error is similar to effect estimate for both alectinib and the interaction between alectinib and on/off treatment status. The EAG recognises that while p-values can be difficult to interpret for complex models fitted with lme4, for more standard LMMs the degrees of freedom and hence p values can be estimated reasonably (see this GLLM FAQ for further details).

Please report the p-values corresponding to Table 40 in B23, and report the method to approximate the degrees of freedom and package used to calculate these (e.g. Kenward-Roger in lmerTest or pbkrtest)

A test for the interaction effect between the treatment arm (ALE/CHE) and treatment status (on/off) was conducted, resulting in a p-value of 0.3263. However, no test was conducted for the intercept. It is not possible to separate the tests for the main effects (treatment arm, treatment status) from the interaction effect in the model that includes the interaction. To address this, the non-significant interaction term was removed from the

model, and tests were performed for the main effects of treatment arm, treatment status, and baseline utility in the model without the interaction.

The EAG notes that a non-significant p-value, $p > 0.05$, is not evidence of no effect in itself. Please comment on the likely power of the health state utility (HSU) value analysis to detect increases in HSU values for alectinib treatment.

Power is a crucial concept in the early stages of a study, as it helps determine the sample size needed to detect an effect of a certain magnitude. However, once a study has been conducted, the uncertainty surrounding the estimated effects is better captured using 95% confidence intervals. In order to further assess the analysis of health state utility values, a bootstrapping technique was applied. This method allows us to obtain parameter estimates along with their corresponding 95% bootstrap confidence intervals. Results are presented in Table 7 below.

Table 7: Utilities by treatment arm and on vs off treatment: estimated parameters and bootstrap confidence intervals

	Estimate	Std. Error	t value	2.5% bootstrap confidence limit	97.5% bootstrap confidence limit
Fixed effects	0.487	0.04201	11.59	0.4049	0.5631
Intercept	0.3912	0.0494	7.918	0.2993	0.484
Baseline Utility	0.01735	0.01487	1.167	-0.01155	0.04647
Alectinib	0.04729	0.005986	7.9	0.03545	0.05877
Off-Treatment	-0.01194	0.01216	-0.982	-0.03631	0.01203
Alectinib*Off-Treatment	-0.01194	0.01216	-0.982	-0.03631	0.01203

The EAG notes that the independent generalised gamma extrapolations for both alectinib and chemotherapy presented in the response to B10 appear to be incorrect in

the updated CEM provided. Please could the company confirm if there are any errors in the values provided, or if there are any other reasons why these extrapolations should not be used (e.g. failure to converge).

The following formulas in the “efficacy” tab in CEM have been corrected, details are provided below:

Previous formula:

AM35: =IF(psa=0,AA34*(1/AA35),AK34*(1/AK35))

BD35: =IF(psa=0,AR34*(1/AR35),BB34*(1/BB35))

Updated formula:

AM35: =IF(psa=0,AA35*(1/AA34),AK35*(1/AK34))

BD35: =IF(psa=0,AR35*(1/AR34),BB35*(1/BB34))

This has no impact on the base case results, and therefore no change to the ICER. An updated CEM has been provided with the response.

Some of the alternative extrapolations for survival for subsequent treatments appear to have been excluded from the plots presented in the response to B11 (for example Figure 5 excludes the Gompertz and generalised gamma extrapolations). Please could the company either provide updated extrapolation plots with all extrapolations included, or an explanation for why some extrapolations have been excluded (e.g. failure to converge).

Since this was an exploratory exercise and NICE's survival analysis TSD does not specifically require the use of the gamma distribution, the gamma distribution was not used. All other distributions were considered and excluded from reporting only if there were issues. The results of the generalised gamma model were excluded from Figure 5 as statistical models did not converge. Figures have been updated to display all distributions and are presented in Figure 3-Figure 6.

Figure 3: Kaplan-Meier data overlaid with extrapolations for radiotherapy in the non- metastatic recurrence health state (as per Figure 5 in CQ response)

Figure 4: Kaplan-Meier data overlaid with extrapolations for chemotherapy in the non- metastatic recurrence health state (as per Figure 6 in CQ response)

Figure 5: Kaplan-Meier data overlaid with extrapolations for no treatment in the non- metastatic recurrence health state (as per Figure 7 in CQ response)

Figure 6: Kaplan-Meier data overlaid with extrapolations for alectinib in the metastatic recurrence (1L) health state (as per Figure 8 in CQ response)

Similarly, the AIC/BIC values for the following extrapolations have not been presented in the response to B11:

- Generalised gamma extrapolation for no treatment in the non-metastatic recurrence health state (Table 24)
- Generalised gamma extrapolation for lorlatinib in the metastatic recurrence (1L) health state (Table 27)

For both instances, the AIC/BIC values for generalised gamma were not presented as statistical models did not converge.

Reference:

1. Jones KWH, Birch, S., Castelli, A., Chalkley, M., Dargan, A., Findlay, D., Forder, J., Gao, M., Hinde, S., Markham, S. Premji, S. Teo, H. Unit Costs of Health and Social Care 2023 Manual. 2023.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Alectinib for adjuvant treatment of ALK-positive non-small-cell lung cancer [ID6368]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Roy Castle Lung Cancer Foundation
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Roy Castle Lung Cancer Foundation is a UK wide lung cancer charity. We fund lung cancer research, work in lung cancer patient care (information, support and advocacy activity) and raise awareness of the disease and issues associated with it. Our funding base is a broad mixture including community, retail, corporate, legacies and charitable trusts. Clearly, our patient group members and contacts are a self-selected group, who have taken the step to seek out information or have accessed specialist support services. As most lung cancer sufferers tend to be older, from lower social class groups and with the five year survival being around 15%, less physically well, we acknowledge that our patients are perhaps not representative of the vast majority of lung cancer patients, who are not so well informed. It is, however, important that the opinions expressed to us, be passed on to NICE, as it considers the place of this product in the management of lung cancer.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in	**RCLCF has received the following funding :** - Amgen (£30,000 for 1 year funding of Global Lung Cancer Coalition (GLCC) project; £15,000 grant for Information Services; £165 Advisory Meeting Honorarium) - BMS (£30,000 for 1 year funding of GLCC project; £1100 for Advisory board Honorarium) - Lilly (£30,000 for 1 year funding of GLCC project) - Boehringer Ingelheim (£30,000 for 1 year funding of GLCC project; £1040 Advisory board Honorarium) - Novartis (£30,000 for 1 year funding of GLCC project); £3656.50 for 4 Advisory Boards and Quarterly Consultations) - Sanofi (£30,000 for1 year funding of GLCC project) - Pfizer (£30,000 for 1 year funding of GLCC project)

the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	- Astra Zeneca (£30,000 for 1 year funding of GLCC project; £19,500 for GLCC Project Translation; £300 for Advisory Board Honorarium) - Daiichi Sankyo (£30,000 for 1 year funding of GLCC project; £131.50 for Advisory Board Honorarium) - Takeda (£30,000 for 1 year funding of GLCC project; £260 Speaker Fee) - Janssen (£24,000 grant funding for Ask The Nurse Service)
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
5. How did you gather information about the experiences of patients and carers to include in your submission?	The Foundation has contact with patients/carers through its UK wide network of Lung Cancer Patient Support Groups, Patient Information Days, patient/carer panel, online forums, Keep in Touch' service and its nurse-led Lung Cancer Information Helpline.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	The ALK gene rearrangement is found in about 3% to 5% of patients with NSCLC. These patients tend to be younger and more likely to be light/non-smokers, as compared to the general lung cancer population. With that in mind, it is our observation that, though a younger, fitter patient group (fewer co-morbidities), ALK positive patients tend to be diagnosed later, as they do not fit the 'typical' lung cancer patient profile. This appraisal, however, is for patients within the Adjuvant setting. So, a highly selected patient group. For patients with early stage lung cancer, who have a surgical resection of the tumour, with curative intent, the 5 year survival rates are reported to be up to 50%, with relapses in distant sites accounting for most failures. Relapse after surgery means that further potentially curative therapy is unlikely. Patients and their carers have continual anxiety that the lung cancer will come back. Symptoms of recurrent disease, such as breathlessness, cough and weight loss are often distressing for patients and also for loved ones to observe. The brain is a common site for recurrence in this type of cancer. Brain metastasis can have a huge impact on a patient and their carers. Symptoms range from headaches, nausea and vomiting, memory problems, seizures, loss of balance, speech disturbance… And on a purely practical level, patients with brain metastasis are prohibited from driving.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Historically, standard care for patients with resectable nsclc has been surgery. Sometimes, with the addition of chemotherapy after surgery (adjuvant) or chemoradiation before surgery (neoadjuvant). In March 2023, NICE approved Nivolumab, with chemotherapy, for the neoadjuvant treatment of resectable nsclc (NICE TA876). There is current considerable interest in the use of immunotherapy in the adjuvant and neoadjuvant settings, with clinical trials, using a number of different agents. There is a need to explore additional therapies in improving outcomes and reducing recurrence in this patient group.
8. Is there an unmet need for patients with this condition?	Yes.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Outcomes of treatment are seen as an advantage of this technology. We do not have any additional data, beyond that publicly available. We note, however, the results of the ALINA trial. Trial participants had ALK positive lung cancer. Those treated with Alectinib after surgery lived longer without their cancer coming back, than those treated with chemotherapy after surgery. In the trial, about 94% of people treated with adjuvant Alectinib were alive 2 years after surgery, without their cancer returning. This compares with 63% of people treated with adjuvant chemotherapy. Update on the study (presented at ESMO meeting in October 2023) showed, at 3 years, disease free survival in the Alectinib group of 88% and 53% in the chemotherapy group. In addition, cancer spread to the brain in fewer people treated with Alectinib than those who received chemotherapy. Alectinib is given orally, twice daily. Chemotherapy is given by intravenous infusion three weekly for up to 4 cycles, requiring of hospital attendance and associated preparation/ administration resource.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Side effects associated with Alectinib. We note, however, in the ALINA study, 5% of people in the Alectinib group and 12% of people in the chemotherapy group stopped treatment early because of side effects.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues

13. Are there any other issues that you would like the committee to consider?	
14. In practice, do all people diagnosed with resectable NSCLC have testing for ALK gene fusions? If not, what proportion do?	
15. Would people with NSCLC that is positive for an ALK gene fusion ever be offered immunotherapy in the neo-adjuvant or adjuvant setting?	
16. What proportion of people in current practice have adjuvant chemotherapy after resection?	

Key messages

17. In up to 5 bullet points, please summarise the key messages of your submission.	• This is the first ALK specific therapy to be appraised, in this adjuvant setting • There is a need to develop therapy options to reduce the risk of recurrence after lung cancer surgery. • Trial data shows considerable benefit with Alectinib after surgery, compared with those who had chemotherapy after surgery. • •

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Alectinib for adjuvant treatment of ALK-positive non-small-cell lung cancer [ID6368]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	British Thoracic oncology Group (BTOG)
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	To support and educate thoracic oncology healthcare professionals, creating a professional community to exchange ideas, information and innovation and to foster the development of research. The overall aim is to represent the needs of people with thoracic malignancies in the UK and ensure they have equitable access to optimal care. We receive funding from our annual conference and registration fees
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	Yes, sponsorship BTOG annual conference 2024 £60,000 + VAT

5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To improve the number of patients alive without cancer relapse after curative surgery for ALK+ NSCLC
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A disease-free survival Hazard Ration of 0.7 would be clinically significant
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, there is a large unmet need since despite curative intent surgery, a large number of patients relapsed and die of their lung cancer

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Currently, such patients undergo surgery and may or may not receive adjuvant (post-operative) chemotherapy contingent on their health status and stage of resected NSCLC.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	Early-Stage and Locally Advanced (non-metastatic) Non-Small-Cell Lung Cancer: ESMO Clinical Practice Guidelines; eUPDATE Sept 2021: https://www.esmo.org/guidelines/guidelines-by-topic/esmo-clinical-practice-guidelines-lung-and-chest-tumours/early-stage-and-locally-advanced-non-metastatic-non-small-cell-lung-cancer-esmo-clinical-practice-guidelines/eupdate-early-and-locally-advanced-non-small-cell-lung-cancer-nsclc-treatment-recommendations2
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Yes; ALK testing is well implemented in England. Surgery is routine in NSCLC for this stage of disease. Whilst these patients may be technically suitable for post-operative adjuvant chemotherapy on the basis of stage, given that the survival benefit of adjuvant chemotherapy ranges from an absolute survival benefit at 5years from 5%-25% (contingent on stage at resection) and toxicities of chemotherapy may be significant, some patients choose not to have chemotherapy, and some oncologists tend not to strongly advocate for it.
9c. What impact would the technology have on the current pathway of care?	Deliverability of adjuvant alectinib will be straightforward as: (i) The number of resected ALK+ NSCLC is small (ALK+ NSCLC generally occurs in younger than typical never smokers, and hence unless undergoing a CT scan for an unrelated problem, asymptomatic early stage ALK+ NSCLC is unlikely to be identified. ALK+ NSCLC is generally identified at stage 3 or 4 when it causes symptoms. These patients will not be screen detected as they do not meet the tobacco exposure criteria for screening invitation). (ii) Alectinib is routinely used as a first-line drug for metastatic ALK+ NSCLC so there is good clinical experience of the drug (iii) Implementation will result in these patients being seen in oncology clinics for alectinib supervision when they would not be otherwise.
10. Will the technology be used (or is it already used) in the same way as current	Yes

care in NHS clinical practice?	
10a. How does healthcare resource use differ between the technology and current care?	Currently patients post operatively undergo either adjuvant chemotherapy or surveillance alone contingent on physician/patient preference. Adjuvant alectinib will replace adjuvant chemotherapy. The role of chemotherapy remains controversial for this indication as the ALINA trial did not allow adjuvant chemotherapy for the intervention arm. Some argue that this allows earlier targeting of the biological cause of the cancer: ALK. However, some argue that ALINA trial has insufficient follow up to safely withdraw chemotherapy (associated with a survival gain) and would argue that the optimal treatment is chemotherapy and then alectinib.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Oncology clinics in secondary care
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	The oncology and ALK testing infrastructure is already established.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes; the benefits are large, clinically significant, and a major step forward for ALK+ NSCLC
11a. Do you expect the technology to increase length of life more than current care?	Yes, although the magnitude of this remains unclear given the relatively short follow-up in the trial data, to date.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	If implemented as the ALINA trial, alectinib is far easier to implement at the health system level than adjuvant chemotherapy (which it would otherwise replace if implemented as per ALINA trial schedule) as it is daily oral tablet treatment for patients to take at home with monthly/two-monthly/three-monthly reviews in the oncology clinic.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Alecitnib should be given for the duration as per the ALINA trial. Patients will be managed for adverse events as per the SPC
15. Do you consider that the use of the technology will result in any	No

substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes; adjuvant alectinib is a ground breaking indication for early ALK+ NSCLC. Whilst the number of patients suitable is small, the clinical benefit from alectinib is huge and has potential (as we have seen with the similar indication, adjuvant osimertinib for EGFR mutant NSCLC) to markedly improve survival.
16a. Is the technology a 'step-change' in the management of the condition?	Yes, the DFS benefit form alectinib is massive and clinically meaningful. This is a step-change therapy for resected ALK+ NSCLC
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes, prior to the ALINA dataset, we had no prior indication for an ALK inhibitor for resected ALK+ NSCLC and we often observed relapses (as per the control arm of the ALINA trial)
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The patient advocates invited to the NICE appraisal will be able to speak more eloquently to this than an oncologist. From the oncologist viewpoint, alectinib is a highly tolerable treatment (by oncological standards) with low grade toxicities as per the trial data and SPC and discontinuation due to adverse events is very unlikely.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	DFS is the most important outcome for this population, and it was measured. Another key outcome is OS but the trial follow up is too immature to see any OS impact let alone a strong effect. The OS benefit will also be confounded by patients in the control arm receiving alectinib (or another NICE approved ALK inhibitor) as first line treatment on relapse, so a large OS benefit may not materialize.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	The relationship between DFS and OS for oncogene-addicted NSCLC is not well defined. However, for adjuvant osimertinib (a biologically equivalent scenario to this), a DFS of similar magnitude did translate to a meaningful OS benefit. Given the large DFS effect size identified in the ALNA trial, I would most surprised if this DFS effect size did not translate to a significant OS benefit.
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a	No

systematic review of the trial evidence?	
20. How do data on real-world experience compare with the trial data?	This is a new indication so there is no significant real-world evidence and no UK real-world evidence base of adjuvant alectinib.

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
21b. Consider whether these issues are different from issues with current care and why.	N/A

Topic-specific questions

22. In practice, do all people diagnosed with resectable NSCLC have testing for ALK gene fusions? If not, what proportion do?	The vast majority of patient undergo ALK testing routinely since these patients have their tumour biopsied to make the diagnosis prior to surgery and reflex ALK testing is standard (mostly based on immunohistochemistry) on all new NSCLC cases. Hence, the penetrance of ALK testing in England is high. This practice is underpinned NICE TA876 (Nivolumab with chemotherapy for neoadjuvant treatment of resectable non-small-cell lung cancer) which mandates ALK testing.
23. Would people with NSCLC that is positive for an ALK gene fusion ever be offered immunotherapy in the neo-adjuvant or adjuvant setting?	No, immunotherapy is ineffective in ALK+ NSCLC and is completely the wrong treatment for their condition. ALK+ patients are excluded from NICE TA876 (Nivolumab with chemotherapy for neoadjuvant treatment of resectable non-small-cell lung cancer)
24. What proportion of people in current practice have adjuvant chemotherapy after resection?	The Chouaid et al. study (Lung Cancer (2018) 124; 310-316) retrospectively collected data on 293 UK patients with resected stage 1B-3A NSCLC between 01 January 2009 and 31 December 2011. Only 33.4% received adjuvant chemotherapy. No changes have occurred in clinical practice since then, so the rate will remain similar now.

Key messages

25. In up to 5 bullet points, please summarise the key messages of your submission.	• Adjuvant alectinib is a step-change key treatment for resected NSCLC • The clinical benefit from adjuvant alectinib is high given the strong DFS hazard ratio • Implementing adjuvant alectinib in England will be straightforward as ALK testing is established and clinicians are used to using alectinib in the metastatic setting • Chemotherapy has previously been standard for resected ALK+ NSCLC but only around one third of resected NSCLC patients eligible for chemotherapy receive it • Adjuvant chemotherapy was withheld for adjuvant alectinib, and many would argue that adjuvant alectinib is better given after completion of adjuvant chemotherapy. For example it is allowed in the biological correlate of EGFR mutant NSCLC, IE adjuvant osimertinib (ADAURA trial, TA761) and improves PFS in the biological correlate of 1st line metastatic osimertinib use (FLAURA2 trial)

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our privacy notice.

BMJ TAG

Alectinib for adjuvant treatment of ALK-positive non-small-cell lung cancer [ID6368]

STA Report

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 166887.

Title:	Alectinib for adjuvant treatment of ALK-positive non-small-cell lung cancer [ID6368]
Produced by:	BMJ Technology Assessment Group (BMJ-TAG)
Authors:	Steve Edwards, Director of Health Technology Assessment, BMJ-TAG, London Nicole Downes, Senior Clinical Evidence Analyst, BMJ-TAG, London Sophie Ip, Senior Health Economist, BMJ-TAG, London Ben Farrar, Senior Clinical Evidence Analyst, BMJ-TAG, London Kate Ennis, Senior Health Economist, BMJ-TAG, London
Correspondence to:	Steve Edwards, BMJ-TAG, BMJ, BMA House, Tavistock Square, London, WC1H 9JR.
Date completed:	19/07/2024
Source of funding:	This report was commissioned by the NIHR Evidence Synthesis Programme as project number 166887.
Declared competing interests of the authors	No competing interests were declared which affect the impartiality of this report. BMJ Technology Assessment Group (BMJ-TAG) and the editorial team of The BMJ work independently to one another. The views and opinions expressed in this report are those of the BMJ-TAG.
Acknowledgments:	The EAG would like to thank Dr Nicole Dorey (Consultant Clinical Oncologist at Torbay and South Devon Foundation Trust Hospital, Torquay) and Dr Nadia Yousaf (Consultant Medical Oncologist at The Royal Marsden Hospital, London) for providing clinical advice throughout the project, and for providing feedback on the clinical sections of the report. The EAG would also like to thank Dr Carles Escriu (Thoracic Medical Oncology Consultant at Clatterbridge Cancer Centre, Liverpool) and Dr Alexandros Georgiou (Consultant Medical Oncologist at Guy's and St Thomas' NHS Foundation Trust, London) for providing feedback on the clinical sections of the report.
Rider on responsibility for report:	The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.
Report reference:	Edwards SJ, Downes N, Ip S, Farrar B, Ennis K. Alectinib for adjuvant treatment of ALK-positive non-small-cell lung cancer [ID6368]: A Single Technology Appraisal. BMJ Technology Assessment Group, 2024.

Contribution of authors:

Steve Edwards	Critical appraisal of the company's submission; validated the statistical analyses; provided feedback on all versions of the report. Guarantor of the report
Nicole Downes	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and drafted the summary, background, decision problem and clinical results sections
Ben Farrar	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and drafted the methods review critique and adverse events sections
Sophie Ip	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections
Kate Ennis	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections

All authors read and commented on draft versions of the EAG report.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

1L	First-line
2L	Second-line
AE	Adverse event
AIC	Akaike information criteria
AJCC	American Joint Committee on Cancer
ALK	Anaplastic lymphoma kinase
ALKi	Anaplastic lymphoma kinase inhibitor
AUC	Area under the curve/area under concentration
BICR	Blinded independent central review
BNF	British National Formulary
BOI	Burden of illness
BSA	Body surface area
BTOG	British Thoracic Oncology Group
CAA	Commercial access arrangement
CCOD	Clinical cut-off date
CDA-AMC	Canadian Drug Agency
CDF	Cancer Drugs Fund
CDSR	Cochrane Database of Systematic Reviews
CE	Cost-effectiveness
CEAC	Cost-effectiveness acceptability curve
CEM	Cost-effectiveness model
CENTRAL	Cochrane Central Register of Controlled Trials
CHMP	Committee for Medicinal Products for Human Use
CHT	Chemotherapy
CI	Confidence interval
CMU	Commercial Medicines Unit
CNS	Central nervous system
COVID	Coronavirus disease
cPAS	Comparator patient access scheme
CPK	Blood creatine phosphokinase
CQ	Clarification question
CRD	Centre for Reviews and Dissemination
CS	Company submission
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DARE	Database of Abstracts of Reviews of Effects
DF	Disease-free

DFS	Disease-free survival
DOR	Duration of response
DSU	Decision Support Unit
EAG	External Assessment Group
EBM	Evidence-Based Medicine
ECOG	Eastern Cooperative Oncology Group
EED	Economic Evaluation Database
EGFR	Epidermal growth factor receptor
eMIT	Electronic market information tool
EORTC	European Organisation for the Research and Treatment of Cancer
EQ-5D	EuroQol Group 5-Dimension Questionnaire
ESMO	European Society for Medical Oncology
EU-CTR	European Union (EU) Clinical Trials Register
GFR	Glomerular filtration rate
GP	General practitioner
HCRU	Healthcare resource use
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRQoL	Health-related quality of life
HS	Health state
HSE	Health Survey for England
HTA	Health Technology Assessment
ICER	Incremental cost effectiveness ratio
ICI	Immune checkpoint inhibitors
ICTRP	International Clinical Trials Registry Platform
IHC	Immunohistochemistry
IPD	Individual patient data
ITT	Intent-to-treat
IV	Intravenous
KM	Kaplan-Meier
LCSS	Lung Cancer Symptom Scale
LY	Life years
MAIC	Matching-adjusted indirect comparison
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
N/A	Not applicable
NCI	National Cancer Institute
NE	Not estimable
NHS	National Health Service
NHSCII	National Health Service Cost Inflation Index

NICE	National Institute for Health and Care Excellence
NMB	Net monetary benefit
NSCLC	Non-small cell lung cancer
OS	Overall survival
OWSA	One-way sensitivity analysis
PAS	Patient access scheme
PBC	Platinum-based chemotherapy
PD	Progressive disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
PF	Progression-free
PFS	Progression-free survival
PH	Proportional hazards
PORT	Post-operative radiation therapy
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient-reported outcomes
PSA	Partitioned survival analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QLQ	Quality of life questionnaire
RCT	Randomised controlled trial
RDI	Relative dose intensity
RET	Rearranged during transfection
RFS	Recurrence-free survival
SBRT	Stereotactic body radiation therapy
SEER	Surveillance, epidemiology, and end results
SF-36	Short-Form 36-Item Health Survey
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SMR	Standardised mortality ratio
STA	Single technology appraisal
TA	Technology appraisal
TKI	Tyrosine kinase inhibitor
TLR	Targeted literature review
TNM	Tumour, node, metastasis
TSD	Technical Support Document
UICC	Union for International Cancer Control
VAS	Visual analogue scale

1 Executive summary

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.5 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

Table 1. Summary of key issues

ID	Summary of issue	Report sections
1	Very immature data for OS from ALINA trial	Sections 2.3.4, 3.3.2, 4.2.5.1, 5.4 and 6.5
2	Choice of extrapolations for DFS data	Sections 4.2.5.2.1 and 4.2.5.2.6
3	Approach for deriving transition probabilities for subsequent treatments	Sections 4.2.5.3.1 and 4.2.5.3.4
4	Uncertainty in subsequent treatment acquisition costs	Section 4.2.7.2

Abbreviations: DFS, disease-free survival; OS, overall survival; PFS, progression-free survival.

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are the choice of extrapolations for both disease-free survival (DFS) following adjuvant treatment, and progression-free survival (PFS) and overall survival (OS) for subsequent treatments.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Decreasing the probability of disease recurrence;
- Increasing the rate of patient survival; and
- Decreasing the rate of adverse events (AEs).

Overall, the technology is modelled to affect costs by:

- Its higher unit price than the current standard of care;
- Reducing the need for subsequent treatment and follow-up care, due to reduced disease recurrence;
- Reducing the need for costly subsequent treatments; and
- Reducing the costs for treating AEs.

The modelling assumptions that have the greatest effect on the ICER are:

- The choice of DFS extrapolation curve;
- The approach used to extrapolate PFS and OS for subsequent treatments;
- The predicted market shares for subsequent treatments; and
- The approach to modelling duration of subsequent treatments.

1.3 The clinical effectiveness evidence: summary of the EAG's key issues

Table 2. Issue 1: Very immature data for OS from ALINA trial

Report section	Sections 2.3.4, 3.3.2, 4.2.5.1, 5.4 and 6.5
Description of issue and why the EAG has identified it as important	Data for OS from the ALINA trial are very immature based on the June 2023 data-cut, with only 6 events across both treatment arms observed (n=2 and n=4 events for alectinib and chemotherapy groups, respectively) in the ITT population. This is a concern given the importance of OS for decision-making in oncology appraisals; the limited data available from ALINA means that conclusions about any impact of the treatments evaluated in ALINA on OS cannot be made. This limitation has also meant that OS data from ALINA have not been utilised by the company in the economic model. The EAG's clinical experts noted that while OS data are immature, alectinib has the potential to make a substantial difference to patients in the adjuvant setting based on the results observed for DFS and CNS DFS.
What alternative approach has the EAG suggested?	The EAG considers this to be an unresolvable limitation of the currently available data from ALINA. The next data-cut for OS is outlined as [redacted] in the CS, which is planned to be descriptive only. The EAG considers it likely that data may still be immature at this time-point.
What is the expected effect on the cost-effectiveness estimates?	Although the OS data from ALINA are not currently used in the economic model, more mature OS data would enable the OS predictions estimated by the economic model to be validated more robustly; the EAG has used the available data to validate the OS predictions to some extent but notes that its use is limited given the very few events that occurred. The availability of more mature OS data from ALINA could lead to its direct inclusion in the economic model and use of different model approaches, the impact of which is unclear.
What additional evidence or analyses might help to resolve this key issue?	The EAG considers this to be an unresolvable limitation currently but considers it to be an important consideration in terms of uncertainty in the decision-making process. Discussion with clinical experts about the plausibility of an impact of alectinib on OS over a longer time period and the relationship between OS and DFS in this indication may be useful in considering this issue; the EAG considers it reasonable that a benefit of alectinib for DFS may be predictive of an OS benefit for alectinib but is concerned that the magnitude of the DFS benefit may not directly translate into the magnitude of the OS benefit.

Abbreviations: CNS, central nervous system; DFS, disease-free survival; EAG, External Assessment Group; ITT, intention to treat; OS, overall survival.

1.4 The cost-effectiveness evidence: summary of the EAG's key issues

Table 3. Issue 2: Choice of extrapolations for DFS data

Report section	Sections 4.2.5.2.1 and 4.2.5.2.6
Description of issue and why the EAG has identified it as important	The outcomes of the CEM are sensitive to the choice of extrapolation for DFS data in the model, since this has a large impact on patient HRQoL as well as, indirectly, affecting long-term survival and costs of subsequent treatment and follow-up care. The company's preferred extrapolations were predominantly selected based on statistical measures of goodness of fit, despite the limited evidence of a substantial difference between the extrapolations in this regard. The EAG considers that the extrapolations selected by the company potentially overestimate the long-term DFS benefit resulting from treatment with adjuvant alectinib.
What alternative approach has the EAG suggested?	The EAG has proposed an alternative approach for selection of extrapolations which prioritises alignment with survival estimates elicited from clinical experts at the company's advisory board as well as goodness of fit.
What is the expected effect on the cost-effectiveness estimates?	The EAG's proposed approach leads to an increase in the ICER.
What additional evidence or analyses might help to resolve this key issue?	The availability of mature DFS data would resolve this uncertainty, but this is not expected to be available within the timelines of this appraisal; therefore, this is considered a key source of uncertainty.

Abbreviations: CEM, cost-effectiveness model; DFS, disease-free survival; EAG, External Assessment Group; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio.

Table 4. Issue 3: Approach for deriving transition probabilities for subsequent treatments

Report section	Sections 4.2.5.3.1 and 4.2.5.3.4
Description of issue and why the EAG has identified it as important	In the CEM, the movement between lines of subsequent treatment, as well as mortality, are modelled using transition probabilities, which are based on PFS and OS for subsequent treatments identified from existing literature. The approach to deriving transition probabilities has a considerable impact on the costs for subsequent treatment acquisition and follow-up care, as well as HRQoL and mortality. The company's approach to deriving transition probabilities assumed transition probabilities were constant over time, although this approach did not provide a good fit for the PFS and OS data informing the model.
What alternative approach has the EAG suggested?	The EAG has developed an addition to the company's CEM which allows transition probabilities to vary over time, which better reflects the PFS and OS data.
What is the expected effect on the cost-effectiveness estimates?	When the extrapolations with the best goodness of fit are selected for all subsequent treatment survival curves, the ICER decreases; however, alternative plausible curve choices result in an increase in the ICER. Therefore, the overall impact on the ICER is uncertain.
What additional evidence or analyses might help to resolve this key issue?	More mature OS data for alectinib in the adjuvant setting would reduce the reliance of the model on survival data from secondary literature sources, which are in general also immature; however, as previously mentioned, it is not anticipated that additional OS data will become available within the timeframe of this appraisal.

Abbreviations: CEM, cost-effectiveness model; EAG, External Assessment Group; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival.

Table 5. Issue 4: Uncertainty in subsequent treatment acquisition costs

Report section	Section 4.2.7.2
Description of issue and why the EAG has identified it as important	Costs for subsequent treatments are a major contributor to the overall costs in the CEM; however, these costs are sensitive to the assumed duration of treatment, as well as the market shares for each treatment. In many cases, the company assumed a limited duration of treatment, while the EAG's clinical experts suggested that patients would receive most subsequent treatments until progression. The market shares are particularly uncertain, as these were based on estimates elicited from the company's clinical experts at an advisory board, rather than based on objective real-world data.
What alternative approach has the EAG suggested?	The EAG proposed an alternative, more robust approach for deriving subsequent treatment costs, which applies a single one-off cost when a patient enters a subsequent treatment health state. The EAG also explored scenarios varying the subsequent treatment market shares, including removing surgery as a treatment option (since no appropriate evidence informing survival following surgery could be identified), and setting market shares equal between treatment arms (since the differences between treatment arms were based on clinician opinion).
What is the expected effect on the cost-effectiveness estimates?	The EAG's alternative method for deriving subsequent treatment costs results in a decrease in the ICER. The scenario removing surgery as a treatment option also reduced the ICER. However, the effect of setting market shares equal between treatment arms depends on the line of treatment – the ICER increases if this scenario is applied in the non-metastatic recurrence and metastatic recurrence (2L) settings, and decreases for the metastatic recurrence (1L) setting. However, in all cases, the ICER remains under £20,000.
What additional evidence or analyses might help to resolve this key issue?	The availability of objective real-world evidence to inform the duration of treatment and market shares for subsequent treatments in clinical practice in the UK would help to reduce uncertainty in subsequent treatment acquisition costs; however, the EAG has been unable to identify any relevant data in this regard.

Abbreviations: 1L, first line; 2L, second line; CEM, cost-effectiveness model; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio.

1.5 Summary of EAG's preferred assumptions and resulting ICER

A summary of the EAG's preferred modelling assumptions, along with effects on cost-effectiveness results, is given in Table 6.

Table 6. EAG preferred assumptions

EAG-preferred assumption	Incremental costs	Incremental QALYs	ICER £/QALY (change from corrected company base case)
Corrected company base case	[redacted]	3.56	[redacted]
No disease-related deaths occur in the disease-free health state	[redacted]	3.56	[redacted]

EAG-preferred extrapolations for DFS	[redacted]	3.91	[redacted]
EAG-preferred approach for deriving transition probabilities for subsequent treatments	[redacted]	3.96	[redacted]
PFS for patients receiving alectinib as a treatment for non-metastatic recurrence is aligned with the ALEX trial	[redacted]	3.51	[redacted]
No difference in assumed cure fraction for alectinib and chemotherapy	[redacted]	3.55	[redacted]
HRQoL for the disease-free health state is assumed equal to age- and sex-adjusted general population norms, with a one-off disutility for adverse events applied at baseline	[redacted]	3.62	[redacted]
Treatment acquisition and administration costs for subsequent treatments are applied as one-off costs upon progression; costs for maintenance pemetrexed as a component of chemotherapy as a subsequent treatment are incorporated	[redacted]	3.56	[redacted]
EAG-preferred approach for treatment acquisition costs	[redacted]	3.56	[redacted]
EAG-preferred assumptions for resource use	[redacted]	3.56	[redacted]
Adverse event costs for subsequent treatments are excluded	[redacted]	3.56	[redacted]
Application of half-cycle correction	[redacted]	3.56	[redacted]
EAG-preferred base case	[redacted]	3.63	[redacted]

Abbreviations: DFS, disease-free survival; EAG, External Assessment Group; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; QALY, quality-adjusted life-year.

Modelling errors identified and corrected by the EAG are described in Section 6.1. For further details of the exploratory and sensitivity analyses done by the EAG, see Section 6.

2 Introduction and background

2.1 Introduction

This report contains the External Assessment Group (EAG)'s critique of the clinical and cost-effectiveness evidence submitted for the Single Technology Appraisal (STA) of alectinib (Alecensa®, Roche) for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive (ALK+) non-small cell lung cancer (NSCLC) who have undergone tumour resection. The company's marketing authorisation for alectinib in this indication (granted in July 2024) is as follows: alectinib as monotherapy as an adjuvant treatment for adult patients with Stage IB (tumours ≥4 cm) to IIIA (7th edition of the Union for International Cancer Control [UICC]/American Joint Committee on Cancer [AJCC]-staging system) ALK+ NSCLC following complete tumour resection. As discussed in Section 2.2.1, this is narrower than the population in the National Institute for Health and Care Excellence (NICE) final scope. Committee for Medicinal Products for Human Use (CHMP) opinion on alectinib in this indication was received on 25 April 2024, with a positive recommendation included for alectinib as, "adjuvant treatment following complete tumour resection for adult patients with ALK+ NSCLC at high risk of recurrence".[1] Alectinib is already recommended by NICE for untreated ALK+ advanced NSCLC as part of TA536 (not the adjuvant setting).[2]

2.2 Background

Within Section B.1 of the company submission (CS), the company provides an overview of:

- Alectinib, including its mechanism of action, indications, dose and method of administration (Section B.1.2 of the CS);
- Lung cancer, particularly NSCLC, including diagnosis and classification, clinical presentation, epidemiology, disease burden, and disease management (Section B.1.3 of the CS).

The EAG summarises this information here and provides additional information provided by its clinical experts.

Lung cancer is the third most commonly occurring cancer in the UK as well as the leading cause of cancer-related mortality.[3] NSCLC is the most prevalent type of lung cancer, accounting for ~90% of all lung cancer cases in England.[4] The majority of patients (~60%) are diagnosed at an advanced (stage IIIB) or metastatic (stage IV) stage of disease as opposed to earlier stages (stage I, II or IIIA).[5] Survival rates vary depending on stage at diagnosis, with advanced and metastatic disease having a

very poor 5-year survival rate (1 to 5%) and estimates being higher for those with earlier stages of disease (3- and 5-year survival rates ranging between 14 and 70% have been reported).[5-8]

A multifaceted approach is required in NSCLC diagnosis, which includes patient history and physical examination as well as advanced imaging and histological examination. Staging through imaging techniques such as computed tomography (CT) and histological classification (e.g. separating into squamous cell carcinoma and non-squamous carcinoma) have an important role in guiding therapeutic strategies and assessing prognosis. The tumour, node, metastasis (TNM) system is the basis of staging according to AJCC/UICC system and is used in UK clinical practice (currently the eighth edition, soon to be the ninth edition), with NSCLC categorised into stages 0 to IV based on factors such as tumour size and spread, lymph node involvement and presence of distant metastases.[9, 10]

The molecular profile of the tumour also plays an important role in guiding treatment choice and the EAG's clinical experts confirmed that most patients in the UK relevant to this appraisal would have this done currently (either post-resection or prior to surgery if targeted neoadjuvant chemo-immunotherapy treatments are being considered) to guide adjuvant or neoadjuvant treatment choice (for example, adjuvant osimertinib use in patients with epidermal growth factor receptor [EGFR]+ tumours); the genetic biomarker of interest in this appraisal is *ALK* rearrangements as the population outlined in the decision problem is specific to ALK+ patients (see Section 2.3). It has been reported that 3-5% of NSCLC cases contain the *ALK* fusion gene,[11, 12] although feedback from the company's expert advisory board was that this is more likely to be 2% based on real-world data (similar to feedback the EAG received from its clinical experts that ALK+ patients comprise 1-2% of the NSCLC population).[13] The identification of this molecular variant is critical as it indicates the use of ALK tyrosine kinase inhibitors (TKIs), which have been shown to improve patient outcomes through targeting and inhibiting the activity of abnormal ALK fusion protein.

Clinical presentation in NSCLC commonly involves persistent cough, dyspnoea and chest pain, with other symptoms including fatigue, infections, haemoptysis and unexplained weight loss. ALK+ NSCLC has been considered to be associated with certain features such as most patients having never smoked or only been a light smoker, younger average age and predominantly adenocarcinoma in terms of tumour histology. The ALK+ NSCLC population is thought to be similar to the EGFR-positive NSCLC population. Although one of the EAG's clinical experts highlighted that real-world UK data has recently suggested a median age of ~70 years for the EGFR+ population, the EAG's clinical experts and peer reviewers agreed that the mean age observed in the ALINA trial is not unreasonable based

on their clinical experience with ALK+ patients (see Section 2.3.1 for further discussion).[14] There is also a propensity for ALK+ patients to develop brain metastases, which affects up to 50-60% of patients over their course of disease and is associated with a symptom burden that can substantially impair quality of life and impact prognosis.[15-18]

2.2.1 Current treatment pathway

For newly diagnosed NSCLC patients who are detected at an early stage (stage I to IIIA), tumour resection is the preferred treatment approach if deemed clinically feasible (data from 2022 shows that 18% and 14% of NSCLC patients had a lung resection in England and Wales, respectively).[19] Despite surgical resection with curative intent, high recurrence rates among patients with stage I to III disease have been reported (ranging from 41 to 76%),[20-24] with only 45% of patients still alive at five years post-surgery.[25] One suggestion is that this high recurrence rate may be attributed to micro-metastatic or distant spread of the disease, which suggests that the use of adjuvant treatments could improve outcomes.[26, 27] This appraisal focuses on the adjuvant use of alectinib as monotherapy in adults with stage IB to IIIA ALK+ NSCLC (seventh edition of UICC/AJCC staging system) that have had complete surgical resection.

Recurrence following surgical resection is common, with 10-50% of stage I-III NSCLC patients developing a locoregional recurrence and the LuCaBIS study indicating that brain metastases occurred in 41% of patients with recurrence.[28, 29] Treatments used for recurrence will differ and will depend on whether it is locoregional or distant; locoregional recurrences may be treated with additional surgery or radiation while distant recurrences will require a systemic approach. Overall survival (OS) for patients with recurrence is poor and proactive approaches such as the use of adjuvant treatments and regular imaging for monitoring may improve patient outcomes.

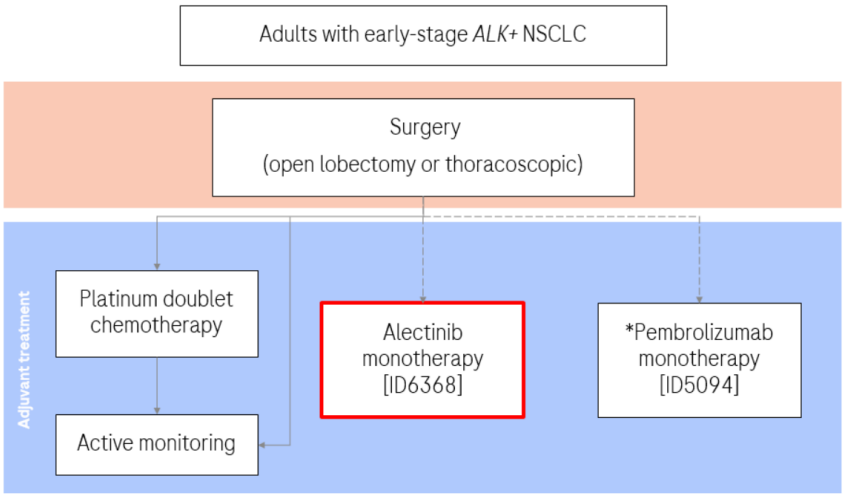
Currently, the only adjuvant treatments that would be suitable for ALK+ NSCLC patients are platinum-based chemotherapy regimens. The company cites evidence that 48-57% of patients with stage IB to IIIA NSCLC have adjuvant chemotherapy, while one of the EAG's clinical experts considered the proportion in UK clinical practice that has adjuvant chemotherapy to be slightly higher.[24] The EAG's clinical experts noted that in UK clinical practice, adjuvant chemotherapy is considered following resection for patients with stage IB disease (if tumour size is ≥4 cm), stage II disease and stage IIIA disease; however, they noted that the use of adjuvant chemotherapy has only been shown to have a modest impact on survival outcomes (as demonstrated in a 2015 Cochrane review and an analysis of the Surveillance, Epidemiology and End Results [SEER]-Medicare database from 2007 to 2019) and that some patients may decline adjuvant chemotherapy due to concerns

about toxicity (including a high incidence of severe side effects such as neutropenia, anaemia and nausea, highlighted by the company) or it may not be deemed suitable due to comorbidities, age (more caution would be taken in those over 75 years of age) or recovery following surgery.[30-32]

The alternative to adjuvant chemotherapy is active monitoring, which (based on the EAG's clinical expert feedback) involves the standard monitoring that patients receiving adjuvant treatment would also receive but in some centres may be individualised if a patient was deemed to be high risk and had declined adjuvant treatment; the EAG's clinical experts noted that while adjuvant chemotherapy has only a small benefit in terms of survival, outcomes for those on active monitoring alone would be still be expected to be slightly worse. The EAG's clinical experts consider alectinib to be well-tolerated in their experience and consider that more patients may be willing to receive an adjuvant treatment, or would be considered suitable for it in terms of comorbidities, were it to be an alternative to adjuvant chemotherapy following surgical resection.

Atezolizumab and osimertinib have in recent years been recommended by NICE via the Cancer Drugs Fund (CDF) for the adjuvant treatment of programmed death-ligand 1 (PD-L1) and EGFR-positive early stage, respectively, (stage II to IIIA for atezolizumab and stage IB to IIIA for osimertinib) NSCLC following complete resection, respectively.[33, 34] ALK TKIs have been successfully used in the advanced/metastatic NSCLC setting for ALK+ patients and alectinib has been shown to have a strong ability to penetrate the central nervous system (CNS); the EAG's clinical experts considered the lack of targeted therapies in the adjuvant setting to be an area of unmet need for ALK+patients.[35, 36] The ALINA trial is the focus of this submission as it assesses the efficacy and safety of adjuvant alectinib compared to adjuvant chemotherapy in stage IB to IIIA NSCLC patients with complete resection.[37, 38] The company positions alectinib in this submission as an alternative to adjuvant chemotherapy (or active monitoring for those not receiving adjuvant chemotherapy for various reasons), as summarised in Figure 1 below. The suitability of the comparators covered by the company in this submission is discussed in Section 2.3; while presented in Figure 1 below, pembrolizumab is not included as a comparator in this appraisal.

Figure 1. Proposed positioning of alectinib for early-stage ALK+NSCLC patients following resection – reproduced from Figure 1 of the CS



The red box indicates the proposed positioning of adjuvant alectinib.

* Subject to NICE appraisal.

Abbreviations: ALK+, anaplastic lymphoma kinase-positive; CS, company submission; NSCLC, non-small cell lung cancer.

2.3 Critique of the company's definition of the decision problem

The company provided a summary of the final scope issued by NICE,[39] together with the rationale for any deviation from it, in Section B.1.1 of the CS. This is summarised in Table 7 below and more detailed comments from the EAG are provided in the subsections that follow. Overall, the EAG considers the decision problem addressed, and the evidence used to address it, to be in line with the NICE final scope or any deviations to be reasonable given the rationale provided but some points of concern are summarised below.

The EAG's clinical experts highlighted some differences in terms of baseline characteristics of the key alectinib trial (ALINA) compared to the UK population (see Section 2.3.1); these were mostly not considered to be major issues by the EAG but the EAG requested that the age used in the economic model be explored to assess the impact on results given evidence from one UK audit of the EGFR+ population (considered to be similar to the ALK+ population) reporting a median age of ~70 years rather than the mean of [redacted] years as observed in ALINA for ALK+ patients.[14] While this was highlighted by one of the EAG's clinical experts, all clinical experts and peer reviewers agreed that the mean age of the ALINA trial was not unreasonable for ALK+ patients and one of the EAG's peer reviewers noted that this discrepancy could be because there is also a large group of people with EGFR+ NSCLC that present >80 years, meaning the average age would be higher than the ALK+ population. Furthermore, the company provided additional UK-based references involving real-world data to support the ALINA trial being in line with the UK population, which the EAG considers

supportive of using the ALINA mean age in the economic model base case, but a scenario analysis has been included around the company's base case (see Section 6.2).

Due to larger differences than anticipated by the EAG between investigator-assessed disease-free survival (DFS) and blinded independent central review (BICR) for recurrences in the chemotherapy group, the EAG requested the impact on results of the economic model be explored (clarification question [CQ] A1). Based on the company's response, the EAG acknowledges that the BICR analysis is primarily based on imaging results and does not consider the additional information available to investigators to make decisions (for example, clinical examination). Therefore, while the EAG notes that the investigator-assessed DFS outcome is likely to be associated with some bias given the unblinded nature of the ALINA trial (see Section 3.2), the EAG agrees that this analysis is based on the most thorough assessment of patients and should be the preference in terms of the base case of the economic model. The EAG has retained the BICR analysis provided by the company in response to CQ A1 as a scenario analysis with results presented in Section 6.2; applying this ICER to the corrected company base case results in the ICER increasing by [redacted].

OS in the ALINA trial is very immature with only 6 events observed at the most recent data-cut. While the EAG considers this to be an unresolvable issue currently, it highlights that there is limited evidence in this appraisal for the impact of adjuvant alectinib compared to adjuvant chemotherapy in terms of OS and has included this as a key issue for consideration in decision-making (Key Issue 1; Table 2). However, the EAG notes that it was not directly used in the economic model.

Table 7. Summary of decision problem – adapted from Table 1 of the CS and the NICE final scope[39]

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope	EAG comment
Population	Adults with ALK+NSCLC who have undergone surgical resection	Per final scope	N/A	The EAG considers the population covered in the company's decision problem to be slightly narrower than the NICE final scope but considers this to be reasonable given it is in line with the population from ALINA and the marketing authorisation for alectinib in this indication. The EAG's clinical experts highlighted a difference in terms of the proportion of Asian patients between the population included in ALINA and the population in UK clinical practice, which is not considered to be a major concern by the EAG. See Section 2.3.1 for further discussion.
Intervention	Alectinib (Alecensa®)	Per final scope	N/A	The intervention covered in the CS and ALINA trial matches the NICE final scope and SmPC. See Section 2.3.2 for further discussion.
Comparator(s)	Established adjuvant clinical management without alectinib, which may include: • Platinum-based chemotherapy;	• Platinum-based chemotherapy; • Active monitoring	**Active monitoring:** • UK clinicians consider active monitoring as an option for a small portion of patients (typically less than 10%). However, this would	Based on feedback from the EAG's clinical experts, the EAG is satisfied that: • The ALINA trial provides randomised evidence for the comparison between alectinib and platinum-based

	• Active monitoring; • Pembrolizumab (subject to NICE appraisal)		only apply to those for whom the risks of adjuvant treatment outweigh the benefits. This approach is generally reserved for patients with a high risk of disease recurrence and issues related to treatment compliance. Clinician decisions are also influenced by the patient's age, post-surgical recovery, comorbidities, performance status, and patient preference. Some clinicians indicated they would not advocate for active monitoring due to high risk of disease recurrence. • As a result, although active monitoring was listed as a comparator, it was only included in the scenario analyses where its efficacy was assumed to match that of platinum-based chemotherapy, due to limited studies demonstrating its effectiveness. In these analyses, the treatment costs for active monitoring were set as zero, and the follow up healthcare resource use was kept as the same as chemotherapy. **Pembrolizumab:**	chemotherapy, with the chemotherapy regimens used being a reasonable reflection of those used in UK clinical practice; • Pembrolizumab would not be a suitable comparator for the ALK+ population. The EAG's clinical experts considered active monitoring to be a relevant comparator given not all patients that are eligible for adjuvant chemotherapy would receive it. While active monitoring has not been included as a main comparator in the economic model, a scenario assuming equivalence to platinum-based chemotherapy in terms of efficacy and follow-up healthcare resource use, with no treatment costs or adverse events included, has been provided by the company (CQ A13). The EAG (based on clinical expert feedback) considers this to be a reasonable and conservative way of exploring cost-effectiveness against this comparator but a correction to the implementation of this in the model was performed by the EAG. See Section 2.3.3 for further discussion.

			• The Company does not consider pembrolizumab as an appropriate comparator for this appraisal, and therefore, has not been included in the economic analysis. • The Company consulted with four national UK clinical experts regarding the use of pembrolizumab for ALK+ NSCLC. The consensus was that pembrolizumab is not an appropriate treatment for ALK+ NSCLC patients, and that they would not prescribe pembrolizumab for patients with this specific genetic alteration. This viewpoint is supported by the British Thoracic Oncology Group (BTOG), which reflected this stance in their comments during a consultation conducted by NICE. • The IMMUNOTARGET registry, also referenced in the European Society for Medical Oncology (ESMO) guidelines for oncogenic-addicted metastatic NSCLC,[40] noted the lack of clinical activity in the ALK group when retrospectively studying patients receiving ICI as monotherapy for advanced NSCLC with at least one oncogenic driver alteration. This trend was also seen in patients	

			with other driver alterations and it was discussed that ICI should only be considered after exhaustion of targeted therapies and in some cases, potentially in all other therapies including standard and salvage chemotherapies.[41] • The PEARLS/ KEYNOTE-091 trial studying pembrolizumab vs placebo as adjuvant therapy for completely resected stage IB-IIIA NSCLC did not mandate ALK status for inclusion in the trial (61% of patients receiving pembrolizumab had unknown status of ALK and 38% were negative for this alteration). As such, no subgroup analysis was performed to evaluate the efficacy of pembrolizumab in these patients.[42] • NICE has agreed to exclude atezolizumab as a comparator in the current evaluation due to Cancer Drugs Fund (CDF) considerations. With both atezolizumab and pembrolizumab belonging to the same class of PD-1/PD-L1 inhibitors, the rationale for excluding atezolizumab should also be applicable to pembrolizumab. The availability and reimbursement status of these	

			treatments do not affect their clinical appropriateness as comparators for ALK+ NSCLC patients.	
Outcomes	The outcome measures to be considered include: • Disease-free survival; • Overall survival; • Adverse effects of treatment; • Health-related quality of life	Per final scope	N/A	All four outcomes listed in the NICE final scope are covered in the ALINA trial, with EQ-5D results requested by the EAG as part of CQ A9. There was a larger difference than anticipated by the EAG in the number of disease recurrence events identified for the chemotherapy group between the primary analysis of disease-free survival (investigator-assessed) and a second analysis using BICR. While the EAG considers the investigator-assessed DFS represents the most thorough assessment of patients on which to base recurrence status based on the company's response to CQ A1, it notes that some bias may be associated with this outcome given the trial was open-label. A scenario analysis using BICR data was provided by the company as part of CQ A1 and has been applied to the company's corrected base case by the EAG. Regarding overall survival, the EAG notes that data for this outcome are immature, with only 6 events in total observed at the June 2023 data-cut and this represents a

				limitation in terms of clinical conclusions. This is included as a key issue in this report for consideration in decision-making (Key Issue 1; Table 2) These data are, however, not used in the economic model. See Section 2.3.4 for further discussion.
Economic analysis	• The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. • The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. • Costs will be considered from an NHS and Personal Social Services perspective. • The availability of any commercial arrangements for the intervention, comparator and subsequent	Per final scope	N/A	N/A

	treatment technologies will be taken into account. • The availability and cost of biosimilar and generic products should be taken into account. • The use of alectinib is conditional on the presence of an ALK gene fusion. The economic modelling should include the costs associated with the diagnostic testing for ALK gene fusions in people with resected NSCLC who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test.			
Subgroups to be considered	If the evidence allows it, the following subgroups will be considered: • Disease stage; • Ethnicity	Per final scope	N/A	Subgroup analyses outlined in the NICE final scope, as well as additional ones prespecified in the ALINA trial, are presented in the CS for the primary outcome of disease-free survival. Overall, the EAG is satisfied that analysing the full population in this appraisal and the ALINA trial is appropriate and that analyses for separate subgroups are not required. See Section 2.3.5 for further discussion.

Special considerations, including issues related to equity or equality	Nothing outlined in the NICE final scope	Nothing outlined by the company in the submission	N/A	N/A

Abbreviations: ALK+, anaplastic lymphoma kinase-positive; BICR, blinded independent central review; CQ, clarification question; CS, company submission; EAG, External Assessment Group; EQ-5D, EuroQol Group 5-Dimension Questionnaire; ICER, incremental cost-effectiveness ratio; ICI, immune checkpoint inhibitors; N/A, not applicable; NICE, National Institute for Health and Care Excellence; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; SmPC, Summary of Product Characteristics.

2.3.1 Population

Alignment to NICE final scope

The population focused on by the company in this submission, including the economic model, is adult patients with stage IB (tumours ≥4 cm) to IIIA (according to the 7th edition of the UICC/AJCC staging system) ALK+NSCLC following complete tumour resection. This is narrower than the NICE final scope (any adults with ALK+NSCLC who have undergone tumour resection) but the EAG considers this to be reasonable given it is in line with the marketing authorisation for alectinib in this indication and the population from the ALINA trial.

Alignment to UK population

On reviewing the baseline characteristics of the ALINA trial, the EAG's clinical experts considered most were in line with the population expected in UK clinical practice. However, the proportion of Asian patients seen in ALINA (55.6% overall) is considered to be high compared to the UK population, despite the ALK mutation being more common in Asian patients.

Regarding the mean age of [redacted] years observed in ALINA, while the EAG's clinical experts and peer reviewers agreed that it may not be an unreasonable estimate of the mean age in the UK ALK+ population, there is some real-world UK data for an EGFR-positive population (which should be similar in terms of characteristics to the ALK+ population) suggesting a median age of 70 years.[14] One of the EAG's peer reviewers noted that this discrepancy could be because there is also a large group of people with EGFR+ NSCLC that present >80 years, meaning the average age would be higher than the ALK+ population.

Further feedback from the EAG's clinical experts was that age and Asian race are not major prognostic factors but could have some prognostic value. For age, feedback was that older patients may have a higher risk of death through comorbidities while younger patients may have a more aggressive cancer and be more likely to experience a recurrence. For Asian race, it is noted that most patients in this category are likely to be from East Asia given the trial sites included for ALINA; feedback from one clinical expert was that East Asian patients may have better outcomes compared to other groups. However, the EAG notes that the subgroup analyses for DFS within ALINA do not appear to be in line with these concerns (see Section 2.3.5); results appear to be very similar across

age groups and a slight difference in terms of point estimates was noted for the Asian subgroup compared to other subgroups.

For this reason, the EAG does not have major concerns about differences in these characteristics relative to the UK population in terms of DFS and the EAG notes that OS from ALINA was not used in the economic model (see Section 4.2.5). However, the EAG requested that the company explore the impact of changing the mean age in the economic model (CQ A5). The company cited various UK-based studies involving real-world data for the ALK+ population supporting a lower age that is more in line with the ALINA trial.[43-45] Therefore, the EAG is satisfied that the mean age observed in the ALINA trial may be a reasonable representation of the UK population and considers it appropriate to use in the base case of the economic model. A scenario analysis using a mean age of 70 years is presented in Section 6.2; applying this scenario to the company's corrected base case results in the incremental cost-effectiveness ratio (ICER) decreasing by [redacted].

The EAG's clinical experts noted that while the same UICC/AJCC staging system is used to stage patients in UK clinical practice, the 8th edition is currently being used (soon to be moving to the 9th edition) rather than the 7th edition used in the ALINA trial. However, they noted that differences between the editions are small and should not affect the applicability of this trial to the UK population. Furthermore, the EAG notes that the 7th edition is specifically mentioned in the indication wording in the Summary of Product Characteristics (SmPC) for alectinib in this indication.[36]

Details of surgery and other treatments prior to randomisation in the ALINA trial were considered to be in line with UK clinical practice by the EAG's clinical experts; the majority of surgeries were lobectomies and neoadjuvant treatments did not appear to be used for any patients (CQ A6). The EAG's clinical experts noted that most lobectomies in UK clinical practice would be performed by minimally invasive surgery, but details of this were not collected in ALINA so this could not be assessed in terms of applicability to UK clinical practice (CQ A11). Furthermore, one of the EAG's peer reviewers noted that the availability of minimally invasive surgery may vary, for example, regions without a cardiothoracic centre may use minimally invasive surgery less often.

The EAG's clinical experts highlighted some groups that were excluded from ALINA but would not be excluded from using ALK inhibitors in UK clinical practice, including those with a human immunodeficiency virus (HIV) diagnosis, a prior history of organ transplant or inadequate renal function (defined in the ALINA protocol as Serum creatinine >1.5 x upper limit of normal or

creatinine clearance <60 mL/min). The EAG's clinical experts noted that renal function does not exclude the use of alectinib in UK clinical practice currently and the SmPC for alectinib allows patients with renal impairment to receive alectinib. The EAG considers that these exclusions may not be uncommon for clinical trials, which tend to recruit a healthier group of patients, and is not aware of any strong reasons why these patients should be excluded from any recommendations made in this appraisal.

Furthermore, patients with stage IIIa N2 disease that, in the investigator's opinion, should receive postoperative radiation therapy, and patients with N3 disease, were also said to be excluded from ALINA. The EAG's clinical experts did not consider these exclusions to be appropriate if disease has been completely resected as postoperative radiation therapy has since been shown to lack efficacy and,[46] while those with N3 disease would usually be considered inoperable, if N3 disease were discovered during surgery then they should not be excluded from adjuvant treatment options as they represent the highest risk group.

A breakdown of the number of patients excluded from the study for these reasons was not available to the EAG but the EAG notes that not all stage IIIa N2 patients appear to have been excluded given some patients with this staging are noted in the clinical study report (CSR).[38] Recommendations that were around at the time of the ALINA protocol adaptation for these patients (Protocol Version 3, 23 April 2018) considered that postoperative radiation therapy should only be used in highly selected patients.[47-50] Therefore, given it was an exclusion that impacted both groups and may only have applied to a small number of patients otherwise eligible for enrolment, the EAG does not have major concerns about the exclusion of this population on the conclusions of the ALINA trial. Similarly, the EAG's clinical experts stated that it was rare for N3 disease to be identified during surgery and it is likely that very few patients were excluded from ALINA solely for this reason. While these populations were not included in ALINA, the EAG's clinical experts noted that they would not want to exclude these populations from any recommendation that alectinib might receive in this indication.

2.3.2 Intervention

The intervention addressed in the CS and economic model matches the NICE final scope.[39] The administration and dose of alectinib used in the ALINA trial matches that described in the SmPC, which is 600 mg (four 150 mg capsules) taken orally twice daily with food (total daily dose of 1200 mg), up to a maximum of 24 months in the adjuvant setting.[36] The timing between surgery and

adjuvant alectinib initiation (mean [redacted]) in the ALINA trial was considered in line with UK clinical practice by the EAG's clinical experts (although it was noted that there would be a window for this that would vary between patients depending on patient recovery, reporting of histology results and an oncology visit being arranged to discuss adjuvant treatment, usually up to 10 to 12 weeks post-surgery) and this was well-balanced between the alectinib and chemotherapy groups.

As with the use of alectinib in other indications, it should be initiated and supervised by a physician experienced in the use of anticancer medicinal products and a validated ALK assay should be performed prior to treatment; the EAG's clinical experts noted that UK patients already have this genomic testing done at surgery and it would not represent an additional resource.[36]

In Section B.1.2 of the CS, alectinib is described as a, "highly selective and potent ALK and rearranged during transfection (RET) tyrosine kinase inhibitor". It is already recommended by NICE for untreated, advanced ALK+ NSCLC.[2]

The EAG reviewed concomitant medications used by patients in the ALINA trial (reported in Section 4.5.1.2 of the CSR) and has no concerns about these; these did not appear to be treatments that would affect outcomes of the ALINA trial.

Furthermore, the EAG's clinical experts considered the use of subsequent treatments in ALINA (following a recurrence) to be largely reflective of UK clinical practice. The use of radiotherapy alone (rather than chemoradiation) as a subsequent treatment in the economic model was highlighted by the clinical experts as inferior and not in line with UK clinical practice. However, one clinical expert noted that this may depend on the fitness of patients and the intention of treatment. The ALINA trial did not capture details on whether radiotherapy was used alone or in combination with chemotherapy (CQ A6). The EAG requested that this be considered in the downstream treatment pathway of the economic model but this was not addressed by the company given clinical experts it consulted did not highlight chemoradiation as a key treatment option (CQ B13); the EAG has addressed this by performing a scenario analysis (see Sections 4.2.2.1, 4.2.5.3.4 and 6.2).

2.3.3 Comparators

Of the three comparators listed in the NICE final scope,[39] the company has covered comparisons against platinum-based chemotherapy and active monitoring in some form, while pembrolizumab has not been included as a comparator in this appraisal. Chemotherapy is the main comparator included in the economic model but the company has provided a scenario comparing alectinib

against active monitoring, where efficacy and follow-up healthcare resource use of active monitoring is assumed to be the same as chemotherapy, but treatment costs and adverse events (AEs) of treatment are excluded. In the original scenario against active monitoring, AEs of treatment were assumed to be the same as chemotherapy for active monitoring but a version with these excluded was provided in response to CQ A13. However, the EAG noted an error in the implementation of this in the model and has corrected this as part of its own scenario analyses (see Sections 4.2.3 and 6.2).

The EAG considers the exclusion of pembrolizumab as a comparator in this appraisal to be reasonable as:

1. It has not yet been recommended by NICE in any population in the adjuvant NSCLC setting (ID3907 is ongoing);[51]
2. The EAG's clinical experts supported the argument put forward by the company that pembrolizumab would not be considered suitable for use in patients with ALK+ NSCLC in UK clinical practice currently due to a demonstrated lack of efficacy of immunotherapy (such as pembrolizumab) in patients with this mutation.[41] This opinion was also shared by the British Thoracic Oncology Group in comments it submitted on the NICE draft scope for this appraisal.[52]

Regarding the use of adjuvant chemotherapy or active monitoring, the company suggests that active monitoring would apply to less than 10% of the eligible population. However, feedback from the EAG's clinical experts was mixed, with one suggesting it could be up to 40% of the population and another more in line with the 10% figure suggested by the company. Feedback from one of the EAG's peer reviewers was also consistent with the company's estimate as they highlighted that they are more likely to have adjuvant treatment given their younger age and because it may also be a requirement to access some TKIs. The EAG's clinical experts agreed that the decision between adjuvant chemotherapy and active monitoring (based on a discussion between the clinician and patient) would be based on factors such as the patient's age, stage of disease, post-surgical recovery, comorbidities, performance status and patient preference. One clinical expert noted that follow-up for patients with active monitoring only would usually be done by surgeons or respiratory physicians rather than oncologists.

Regardless of the proportion that do have active monitoring in clinical practice, the EAG considers the company's approach to assessing the cost-effectiveness of alectinib compared to active

monitoring to be reasonable. While it may be simplistic to assume the same efficacy and follow-up healthcare resource as platinum-based chemotherapy (and exclude treatment costs and AEs associated with treatment), it is a conservative approach and the EAG's clinical experts confirmed that outcomes for patients on active monitoring would be expected to be worse than those receiving adjuvant chemotherapy; even though the benefit of adjuvant chemotherapy is only considered to be small and may not outweigh the risks in some patients, there is still some benefit associated with this treatment over active monitoring for most patients. The EAG's clinical experts also noted that there is no reason to expect alectinib efficacy to differ in those that would have active monitoring instead of adjuvant chemotherapy (reasons for avoiding chemotherapy are usually for reasons unrelated to the cancer diagnosis) and that alectinib may be a suitable option for many patients that would otherwise have active monitoring given there are fewer concerns about toxicity with alectinib compared to chemotherapy.

While an indirect treatment comparison against active monitoring would have been an alternative to the approach currently taken by the company, the EAG notes that a formal feasibility assessment for this was not performed by the company and it is unclear whether any suitable studies would have been available (see Section 3.1). However, the EAG considers that any indirect treatment comparison would itself be associated with considerable uncertainty. The EAG is satisfied with the company's current, conservative approach to the comparison of alectinib against active monitoring in its scenario analysis provided as part of CQ A13; however, the EAG noted an error in the implementation of this scenario in the company's analysis and has included a corrected version in its own scenario analyses (see Sections 4.2.3 and 6.2).

Regarding the comparison against adjuvant chemotherapy, the EAG's clinical experts considered the platinum-based chemotherapy regimens used in the ALINA trial to be a reasonable reflection of those in UK clinical practice. While some slight differences in terms of which is most commonly used were noted in the trial compared to UK clinical practice, there may be variation in this across UK centres (for example, some may have a preference for cisplatin while others use carboplatin more commonly as part of the platinum-doublet chemotherapy) and the EAG's clinical experts noted that platinum-doublet chemotherapy regimens are considered to be largely equivalent in terms of efficacy, with cisplatin-based regimens associated with more toxicity. Therefore, the EAG considers ALINA to be an appropriate source of evidence for adjuvant platinum-based chemotherapy in this appraisal. The quality of this trial as assessed by the EAG is discussed in Section 3.2.

As noted above in Section 2.3.2, the EAG has no major concerns about concomitant medications or subsequent used by patients in the ALINA trial but requested that the use of chemoradiation (rather than radiotherapy alone) be considered in the downstream treatment pathway of the economic model, which was not provided by the company (CQ B13). The EAG has addressed this by performing a scenario analysis (see Sections 4.2.2.1, 4.2.5.3.4 and 6.2).

2.3.4 Outcomes

All four outcomes listed in the NICE final scope were captured in the ALINA trial and are covered in the CS. This includes DFS, OS, AEs and health-related quality of life (HRQoL). Information is provided in the CS with additional information presented in the CSR. As part of CQ A9, the EAG requested additional information on the EuroQol Group 5-Dimension Questionnaire (EQ-5D) results from ALINA, which was provided by the company. The CS also provides data on CNS DFS but this outcome is not used in the economic model. See Section 3.3 for a discussion of the results from the ALINA trial. Outcomes from ALINA used in the economic model in some form are: DFS, AEs (grade 3 to 5 events related to treatment with a difference in incidence rate of at least 2% between treatment arms; the EAG corrected this in the economic model to exclude appendicitis events given there was not a 2% different between groups for this AE) and EQ-5D-5L.

The EAG had some concerns about differences between the primary DFS analysis (investigator-assessed) and the secondary DFS analysis (BICR); there was a larger difference than anticipated by the EAG particularly for the number of recurrences confirmed in the chemotherapy treatment group, with fewer events based on the BICR (see Section 3.3.1 for a comparison of the results of these two analyses). While the conclusions based on hazard ratios (HRs) from the two analyses may not change in terms of the benefit of alectinib, the EAG was unsure whether an impact on the ICER may be seen if modelling of DFS were to be based on these data instead of investigator-assessed data. Therefore, the EAG requested that the company explore this in its economic model, which was performed by the company in response to CQ A1. Based on the company's response, the EAG acknowledges that the BICR analysis is primarily based on imaging results and does not consider the additional information available to investigators to make decisions (for example, clinical examination). Therefore, while the EAG notes that the investigator-assessed DFS outcome is likely to be associated with some bias given the unblinded nature of the ALINA trial (see Section 3.2), the EAG agrees that this analysis is based on the most thorough assessment of patients and should be the preference in terms of the base case of the economic model. The EAG has retained the BICR analysis provided by the company in response to CQ A1 as a scenario analysis with results presented in

Section 6.2; applying this ICER to the corrected company base case results in the ICER increasing by [redacted].

For OS, as noted by the company, the data are very immature, with only 6 events (n=2 for alectinib and n=4 for chemotherapy) in total across the two treatment arms in ALINA observed at the June 2023 data-cut. For this reason, the company has not used OS data from ALINA in the trial and has instead used other approaches (see Section 4.2.5). The EAG considers this to be a limitation in terms of there being a lack of data to make firm conclusions about the impact on OS but considers this to be unresolvable until more data are available from ALINA. The next data-cut for OS is anticipated in [redacted] but the company notes that this will be descriptive only and the EAG considers the data may still be immature by this point. The EAG has included this as a key issue for consideration in decision-making given OS is usually a key consideration in oncology appraisals (Key Issue 1; Table 2). The EAG's clinical experts noted that while OS data is immature, alectinib has the potential to make a substantial difference to patients in the adjuvant setting based on the results observed for DFS and CNS DFS currently.

2.3.5 Subgroups

Subgroup analyses outlined in the NICE final scope were related to disease stage and ethnicity. Results of these subgroup analyses for DFS (investigator-assessed) have been provided in Figure 8 of the CS (reproduced in Figure 6 of Section 3.3.5). The EAG discusses these results in Section 3.3.5 but notes that the results are largely consistent across the subgroup analyses; the most notable difference is that the Asian subgroup has a point estimate suggesting less of a benefit for adjuvant alectinib over adjuvant chemotherapy compared to the non-Asian subgroup, but the estimates are still consistent with an overall benefit of adjuvant alectinib and the EAG's clinical experts were not able to explain this observation (one clinical expert expected the opposite might be observed although peer reviewers considered there to be no strong prospective evidence to suggest race as a prognostic indicator). Furthermore, the EAG notes that these subgroup analyses should be interpreted with caution given the trial is not powered to detect differences within these and there is insufficient data to conclude there are differences between any subgroups.

Given there were no large concerns about differences in the relative efficacy of adjuvant alectinib compared to adjuvant chemotherapy across subgroups for DFS within ALINA, the EAG considers use of the overall population in the submission and economic model to be appropriate. The EAG did not request subgroup analyses for other outcomes given the number of events for outcomes such as

central nervous system DFS and OS were lower than DFS and unlikely to provide meaningful information.

3 Clinical effectiveness

3.1 Critique of the methods review

The company conducted a clinical systematic literature review (SLR) in order to identify randomised controlled trials (RCTs) that:

- Assessed the efficacy and safety of adjuvant treatments for resectable early-stage (Stage I–III) non-small cell lung cancer (NSCLC); and/or
- Reported health related-quality of life (HRQoL) outcomes or other patient reported outcomes following adjuvant treatment for resectable early-stage NSCLC.

The External Assessment Group (EAG) summarises the SLR methods in Table 8. The EAG considers the company SLR to be appropriate, and notes that the SLR was broader than would have been necessary given the final scope issued by the National Institute for Health and Care Excellence (NICE) and the decision problem addressed by the company in the company submission (CS). The latest update to the SLR was performed in September 2023, i.e., eight months prior to the submission, which may have missed some recent evidence. However, the EAG considers it unlikely that any evidence relevant to the present submission would have been missed because:

- The ALINA trial provides head-to-head data comparing alectinib to chemotherapy for the adjuvant treatment of resected anaplastic lymphoma kinase-positive (ALK+) NSCLC, and the ALINA trial clinical study report (CSR) was provided by the company; and
- Pivotal trials of adjuvant chemotherapy were completed before 2023 and the pivotal pembrolizumab trial in the adjuvant NSCLC setting was also identified in the SLR.[53]

Table 8. Summary of EAG's critique of the methods implemented by the company to identify evidence relevant this appraisal

Systematic review step	Section of CS in which methods are reported	EAG's assessment of robustness of methods
Data sources	Appendix D.1.3	**Appropriate**. The following databases were searched: • EMBASE; • MEDLINE® and MEDLINE® In-Process; • Cochrane Central Register of Controlled Trials; and • Cochrane Database of Systematic Reviews.

		In addition, the abstracts of the following five oncology conferences were hand searched from 2020 to 2023: • American Society of Clinical Oncology Annual Meeting; • European Society for Medical Oncology Congress; • World Conference on Lung Cancer; • European Society for Medical Oncology – Immuno-oncology; and • European Lung Cancer Congress. In addition, the following trial registries were searched: Trial registries: • EU Clinical Trials Register (www.clinicaltrialsregister.eu); • US National Institute of Health Database (ClinicalTrials.gov); and • World Health Organisation International Clinical Trials Registry Platform.
Search strategies	Appendix D.1.4	**Appropriate** Searches were broad and appropriately limited by disease stage (locally advanced, resectable, stage I to stage III NSCLC) and study design (clinical trials). Limits were defined using both keywords and subject heading terms. The most recent SLR update searches were conducted on 14th September 2023. The EAG notes this was eight months prior to the company submission, and that this may have led to some relevant records being missed. For example, the company's pivotal trial – ALINA – was not reported as being identified in the SLR, despite a conference abstract being published in October 2023.[54] However, the EAG notes the risk of key data being missed is low as the company presented all relevant ALINA data in the CS, and provided the ALINA CSR. In addition, key comparator data were not missing as: • The ALINA trial provided a direct comparison between alectinib and adjuvant chemotherapy; • Pivotal trials of adjuvant chemotherapy were captured in the SLR and are expected to have been published before October 2023; • While adjuvant pembrolizumab was not considered a comparator by the company, the SLR nevertheless identified the pivotal KEYNOTE-091 trial for the adjuvant setting;[53] and • The EAG is satisfied with the company's approach to including active monitoring as a comparator in this appraisal by assuming clinical equivalence to adjuvant chemotherapy given this is likely to be a conservative approach, but a correction to the implementation of this was required by the EAG (see Sections 2.3.3 and 4.2.3).
Inclusion criteria	Appendix D.1.2	**Appropriate**

		The EAG considers the inclusion criteria to be broader than the final scope issued by NICE and the decision problem addressed by the company in the CS. Hence, the EAG considers it unlikely any studies relevant to the decision problem have been missed.
Screening	Appendix D.1.5	**Appropriate** Title/abstract review and full-text review were completed by two independent reviewers, with a third reviewer resolving any discrepancies.
Data extraction	Additional SLR document provided	**Appropriate** Data from the final set of included studies were extracted into a Microsoft Excel data extraction sheet. Relevant data from each study were extracted by two independent reviewers and any discrepancies were resolved by a third reviewer.
Tool for quality assessment of included study or studies	Appendix D.2, Table 8 of the CS	**Some concerns** Quality assessments for ALINA and all other trials identified in the SLR were completed using the seven-domain Cochrane tool for assessing risk of bias.[55] Free-text justifications were not provided for the quality assessment of ALINA, making it difficult to assess the appropriateness of the judgements. The EAG performed its own assessment of risk of bias in ALINA in Section 3.2.

Abbreviations: CS, company submission; EAG, External Assessment Group; NICE, National Institute for Health and Care Excellence; NSCLC, non-small cell lung cancer; SLR, systematic literature review

After the final SLR update in September 2023, a total of 9,022 records were identified through data base searching. After removal of 1,498 duplicates, 7,353 records were excluded at title and abstract review. One hundred and seventy-one records entered full text review, along with 51 records identified through conference and bibliography searching. Of these, 92 records were excluded, leaving 130 records corresponding to 66 primary studies included in the SLR. Of these:

- No studies included an alectinib arm;
- 14 studies compared adjuvant chemotherapy to no intervention or placebo only;
- 27 studies included head-to-head comparisons of adjuvant chemotherapy;
- 20 studies included comparisons between immunotherapy (6), tyrosine kinase inhibitors (13), an interleukin-1 beta inhibitor (1) and either adjuvant chemotherapy or observation; and
- Five studies compared postoperative radiotherapy to adjuvant chemotherapy or observation.

As discussed in Section 2.3.3, the company made an assumption of equivalence in terms of clinical efficacy between active monitoring and adjuvant chemotherapy in order to include a comparison against active monitoring in the appraisal. This was performed by the company as it highlighted the lack of available evidence for active monitoring in this area. In response to clarification question (CQ) A14, the company explained that a formal feasibility assessment was not performed for active monitoring studies in this setting, with the rationale being that experts considered it relevant for only 10% of the population and the approach being a conservative one.

While it is possible that some studies comparing adjuvant chemotherapy to active monitoring may be available that could have been used in an indirect comparison against alectinib, the EAG agrees that the approach used by the company is conservative based on feedback from the EAG's clinical experts (note that the EAG prefers the scenario with adverse events (AEs) of chemotherapy excluded in response to CQ A13 but a correction to the implementation of this was required by the EAG; see Sections 4.2.3 and 6.2), and notes that any indirect comparison would be associated with its own limitations. Therefore, the EAG is satisfied with the approach to this comparison and prefers results from the EAG scenario analysis in Section 6.2.

3.2 Critique of ALINA

One RCT (ALINA, NCT03456076) comparing adjuvant alectinib with adjuvant chemotherapy in patients with completely resected stage IB (tumours ≥4 cm) to stage IIIA ALK-positive (ALK+) NSCLC (based on the 7th edition of the Union for International Cancer Control [UICC]/American Joint Committee on Cancer [AJCC] staging system) is the focus of this submission.[37] This study is an open-label, phase III RCT with multiple centres globally (113 centres in 26 countries worldwide, including three UK centres). The company included its own risk of bias assessment for this study in Table 8 of the CS, with its conclusion being that ALINA has a low risk of bias. The EAG has provided its own risk of bias assessment in Table 9 below.

The EAG considers the main concern to be the open-label nature of the trial; while this may not be an issue for outcomes that are considered largely objective, it may be an issue for the investigator-assessed version of the disease-free survival (DFS) analysis and the central nervous system (CNS) DFS outcome given there are elements of these assessments that will have been at least partially subjective. While blinded independent central review (BICR) versions of these analyses would be

associated with reduced bias, the EAG acknowledges that the analysis based on the most thorough assessment is likely to be more informative and prefers the use of investigator-assessed DFS in its base case (see Section 2.3.4). This is unlikely to be an issue for overall survival (OS) but a lack of blinding could have an impact on HRQoL outcomes and any AEs that are at least partially subjective. For this reason, the EAG does not agree with the company's conclusion that there is a low risk of bias associated with ALINA.

As discussed in Sections 2.3.3 and 3.1, while a comparison against active monitoring was included as a scenario in this appraisal, this was performed using assumptions of equivalence to adjuvant chemotherapy in terms of effectiveness rather than being informed by any specific studies, an approach which the EAG considers to be reasonable (however, a correction in the implementation of this in the economic model was required by the EAG as described in Section 4.2.3).

Table 9. EAG's summary of the design, conduct and analysis of ALINA

Aspect of trial design or conduct	Source where information is reported	EAG's critique
Randomisation	Section B.2.3.1 of CS	**Appropriate** Randomised 1:1 to receive adjuvant alectinib or adjuvant chemotherapy using an interactive voice or web-based response system. Randomisation was performed centrally and was stratified by: • Extent of disease (stage IB [tumours ≥4 cm] vs Stage II vs Stage IIIA); and • Race (Asian vs non-Asian).
Concealment of	Section B.2.	**Appropriate** An interactive third-party system was used for randomisation. While there is not a clear statement to support this, this means it is likely that the randomised allocation sequence was concealed from study investigators/recruiters when deciding if patients met eligibility criteria for the trial. If this

treatment allocation	3.1 of CS	concealment was not in place, there is a risk of selection bias in terms of which patients are ultimately included in the trial. The company's critique in Table 8 of the CS also suggests that allocation concealment was achieved but no details of this are provided.
Eligibility criteria	Section B.2.3.1 and of the CS; Section 3.3.1 of the CSR; ALINA protocol	**Appropriate** The EAG's clinical experts highlighted that some of the groups excluded from the ALINA trial would not be excluded from adjuvant treatment in UK clinical practice. The EAG considers that most of these exclusions are not uncommon for clinical trials and has no major concerns about them. For others, including those with N3 disease and those with N2 disease thought to be suitable for postoperative radiotherapy, the EAG notes that this likely applied to very few patients and should not impact the outcomes of the trial (see Section 2.3.1) The trial population is narrower than the NICE final scope but is in line with the marketing authorisation for alectinib in this indication (see Section 2.3.1).
Blinding	Section 3.4.2 of the CSR	**Risk of bias due to open-label nature** Study is open-label with patients and investigators not being blinded to treatment assignment. This is likely to introduce bias that would not be present in a blinded study. Outcome assessors did not appear to be blinded to treatment assignment either in the primary analyses. There was a larger difference than expected by the EAG between the investigator-assessed DFS outcome and a version based on BICR particularly for the number of recurrences in the chemotherapy group (see Section 2.3.4); while the EAG considers this may largely be explained by the difference in information available to assessors in the two analyses (investigator-assessed was based on more information), it is possible that the investigator-assessed analysis is associated with some bias given there are some subjective elements involved. However, the EAG's preference is for the analysis based on investigator assessment given it is based on a

		larger amount of information (see Section 2.3.4). There may also be some bias associated with the CNS DFS outcome given this was also based on investigator assessment. The concern in terms of bias introduced due to a lack of blinding is also likely to apply to HRQoL outcomes and adverse events where there is a degree of subjectivity involved. However, it is likely to be less of a concern for completely objective outcomes such as OS.
Baseline characteristics	Section B.2.3.2 of the CS	**Some minor imbalances between arms and some discrepancies compared to the UK population but no major concerns** Baseline characteristics for adjuvant alectinib and adjuvant chemotherapy groups within ALINA are fairly well balanced overall, with the following being more imbalanced: • Slightly more patients <65 years in the alectinib group (79.2% vs 73.2%); • More patients with stage IB disease in the alectinib group based on the eCRF data ([redacted]); • More female patients in the alectinib group (57.5% vs 46.5%); • More patients that had never smoked in the alectinib group (64.6% vs 55.1%). While this has the potential to introduce bias, the EAG considers the risk of this overall to be low given some factors are not considered to be prognostic, with others potentially associated with a small risk of bias in opposing directions: • Feedback from its clinical experts was that sex and smoking history are not considered to be major prognostic factors; • For the difference in terms of disease stage, it is possible that slight bias in favour of alectinib is introduced based on this imbalance given a higher stage is associated with worse prognosis, but the EAG considers the differences between arms for other stages to be relatively small. • For age, one clinical expert mentioned that a younger age may be indicative of a more aggressive cancer (biasing against alectinib) but that a higher age may also mean a higher risk of death due to comorbidities (biasing in favour of alectinib). Given there are no major imbalances reported for disease-related characteristics to support more aggressive cancer in the alectinib group, the EAG considers that overall bias may favour of alectinib given the higher risk of comorbidities in older age groups. However, the EAG considers this risk of bias to be small and that age alone is unlikely to be a major driver of outcomes. Some concerns about the applicability of the trial population to the UK population are also described in Section 2.3.1 in terms of the proportion of Asian patients included in the trial; the EAG does not consider the increased proportion of Asian patients compared to UK clinical practice to be a major concern.
Dropouts	Figure 3 of the CS	**Some differences between groups but no major concerns** The EAG notes that there is a slight difference in the proportion of patients that discontinued treatment in the trial, with it being [redacted] In terms of study discontinuation, this was [redacted]), with this mostly explained by a

		[redacted] There were also [redacted] The EAG does not consider this to be a major issue given the i[redacted] may not necessarily be related to disease recurrence or be an indicator of future disease recurrence. Even if it were to be related, any bias introduced would likely favour [redacted] would have been censored in the analysis of DFS at some point for this reason.
Statistical analysis		
Sample size and power	Section B.2.4.2 of the CS; ALINA protocol.	**No concerns** Approximately 255 patients were expected to be randomised into ALINA, with 257 ultimately randomised to treatment. Patients with stage IB disease were to be capped at 25% and the aim was for a minimum of 191 patients with stage II to IIIA disease to be included (this was achieved, with 231 patients within these stages included). The sample size and number of events required to demonstrate efficacy with regards to the primary efficacy endpoint (DFS primary analysis) were based on: • Overall two-sided significance level of 0.05 in the stage II to IIIA subpopulation and the ITT population; • 80% power to detect a HR of 0.55 in the stage II to IIIA subpopulation or a HR of 0.58 in the ITT population for alectinib vs chemotherapy; • One interim analysis of DFS when ~67% of the total DFS events have occurred (~59 DFS events for the stage II to IIIA subpopulation, ~[redacted] for the ITT population), with use of Lan-DeMets approximation to the O-Brien-Fleming boundaries. Based on this, the primary DFS analysis was planned to be conducted after ~89 DFS events occurred in the stage II to IIIA subpopulation. DFS would only be tested in the ITT population if a significant result was observed for the subpopulation (for the interim as well as primary analysis).
Analysis for estimate of effect	Sections B.2.6 and B.2.10 of the CS	**Appropriate** Results within the ITT population have been provided for all efficacy outcomes, with adverse events assessed in the safety population.
Handling of mis	Section 5.1.	**Appropriate** There does not appear to have been any imputation performed and patients with missing disease assessments were censored at the time of their last visit. Missing data is described in the CSR as being minimal. Various sensitivity analyses employing alternative censoring rules were performed for the DFS outcome to assess the impact of missing disease assessments, stratification errors,

sing data	2.3 of the CSR; ALINA protocol	the COVID-19 pandemic and the Russia-Ukraine conflict, all of which showed similar results to the main analysis for the ITT population.
Outcome assessment	Sections B.2.6 and B.2.10 of the CS; ALINA protocol	**Appropriate** The EAG considers the outcomes assessed to be appropriate and cover those in the NICE final scope and to have used appropriate methods/questionnaires. The primary efficacy outcome was DFS as per investigator assessment, with OS and CNS DFS being notable secondary outcomes, alongside HRQoL outcomes and adverse events. All outcomes collected in the trial appear to have been reported either in the CS or the CSR, or provided by the company when requested by the EAG (for EQ-5D results).

Abbreviations: BICR, blinded independent central review; CNS, central nervous system; CS, company submission; CSR, clinical study report; DFS, disease-free survival; EAG, External Assessment Group; HR, hazard ratio; HRQoL, health-related quality of life; ITT, intention to treat; NICE, National Institute for Health and Care Excellence; OS, overall survival.

3.3 Critique of the clinical effectiveness analysis and interpretation

The EAG presents results for the key outcomes from ALINA in the sections that follow. Of the efficacy outcomes, DFS is the only one to be used in the economic model but results for OS and CNS DFS are also presented given they are important outcomes based on the EAG's clinical expert

feedback. Results for EuroQol Group 5-Dimension Questionnaire (EQ-5D) are also briefly discussed given these results were mapped for inclusion in the economic model and AEs are also covered, with those included in the economic model highlighted. Issues related to the clinical effectiveness as implemented in the economic model are discussed in Section 4.2.5.

The EAG notes that at the June 2023 data-cut, 20.3% of alectinib patients had treatment that was ongoing, which was not the case for any chemotherapy patients; this is because alectinib could be used up to 2 years and chemotherapy for 4 cycles. The median duration of exposure to treatment was 23.9 months for alectinib and 2.1 months for chemotherapy. Some patients received alectinib up to [redacted] Table 19 of the CS); the EAG is unsure as to why this may be the case but considers it possible that it is related to AEs that required dose interruption (27.3% of alectinib patients were said to have required treatment interruption in Section B.2.10.7 of the CS) given the treatment duration is calculated as the date of the last study drug administration minus the date of the first study drug administration plus one day (Table 19 of the CS). The EAG is not concerned about the proportion of patients with ongoing alectinib treatment at this data-cut because:

- There is no reason to believe that those with ongoing treatment are different in terms of characteristics (and risk of recurrence) to those that have completed treatment;
- The company's response to CQ A2 indicates that [redacted] recurrences in the alectinib group occurred in patients that had completed 24 months of treatment, meaning it is unlikely that completion of treatment in these patients would lead to a large change in terms of DFS;
- The mean and median treatment duration were close to 24 months ([redacted] and 23.9 months, respectively) and the maximum duration of treatment was [redacted] (Table 19 of the CS), which the EAG considers may be related to dose interruptions required due to AEs in some patients as explained in the preceding paragraph. Overall, [redacted] of the alectinib treatment group had a treatment duration that was >24 months.

In response to CQ A4, the company confirmed that [redacted] patients in the alectinib arm had a subsequent anti-cancer treatment without a recurrence having occurred. The treatments were [redacted] and details on the rationale for using an additional anti-cancer treatment in the absence of recurrence for each patient were not available. The company considers this would have minimal impact on the results of ALINA given patients were in the disease-free state before receiving these

additional treatments and because [redacted] patients were affected. Most of the EAG's clinical experts and peer reviewers considered that the use of a subsequent anti-cancer treatment before recurrence would not be considered in UK clinical practice; however, the EAG agrees that any impact on the results of ALINA is likely to be small.

3.3.1 Disease-free survival

The primary outcome of the ALINA trial was DFS, defined as being free from disease recurrence and death. Data for this outcome from ALINA were used in the economic model (with extrapolations and adjustments performed) to inform transitions from the disease-free state in the model (see Section 4.2.5). The primary analysis was based on investigator assessment but a BICR version was also provided as an appendix to the CSR. As detailed in Section 2.3.4, the EAG considers the investigator-assessed analysis to be most appropriate given it is based on more information than the BICR analysis but highlights that there is a potential risk of bias given the open-label nature of the trial (see Section 3.2). The company provided a scenario analysis using the BICR analysis as requested as part of CQ A1 (see Section 6.2); this scenario increases the corrected company base case ICER by [redacted].

The EAG focuses on the results of the intention to treat (ITT) population and presents the results of the investigator-assessed and BICR analyses in Table 10 below. Both analyses are consistent with there being a large benefit of alectinib compared to chemotherapy as an adjuvant treatment, with 95% confidence intervals (CIs) for both analyses being consistent with this conclusion suggesting statistically significant differences. Kaplan-Meier (KM) curves for these two analyses are presented in Figure 2 and Figure 3.

However, while the conclusions of the two analyses may be the same, the EAG notes that the number of recurrence events in the chemotherapy arm is reduced by [redacted] events in the BICR analysis, a larger difference than anticipated by the EAG. Furthermore, in the CSR appendix provided that details the BICR analysis, the company describes a concordance rate between analyses of [redacted] for alectinib and [redacted] for chemotherapy in the ITT population and the 2- and 3-year DFS rates for chemotherapy are impacted slightly with it being higher in the BICR analysis ([redacted] at for 2 years, [redacted] for 3 years). Slight differences can also be seen between the KM curves as shown in Figure 2 and Figure 3. Based on this information, the EAG requested that the impact of this be explored in the economic model as part of CQ A1. As discussed in Section 2.3.4, the EAG's preference is for the investigator-assessed analysis given it is based on the largest amount of

information but notes that some bias may be associated with this outcome given the open-label nature of the ALINA trial (see Section 3.2). The results of the scenario analysis using BICR data when applied to the company's corrected base case is presented in Section 6.2.

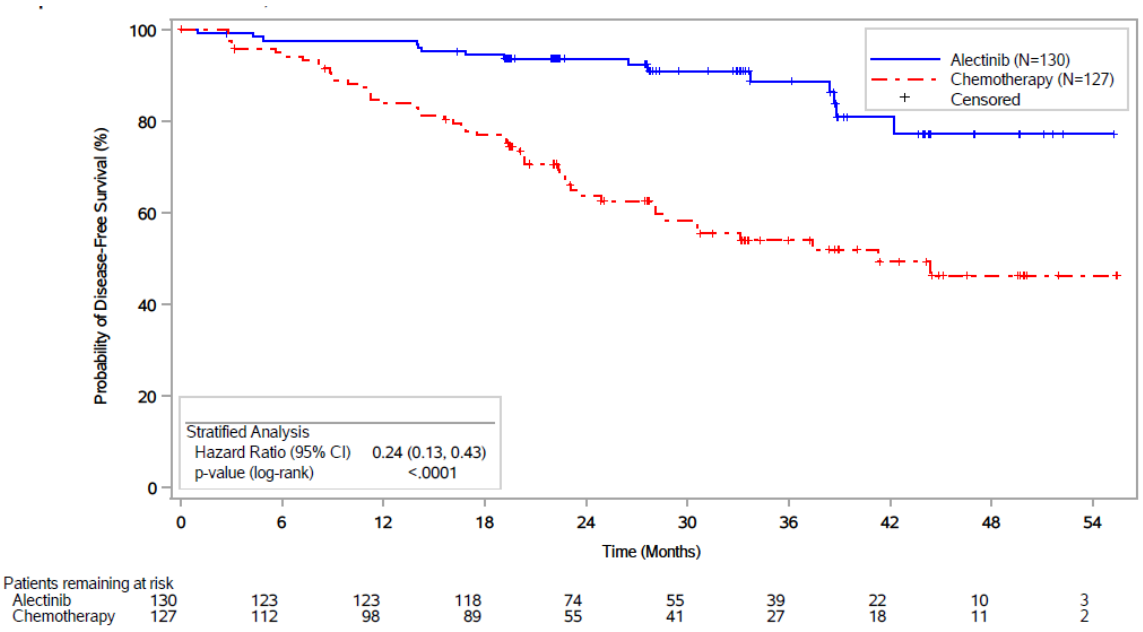
Results for subgroup analyses included in ALINA for the DFS outcome (per investigator assessment) are reported in Section 3.3.5 below.

Table 10. Investigator-assessed and BICR analyses of DFS in the ITT ALINA population – 26 June 2023 data-cut

Analysis	Alectinib (N=130)	Chemotherapy (N=127)
Investigator-assessed		
Patients with event, n (%)	15 (11.5%)	50 (39.4%)
Median (95% CI) DFS, months	NE	41.3 (28.5 to NE)
Stratified HR (95% CI)	0.24 (0.13 to 0.43)	
p-value	<0.0001	
BICR		
Patients with event, n (%)	[redacted]	[redacted]
Median (95% CI) DFS, months	[redacted]	[redacted]
Stratified HR (95% CI)	[redacted]	
p-value	[redacted]	

Abbreviations: BICR, blinded independent central review; CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; ITT, intention to treat; NE, not estimable.

Figure 2. KM plot of DFS in ALINA ITT population – investigator-assessed – reproduced from Figure 5 of the CS



Abbreviations: CI, confidence interval; CS, company submission; DFS, disease-free survival; ITT, intention to treat; KM, Kaplan-Meier.

Figure 3. KM plot of DFS in ALINA ITT population – BICR analysis – reproduced from Figure 1 in the response to CQ A1

Abbreviations: BICR, blinded independent central review; CI, confidence interval; DFS, disease-free survival; ITT, intention to treat; KM, Kaplan-Meier.

3.3.2 Other survival outcomes

OS and CNS DFS are other survival outcomes also reported in ALINA, although these were not utilised in the model. OS is incorporated into the economic model using alternative methods given the data from OS was not considered to be mature enough (see Section 4.2.5). Despite being described as an important outcome for ALK+ NSCLC patients in the CS and highlighted by the EAG's clinical experts as an important outcome, this outcome was not explicitly included in the economic model.

Results for these two outcomes are presented in Table 11, Figure 4 and Figure 5 below; results indicate very similar event rates between the two groups for OS, with a difference of only two events, but a statistically significant benefit of alectinib in terms of CNS DFS. Equivalent KM plots are presented in Figure 4 and Figure 5. As noted in Section 2.3.4, the data currently available for OS are very immature and the EAG does not consider it possible to draw firm conclusions based on the current data. This is considered to be a limitation of this appraisal given OS is usually a key outcome for consideration in oncology appraisals and the EAG has included this as a key issue for consideration in decision-making (Key Issue 1; Table 2).

Given the observed benefit for alectinib in ALINA for CNS DFS, the EAG is surprised that it has not been considered in the economic model and considers it may be a potentially uncaptured benefit of alectinib (see Section 4.2.1). However, the EAG notes that the CNS DFS outcome may be associated with some bias as highlighted for the primary DFS analysis given it is based on investigator assessment (see Section 2.3.4 and 3.3.1).

Table 11. OS and CNS DFS (investigator-assessed) in the ITT ALINA population – 26 June 2023 data-cut

Analysis	Alectinib (N=130)	Chemotherapy (N=127)
OS		
Patients with event, n (%)	2 (1.5%)	4 (3.1%)
Median (95% CI) DFS, months	[redacted]	[redacted]
Stratified HR (95% CI)	[redacted]	
p-value	[redacted]	
CNS DFS		
Patients with event, n (%)	5 (3.8%)	18 (14.2%)
CNS disease recurrence, n	4	14
Death, n	1	4
Median (95% CI) DFS, months	[redacted]	[redacted]
Stratified HR (95% CI)	0.22 (0.08 to 0.58)	
p-value	[redacted]	

Abbreviations: CI, confidence interval; CNS, central nervous system; DFS, disease-free survival; HR, hazard ratio; ITT, intention to treat; NE, not estimable; OS, overall survival.

Figure 4. KM plot of OS in ALINA ITT population – reproduced from Figure 6 of the CS

Abbreviations: CI, confidence interval; CS, company submission; ITT, intention to treat; KM, Kaplan-Meier; OS, overall survival.

Figure 5. KM plot of CNS DFS in ALINA ITT population – reproduced from Figure 7 of the CS

Abbreviations: CI, confidence interval; CNS, central nervous system; CS, company submission; ITT, intention to treat; KM, Kaplan-Meier.

3.3.3 Health-related quality of life

HRQoL was captured in ALINA using the Short-Form 36-Item Health Survey version 2 (SF-36v2) and the EQ-5D-5L questionnaire. The latter was mapped to EQ-5D-3L to obtain utility values for use in the economic model (see Section 4.2.6). For both, higher scores indicate a better quality of life. The EAG has not discussed these results in detail but notes that results from ALINA can be found in Section B.2.6.3.3 of the CS and in response to CQ A9.

In summary, at week 12, SF-36 results demonstrate that scores indicated better quality of life for alectinib across most domains or scores were otherwise similar. When compared to baseline, most domains showed some improvement at week 12 for alectinib while there was limited change or slight worsening in the chemotherapy group. Any improvements observed at week 12 for alectinib were generally maintained or improved upon slightly by the 96-week follow-up. However, at the latest follow-up for the chemotherapy arm, scores generally improved compared to week 12, which may not be unexpected given the toxicity known to be associated with chemotherapy.

For EQ-5D-5L, there was a minimal impact observed at week 12 for both treatment groups in terms of utility and visual analogue scale (VAS) scores; scores remained almost identical to baseline in the alectinib group while very slight changes in the chemotherapy group were observed (slight worsening in utility score and slight improve based on VAS scores). By week 96 or follow-up visit 7, scores in both groups had improved slightly compared to week 12 (CQ A9).

3.3.4 Safety

The company provides an overview of the AEs associated with alectinib and chemotherapy treatment in ALINA in Section B.2.10 of the CS. In ALINA, recorded AEs were mapped to the Medical Dictionary for Regulatory Activities (MedDRA) 26.0 thesaurus terms, and severity was graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Due to the differences in treatment duration between alectinib and chemotherapy, and because AEs were only collected up until 28 days after the last dose of alectinib or the end of the last chemotherapy cycle, the median duration of safety follow-up was considerably longer for the alectinib arm (median duration of safety follow up: [redacted]) than for chemotherapy arm (median duration of safety follow up: [redacted]). The EAG does not consider this difference to be a major issue given feedback from its clinical experts that most AEs associated with alectinib would

be expected to develop within a few months of starting treatment, with there being potential for toxicity to build with chemotherapy throughout cycles. An overview of the total AEs reported in ALINA is presented in Table 12.

Table 12. Overview of adverse events (safety-evaluable patients) – reproduced from Table 18 of the CS.

	Alectinib (N=128)	Chemotherapy (N=120)
All AEs		
Total number of patients with at least one AE	126 (98.4%)	112 (93.3%)
Total number of AEs	[redacted]	[redacted]
Total number of patients with at least one		
AE with fatal outcome (Grade 5)	0	0
Grade 3-5 AE	38 (29.7%)	37 (30.8%)
Serious AE	17 (13.3%)	10 (8.3%)
Serious AE leading to withdrawal from treatment	1 (0.8%)	4 (3.3%)
Serious AE leading to dose modification/interruption	7 (5.5%)	4 (3.3%)
Related serious AE	2 (1.6%)	8 (6.7%)
AE leading to withdrawal from treatment	7 (5.5%)	15 (12.5%)
AE leading to dose modification/interruption	[redacted]	[redacted]
Related AE	120 (93.8%)	107 (89.2%)
Related AE leading to withdrawal from treatment	[redacted]	[redacted]
Related AE leading to dose modification/interruption	[redacted]	[redacted]
Selected AEs*		
Total number of patients with at least one selected AE		
Any grade	[redacted]	[redacted]
Grade 3-5 AE	[redacted]	[redacted]
Serious AE	[redacted]	[redacted]
Leading to discontinuation	[redacted]	[redacted]
Leading to dose modification	[redacted]	[redacted]

Investigator text for AEs encoded using MedDRA version 26.0. Percentages are based on N in the column headings.

Multiple occurrences of the same AE in one individual are counted only once except for "Total number of AEs" row in which multiple occurrences of the same AE are counted separately.

Includes AEs with onset from first dose of study drug.

*Selected AEs include: Gastrointestinal AEs, Haematologic Abnormalities, Muscular AEs/CPK increases, Hepatocellular or cholestatic damage AEs, Abnormal liver function tests, Dysgeusia, Oedema, Bradycardia, Vision Disorders, and Interstitial Lung Disease.

[redacted]

Abbreviations: AE, adverse event; CS, company submission; MedDRA, Medical Dictionary for Regulatory Activities

The total number of patients with at least one AE was higher in the alectinib arm (126/128, 98.4%) than the chemotherapy arm (112/120, 93.3%), and the most common AEs differed between alectinib and chemotherapy. In the alectinib arm, the three most common AEs were increased blood creatine phosphokinase (43.0%), constipation (42.2%) and increased aspartate aminotransferase (41.4%), whereas in the chemotherapy arm, the three most common AEs were nausea (72.5%), decreased appetite (29.2%) and anaemia (25.8%). A full summary of common AEs reported in ≥10% of patients in either treatment arm is reproduced in Table 13. The EAG's clinical experts considered alectinib to be a well-tolerated treatment in their experience and noted that many of the AEs associated with it can be managed using dose interruptions or modifications, which the EAG considers is supported by the data from ALINA.

Table 13. Summary of common adverse events (≥10% incidence in either treatment arm) – reproduced from Table 21 of the CS.

MedDRA System Organ Class MedDRA Preferred Term	Alectinib (N=128)	Chemotherapy (N=120)
Gastrointestinal disorders		
Nausea	10 (7.8%)	87 (72.5%)
Constipation	54 (42.2%)	30 (25.0%)
Vomiting	9 (7.0%)	30 (25.0%)
Diarrhoea	16 (12.5%)	10 (8.3%)
Investigations		
Aspartate aminotransferase increased	53 (41.4%)	6 (5.0%)
Blood creatine phosphokinase increased	55 (43.0%)	1 (0.8%)
Alanine aminotransferase increased	43 (33.6%)	11 (9.2%)
Blood bilirubin increased	43 (33.6%)	1 (0.8%)
Blood alkaline phosphatase increased	32 (25.0%)	4 (3.3%)
Blood creatinine increased	19 (14.8%)	6 (5.0%)
White blood cell count decreased	2 (1.6%)	23 (19.2%)
Neutrophil count decreased	3 (2.3%)	21 (17.5%)
Weight increased	17 (13.3%)	1 (0.8%)
General disorders and administration site conditions		
Fatigue	18 (14.1%)	16 (13.3%)
Asthenia	14 (10.9%)	19 (15.8%)
Malaise	6 (4.7%)	16 (13.3%)
Oedema peripheral	13 (10.2%)	1 (0.8%)
Infections and infestations		

COVID-19	37 (28.9%)	1 (0.8%)
Metabolism and nutrition disorders		
Decreased appetite	7 (5.5%)	35 (29.2%)
Blood and lymphatic system disorders		
Anaemia	30 (23.4%)	31 (25.8%)
Neutropenia	2 (1.6%)	19 (15.8%)
Musculoskeletal and connective tissue disorders		
Myalgia	36 (28.1%)	2 (1.7%)
Skin and subcutaneous tissue disorders		
Rash	18 (14.1%)	7 (5.8%)
Nervous system disorders		
Headache	14 (10.9%)	8 (6.7%)
Dysgeusia	13 (10.2%)	3 (2.5%)
Respiratory, thoracic and mediastinal disorders		
Cough	19 (14.8%)	4 (3.3%)
Dyspnoea	13 (10.2%)	3 (2.5%)
Injury, poisoning and procedural complications		
Product dose omission issue	[redacted]	[redacted]
Product dose omission in error	[redacted]	[redacted]

Investigator text for AEs encoded using MedDRA version 26.0. Percentages are based on N in the column headings.

For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. Includes AEs with onset from first dose of study drug.

Abbreviations: AE, adverse event; CS, company submission; MedDRA, Medical Dictionary for Regulatory Activities

Grade 3 to 5 AEs related to study treatment were considered for inclusion in the cost effectiveness model, and the number of patients experiencing grade 3 to 5 AEs was similar between the alectinib arm, n=38 (29.7%), and the chemotherapy arm, n=37 (30.8%). Only Grade 3 to 5 AEs for which there was a difference in incidence rate of at least 2% between the treatment arms were ultimately included in the cost effectiveness model. A breakdown of all Grade 3 to 5 AEs related to study treatment, and those included in the cost effectiveness model, is presented in Table 14.

The EAG notes that most of the AEs highlighted under special warnings/precautions for use in the Summary of Product Characteristics (SmPC) for alectinib did not meet the criteria required for inclusion in the economic model (grade 3-5 events related to study treatment with a difference of at least 2% between treatment arms) as there were very few treatment-related events observed,[36] including interstitial lung disease/pneumonitis, elevations in alanine aminotransferase, aspartate aminotransferase and bilirubin, severe myalgia, bradycardia, haemolytic anaemia, gastrointestinal

perforation and photosensitivity. The only exception was increased blood creatine phosphokinase which has been included in the model as outlined in Table 14 below.

Table 14. Occurrence of Grade 3 to 5 adverse events related to study treatment during adjuvant treatment (ALINA; safety-evaluable patients; CCOD 26/Jun/23) – adapted from Table 32 of the CS and page 239 of the CSR: Grade 3-5 Adverse Events Related to Study Treatment, Safety-Evaluable Patients

Adverse events	Alectinib (N = 128)	Chemotherapy (N = 120)
AEs included in CE model: Grade 3 to 5 treatment-related AEs with a difference in incidence rate of at least 2% between treatment arms		
Neutrophil count decreased	0 (0)	12 (10)
Blood creatine phosphokinase increased	8 (6.25)	0 (0)
White blood cell count decreased	0 (0)	4 (3.33)
Neutropenia	0 (0)	10 (8.33)
Nausea	0 (0)	5 (4.17)
Asthenia	0 (0)	3 (2.5)
AEs not included in CE model		
Alanine aminotransferase increased	2 (1.56)	0 (0)
Blood bilirubin increased	2 (1.56)	0 (0)
Aspartate aminotransferase increased	1 (0.78)	0 (0)
Blood creatine increased	1 (0.78)	0 (0)
Liver function test increased	1 (0.78)	0 (0)
Anaemia	0 (0)	1 (0.83)
Febrile neutropenia	0 (0)	1 (0.83)
Leukopenia	0 (0)	1 (0.83)
Constipation	1 (0.78)	1 (0.83)
Vomiting	0 (0)	2 (1.67)
Abdominal pain	0 (0)	1 (0.83)
Diarrhoea	1 (0.78)	0 (0)
Epigastric discomfort	0 (0)	1 (0.83)
Regurgitation	0 (0)	1 (0.83)
Stomatitis	1 (0.78)	0 (0)
Fatigue	1 (0.78)	2 (1.67)
Decreased appetite	0 (0)	1 (0.83)
Hypertriglyceridaemia	1 (0.78)	0 (0)
Type 2 diabetes mellitus	0 (0)	1 (0.83)

Appendicitis	1 (0.78)	0 (0)
Urinary tract infection	0 (0)	1 (0.83)
Cough	1 (0.78)	0 (0)
Pneumonitis	1 (0.78)	0 (0)
Pulmonary embolism	0 (0)	1 (0.83)
Rash	1 (0.78)	0 (0)
Rash maculo-papular	1 (0.78)	0 (0)
Embolism	0 (0)	1 (0.83)
Lymphoedema	1 (0.78)	0 (0)
Hyperbilirubinaemia	1 (0.78)	0 (0)
Myalgia	1 (0.78)	0 (0)

Investigator text for AEs encoded using MedDRA version 26.0. Grading based on NCI CTCAE 5.0. Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately. Includes AEs with onset from first dose of study drug.

Abbreviations: AE, adverse event; CCOD, clinical cut-off data; CE, cost-effectiveness; CS, company submission; CSR, clinical study report; CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regularity Activities; NIC, National Cancer Institute.

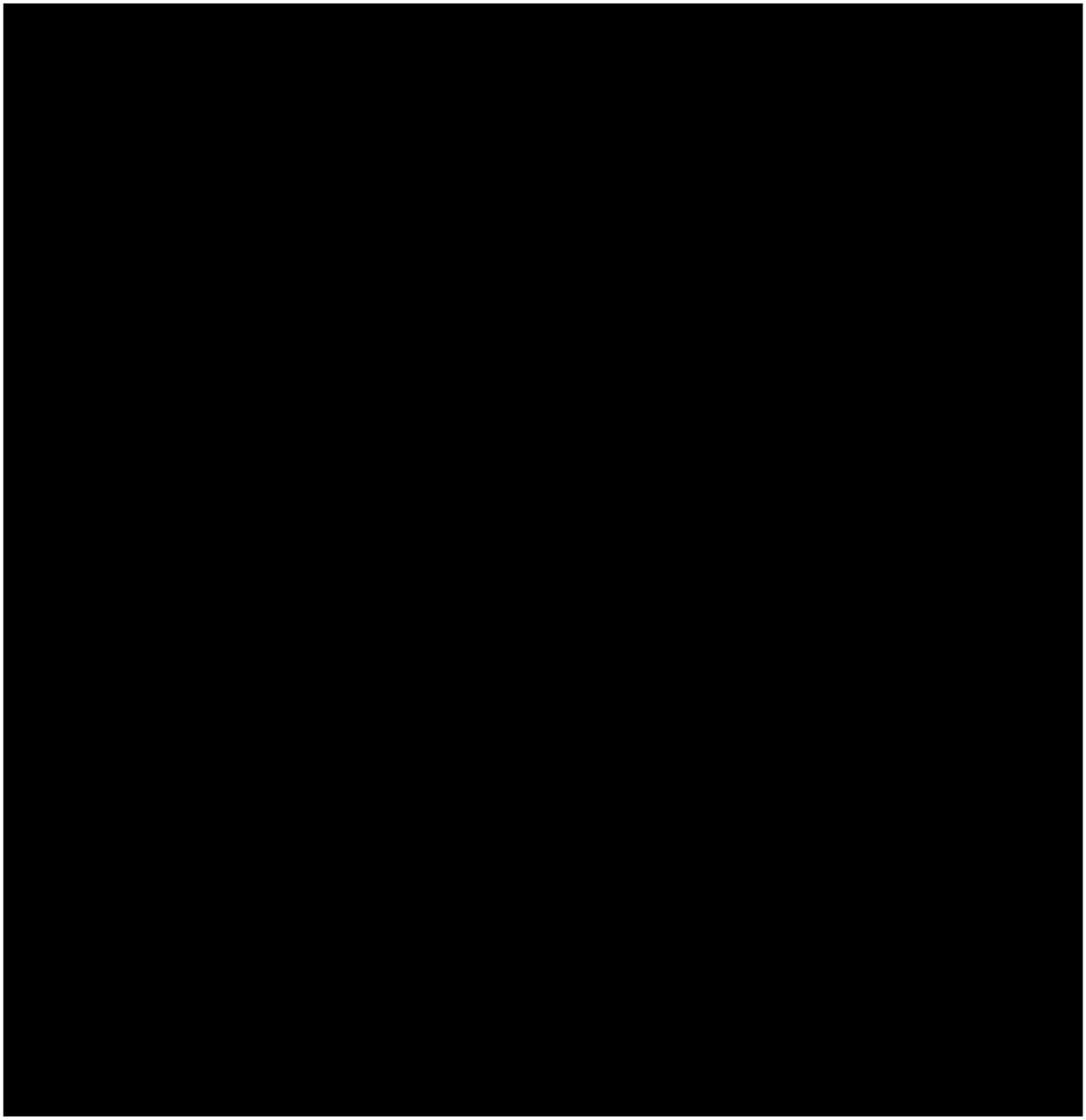
3.3.5 Subgroups

The ALINA trial included various subgroup analyses for the primary DFS analysis (investigator-assessed), including for disease stage and ethnicity outlined in the NICE final scope. These results are presented in Figure 6 below. The results demonstrate that for most subgroups, the relative effect of alectinib vs chemotherapy as an adjuvant treatment does not differ hugely. The EAG considers the most notable difference to be for the Asian vs non-Asian subgroup, with results suggesting less of a benefit for alectinib in the Asian subgroup, although the point estimate and confidence interval was still suggestive of a significant benefit of alectinib. The EAG's clinical experts and peer reviewers were not able to explain this observation and the EAG notes that these subgroup analyses should be interpreted with caution given the trial is not powered to detect differences within these and there is insufficient data to conclude there are differences between any subgroups. As discussed in Sections 2.3.1 and 2.3.5, the EAG considers the focus on the whole ITT population in the economic model to be appropriate.

Other slightly larger differences are noted for Eastern Cooperative Oncology Group (ECOG) score 0 to 1 and regional lymph node stage but the EAG's clinical experts considered there to be no clinical rationale to support a difference across these subgroups or considered the results were not in the

direction that would be anticipated were there to be a difference. Therefore, the EAG considers these are likely to be chance observations.

Figure 6. Subgroup analyses for DFS (investigator-assessed) in the ALINA ITT population – reproduced from Figure 8 of the CS



Abbreviations: AJCC, American Joint Committee on Cancer; CI, confidence interval; CS, company submission; DFS, disease-free survival; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; ITT, intention to treat; IxRS, interactive Voice/web response system; NE, not estimable.

3.4 Conclusions of the clinical effectiveness section

The EAG considers the decision problem addressed by the company to be appropriate, with any differences relative to the National Institute for Health and Care Excellence (NICE) final scope being in line with the marketing authorisation for alectinib in this indication or supported by clinical rationale (see Section 2.3). The SLR performed to identify clinical evidence could have been updated more recently and ALINA was not identified as part of these searches, but the EAG considers it unlikely that any relevant studies have been missed (see Section 3.1).

The EAG considers the ALINA trial to be at some risk of bias given its open-label nature, which will affect outcomes with at least some element of subjectivity, such as investigator-assessed DFS, HRQoL outcomes and some AEs (see Section 3.2). Feedback from the EAG's clinical experts highlighted that the proportion of Asian patients in ALINA may differ compared to the UK population. As outlined in Section 2.3.1, the EAG does not consider this to be a major areas of concern. The impact of mean age has been explored as a scenario in the economic model but the EAG is satisfied that the mean age of the ALINA trial is a reasonable representation of the UK ALK+ population.

The inclusion of a conservative scenario for the comparison against active monitoring where clinical efficacy and follow-up healthcare resource use is assumed to be equivalent to adjuvant chemotherapy and other costs (treatment costs and AE costs) are excluded (as provided in the company's response to CQ A13) is considered to be reasonable; however, a correction to the implementation of this in the economic model was required by the EAG (see Sections 4.2.3 and 6.2). While an alternative would have been to perform an indirect treatment comparison, this would itself be associated with limitations and the EAG is satisfied that the scenario included (as corrected by the EAG) is likely to be conservative (see Sections 2.3.3 and 3.1).

The exclusion of pembrolizumab as a comparator is considered to be reasonable by the EAG, with EAG's clinical experts highlighting that immunotherapy (such as pembrolizumab) would not normally be considered in ALK+ NSCLC patients as adjuvant or first-line treatment. It has also not yet received a recommendation for NICE in any adjuvant NSCLC population (see Section 2.3.3).

The EAG initially had concerns about differences between investigator-assessed DFS and a secondary analysis based on BICR, particularly for the chemotherapy group. However, based on the company's response to CQ A1 the EAG agrees that investigator-assessed DFS is likely to be the most useful

assessment for use in the base case of the economic model given it is based on the most available information, although it should be considered to be at a small risk of bias given the unblinded nature of the ALINA trial (see Sections 2.3.4 , 3.2 and 3.3.1). This has been explored as a scenario in the economic model.

Data for OS from ALINA are very immature, with only 6 events observed across the two arms up to the June 2023 data-cut, meaning these data were not considered suitable for use in the economic model and other approaches were used by the company (see Section 2.3.4, 3.3.2 and 4.2.5). While this is an unresolvable issue currently, the EAG highlights this as a key issue of this appraisal given OS is usually an important component of oncology appraisals and the data here are too immature to draw conclusions from or for use in validating the OS predictions from the economic model (Key Issue 1; Table 2). The EAG's clinical experts noted that while OS data is immature, alectinib has the potential to make a substantial difference to patients in the adjuvant setting based on the results observed for DFS and CNS DFS currently. The EAG considers it plausible that the benefit of alectinib observed for DFS is likely to translate into a benefit in OS but the magnitude of the OS benefit is unpredictable.

Clinical effectiveness results from ALINA show statistically significant benefits of alectinib compared to chemotherapy for DFS and CNS DFS outcomes, with data too immature to draw conclusions for OS (see Sections 3.3.1 and 3.3.2). Some small potential benefits of alectinib on HRQoL were observed for the SF-36 results at week 12 but these were small and very limited differences were observed when EQ-5D-5L results are considered (see Section 3.3.3). Based on the CNS DFS results observed in ALINA and feedback from the EAG's clinical experts, the EAG considers the impact of alectinib on reducing CNS events may be an uncaptured benefit of alectinib in this appraisal given these data are not included in the economic model (see Section 3.3.2).

In terms of safety, more events overall were observed with alectinib but proportions with grade 3 to 5 events were similar. Based on the EAG's clinical experts' experience with alectinib in other indications, it is a well-tolerated treatment that can be managed with dose modifications or interruptions, which appears to be supported by data from ALINA. AEs mentioned in the SmPC for alectinib were reported in the CSR, with very few treatment-related events occurring, with the exception of increased blood creatine phosphokinase which was included in the economic model (see Section 3.3.4).

The EAG is satisfied that focusing on the overall ALINA population in the clinical analysis and in the health economic model is reasonable given most subgroups strategies showed limited differences between subgroups. For one analysis where a slightly larger difference was observed, the observation could not be explained by the EAG's clinical experts and was, therefore, not considered to be a major concern by the EAG (see Section 3.3.5).

4 Cost effectiveness

The company presented a cost-effectiveness analysis of alectinib compared to platinum-based chemotherapy for adjuvant treatment of anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC). Table 15 summarises the deterministic results of the cost-effectiveness model (CEM) using the company's preferred base case, post-clarification. The costs presented here include a [redacted] patient access scheme (PAS) discount for alectinib; results including the PAS for other treatments included in the model as subsequent treatments are given in the confidential appendix.

Table 15. Company's base case results

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Alectinib	[redacted]	12.40	9.90	-	-	-	-
Platinum-based chemotherapy	[redacted]	8.51	6.60	[redacted]	3.89	3.30	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year

4.1 EAG comment on the company's review of cost effectiveness evidence

4.1.1 Systematic reviews previous cost-effectiveness analyses, HRQoL, costs and resource use

The company undertook three systematic literature reviews (SLRs) to identify evidence related to previous cost-effectiveness analyses, health-related quality of life (HRQoL) and cost and resource use for early-stage NSCLC. For all three SLRs, searches were initially run in March 2021, with subsequent updates conducted in July 2022, July 2023 and September 2023. Searches used disease terms for early-stage NSCLC combined with economic and HRQoL search filters. The source of the search filters was unclear; however, the External Assessment Group (EAG) considers the terms used to be comprehensive. A summary of the EAG's critique of the methods implemented by the company to identify relevant evidence is presented in Table 16.

Table 16. EAG's critique of company's systematic literature review for existing cost-effectiveness, HRQoL, resource use and cost evidence

Systematic review step	Section of CS in which methods are reported			EAG assessment of robustness of methods
	Cost effectiveness evidence	HRQoL evidence	Resource use and costs evidence	
Search strategy	Appendix G	Appendix H	Appendix I	**Appropriate** Electronic database searches included: MEDLINE; Embase; Evidence-based medicine (EBM) Reviews; Econlit; Centre for Reviews and Dissemination (CRD) DARE; CRD HTA database and CRD EED. A comprehensive range of conference websites were hand searched for the years 2018-2023. Additional grey literature searches included: HTA and regulatory websites (see section G.2.1, Appendix G of company submission).
Inclusion/ exclusion criteria	Appendix G, Table 37	Appendix H, Table 58	Appendix I, Table 75	**Appropriate.** Date limits were applied only to healthcare cost and resource use studies (2011 to present) to represent the most up-to-date cost data. The EAG considers this appropriate. The EAG notes that studies relating to HRQoL were excluded if they were based on the advanced/metastatic population. While appropriate for the primary population of interest related to adjuvant alectinib treatment, this excluded any studies with utility values for the advanced and metastatic health states used in the model
Screening	Appendix G	Appendix H	Appendix I	**Appropriate**
Data extraction	Appendix G	Appendix H	Appendix I	**Appropriate**
Quality assessment of included studies	Appendix G	Appendix H	Appendix I	**Partly appropriate** The company stated that quality assessment of cost-effectiveness studies was conducted using criteria

				described by NICE for manufacturer submissions. A narrative quality assessment of included studies was provided. A short narrative description of quality assessment of included studies was included for the HRQoL search. Cost and resource use studies are stated to be assessed using a published checklist (Molinier *et al.* 2008),[56] however this is not presented.

Abbreviations: CS, company submission; EAG, External Assessment Group; HRQoL, health related quality of life.

The company's economic evaluation SLR identified 64 studies for inclusion. Of these, 36 were full text publications, 22 abstracts, five health technology appraisal (HTA) submissions and one National Institute for Health and Care Excellence (NICE) guideline. A full description of the included studies is provided in Section G.6.2 of Appendix G of the company submission (CS). Of the five HTA submissions identified only three were discussed, which were previous NICE technology appraisals (TA761 – adjuvant osimertinib,[34] TA823 – atezolizumab,[33] TA876 – nivolumab).[57] The remaining two HTA submissions were the Canadian Drug Agency (CDA-AMC) appraisal for adjuvant osimertinib and Scottish Medicines Consortium (SMC) appraisal for atezolizumab.

The HRQoL SLR included 32 studies, of which 29 were full-text publications and three were conference abstracts. As previously noted, studies focusing on advanced or metastatic NSCLC were excluded. During the economic evaluation SLR, the company also noted the sources used for utility values in the cost-utility analyses extracted and if these were separately identified in the HRQoL SLR.

The cost and resource use SLR identified 133 studies for inclusion. The company then applied additional inclusion criteria of full publications only, priority countries of interest and sample size > 200. This resulted in 55 studies included in the final review. While it is unclear if any studies of relevance may have been excluded due to a smaller sample size, the EAG is satisfied with the approach taken. Only two studies included data on the UK, both of which were part of larger multinational analyses and as such may not be appropriate for use in the current technology appraisal.

While the EAG is mainly satisfied with the SLRs conducted by the company, the EAG considers the latest search undertaken in September 2023 to be at risk of missing recent relevant studies.

4.1.2 *Systematic review of clinical trial evidence for treatment efficacy for locally advanced or metastatic ALK+ NSCLC*

As well as the SLRs described above to identify existing cost-effectiveness evidence described above, the company also conducted reviews to identify efficacy evidence for patients with non-metastatic and metastatic recurrence to characterise downstream disease stages in the CEM. In particular, the company conducted an SLR in September 2023 to identify clinical evidence for locally advanced or metastatic ALK+ NSCLC; this encompassed efficacy, safety, HRQoL, and other patient-reported outcomes (PROs). Notably, this SLR was limited to randomised controlled trials (RCTs). It should also be noted that this SLR was conducted eight months prior to the CS; therefore, it cannot be guaranteed that potentially relevant alternative parameter sources have not been excluded.

Full details of the methodology employed in this SLR are given in the report provided as a supplementary reference; a summary of the EAG's critique of the methodology is given in Table 17.

Table 17. EAG's critique of company's systematic literature review for clinical evidence for locally advanced or metastatic ALK+ NSCLC

Systematic review step	Section of report in which methods are reported	EAG assessment of robustness of methods
Search strategy	3.2	**Appropriate.** Electronic database searches included: MEDLINE; Embase; Cochrane Database of Systematic Reviews (CDSR); and Cochrane Central Register of Controlled Trials (CENTRAL). Trial registries were also searched, including clinicaltrials.gov, EU Clinical Trials Register (EU-CTR) and International Clinical Trials Registry Platform (ICTRP). An appropriate selection of conference websites was hand searched for the years 2021-2023. Biographies of SLRs published in 2021-2023 were also reviewed to ensure all relevant trials were identified.
Inclusion/exclusion criteria	3.3	**Appropriate.** Included studies were limited to locally advanced or metastatic (Stage IIIB or IV) ALK+ NSCLC; studies reporting outcomes for other disease stages or mutation statuses were explicitly excluded. Studies including adjuvant therapies as comparators were also excluded. Study design was confined to primary studies conducted in humans and SLRs. Primary studies were limited to RCTs. Only SLRs from 2018 onwards were considered; SLRs were only noted for the purpose of citation-chasing.
Screening	3.4	**Appropriate.**

Data extraction	3.5	**Appropriate.**
Quality assessment of included studies	3.6, Appendix 7	**Partly appropriate.** Quality assessment was conducted using the NICE guidelines manual quality checklist for RCTs; only limited details of the findings of the quality assessment for included studies were presented.

Abbreviations: ALK+, anaplastic lymphoma kinase positive; EAG, External Assessment Group; NICE, National Institute for Health and Care Excellence; NSCLC, non-small cell lung cancer; RCT, randomised controlled trial; SLR, systematic literature review.

The 17 studies identified for inclusion in the SLR included 14 Phase III RCTs, one Phase II RCT, one Phase I RCT, and one RCT with phase not specified. All trials assessed an ALK inhibitor (ALKi) compared to either another ALKi, the same ALKi with differing dosage, or chemotherapy. Six of the trials were treatment-naïve patients, with the remaining trials allowing patients who had received prior chemotherapy or ALKi treatment. An overview of all included studies is given in Appendix 4 of the SLR report.

The key efficacy outcomes assessed in the SLR included progression-free survival (PFS), available from all 17 studies, and overall survival (OS), reported in 15 of the identified studies. The reported efficacy outcomes included PFS for the ASCEND-4 trial (which compared ceritinib with chemotherapy in the treatment-naïve population), the ALEX trial (which compared alectinib with crizotinib in the treatment-naïve population), the CROWN trial (which compared lorlatinib with crizotinib in the treatment-naïve population) , and the ALTA-1L trial (which compared brigatinib with crizotinib in the ALKi-naïve population), which were all ultimately used to parametrise effectiveness of subsequent treatments in the CEM.[58-61] The reported OS outcomes for the ALUR trial (which compared alectinib with chemotherapy in the ALKi-pretreated population) identified in the SLR were also used in the CEM, although other studies reporting OS either included the same interventions as the ALUR trial, or other interventions which were considered irrelevant for use in the CEM.

The SLR also assessed safety outcomes, including incidence of specific AEs, available for 15 studies, although these were not used in the CEM.

The HRQoL outcomes captured by the SLR included PROs assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 (EORTC QLQ-C30), European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer–Specific Module (EORTC QLQ-LC13), Lung Cancer Symptom Scale (LCSS), and EuroQol Group 5-Dimension Questionnaire (EQ-5D). EQ-5D data were available for six trials identified in the SLRs;

two trials reported EQ-5D-5L outcomes (ASCEND-4 and ASCEND-5), with the remainder reporting only EQ-5D-VAS (visual analogue scale) scores. However, both of these studies only presented improvement in HRQoL for patients receiving ceritinib compared to chemotherapy, which was not relevant for parametrising the CEM.

4.1.3 Targeted review of real-world evidence for clinical burden and treatment patterns in early NSCLC

In order to consider a wider range of evidence sources, the SLR described above was supplemented by an existing targeted literature review (TLR) of real-world evidence of clinical burden and treatment patterns in early NSCLC conducted in April 2021. This TLR was primarily leveraged by the company to inform PFS for patients experiencing locoregional recurrence in the CEM. However, the following areas were also explored:

- The time a patient is disease-free before they can be considered cured;
- Whether long-term survivors have the same risk of dying as the general population;
- Treatment received by patients with locoregional recurrence.

Included studies were limited to prospective and retrospective observational studies conducted in the UK, France, Italy, Spain, Germany, Netherlands, USA, Japan, and South Korea from 2006 onwards.

The EAG acknowledges that this TLR was not intended to be a comprehensive review of relevant literature, and was an existing resource which was drawn on to supplement the SLR described above, rather than an analysis conducted specifically to support this appraisal. However, there are several limitations to the methodology employed, as follows:

- It is possible that potentially relevant studies have been published in the three years since the searches were originally run. The EAG requested that the company rerun the searches during the clarification stage, but the company was unable to do this in the time available.
- The searches conducted were limited to the Medline database, with additional targeted searches in PubMed, as well as conference abstracts from a limited number of conference websites, restricted to the last three editions.
- No details of excluded studies are included, and a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram is not presented.
- No details of the screening or data extraction process are given.

- No quality assessment of included studies has been conducted.

As a result, the TLR cannot be considered a comprehensive review of relevant literature. However, the TLR did note several sources from existing literature which are informative for the economic model:

- 11 studies were identified which reported PFS for patients with locoregional recurrence. The interventions included in the identified studies were radiotherapy, chemotherapy, chemoradiotherapy and stereotactic body radiation therapy (SBRT). No identified studies were specific to the UK. One of the identified studies (Nakamichi *et al.* 2017) was used to parametrise PFS for patients receiving radiotherapy or surgery in the non-metastatic recurrence health state in the CEM.[62]
- 41 studies were identified which reported recurrence-free survival (RFS), survival without development of second primary lung cancer, or disease-free survival (DFS). However, none of the identified studies were specific to the UK context, and the majority reported outcomes for patients who underwent surgery without adjuvant treatment, so none are directly relevant to this appraisal.
- 7 studies were identified which reported conditional relative or relative survival for patients with NSCLC. Once again, no studies specific to the UK context were identified, although one study reported comparative outcomes for the UK and USA. No studies controlled for death due to primary NSCLC, and are therefore not directly relevant to this appraisal.
- 5 studies were identified which reported HRQoL outcomes; one of these studies (Grutters *et al.* 2010) reported EQ-5D outcomes for patients with Stage I, Stage II and Stage III NSCLC, although this was not used in the CEM, since data from the ALINA trial were available.[63]
- 9 studies were identified which reported on treatment received by patients with locoregional recurrence. The identified studies were conducted in Japan, South Korea and USA, and are therefore unlikely to be representative of UK clinical practice.

Although the TLR identified some sources which were used to parametrise the CEM, the EAG notes that due to date and the limitations in methodology described above that the company may not have definitively identified all potentially appropriate data sources for relevant inputs in the CEM. The EAG also notes that the searches for studies reporting PFS and treatment received were confined to locoregional recurrence. Therefore, no searches were carried out by the company to identify real-world evidence, which could be used to inform subsequent treatment efficacy in the

metastatic setting. Furthermore, the company did not conduct any searches to identify studies relevant to treatment in the metastatic setting which were not limited to the ALK+ patient population, although mutation-agnostic studies were used to inform efficacy in the non-metastatic recurrence setting.

The EAG considers that the company's chosen efficacy inputs for subsequent therapies are appropriate in most cases (see Section 4.2.5.3.2 for further details). However, it cannot be certain on the basis of the SLR and TLR described above that all potentially relevant studies have been considered for inclusion.

4.2 Summary and critique of company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 18 summarises the EAG's assessment of the company's economic evaluation against the requirements set out in the NICE reference case checklist for the base-case analysis, with reference to the NICE final scope outlined in Section 2.

Table 18. NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	The company's CEM includes all relevant health effects, with the exception of benefits related to reduced development of CNS metastases for patients treated with adjuvant alectinib. When asked to comment on the exclusion of CNS metastases-related benefits, the company only stated that the approach taken was conservative.
Perspective on costs	NHS and PSS	The company's CEM includes costs from an NHS and PSS perspective.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	The company's CEM presents a cost-utility analysis. A fully incremental analysis is not required since chemotherapy is the only major comparator of interest.
Time horizon	Long enough to reflect all important differences in costs or	The company's CEM includes a 40-year time horizon; the EAG is content that this represents a

	outcomes between the technologies being compared	lifetime horizon in the patient population of interest.
Synthesis of evidence on health effects	Based on systematic review	The company's CEM parametrises efficacy based on the ALINA trial, an SLR of efficacy of interventions in the advanced and metastatic NSCLC setting focusing on RCTs, and a TLR of efficacy of interventions in non-metastatic recurrence focusing on cohort studies.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	The company's CEM expresses health effects in terms of QALYs based on EQ-5D-3L data.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	The company's CEM parametrises utilities based on EQ-5D data based on responses elicited from patients in the ALINA trial.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	The EQ-5D data used in the company's CEM are based on an appropriate UK tariff.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	The company's CEM considers all QALYs to be equal regardless of patient characteristics.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Appropriate sources for costs (including eMIT, BNF, NHS reference costs and PSSRU costs) are used in the company's CEM.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	The company's CEM includes a 3.5% discount rate for both costs and health effects.

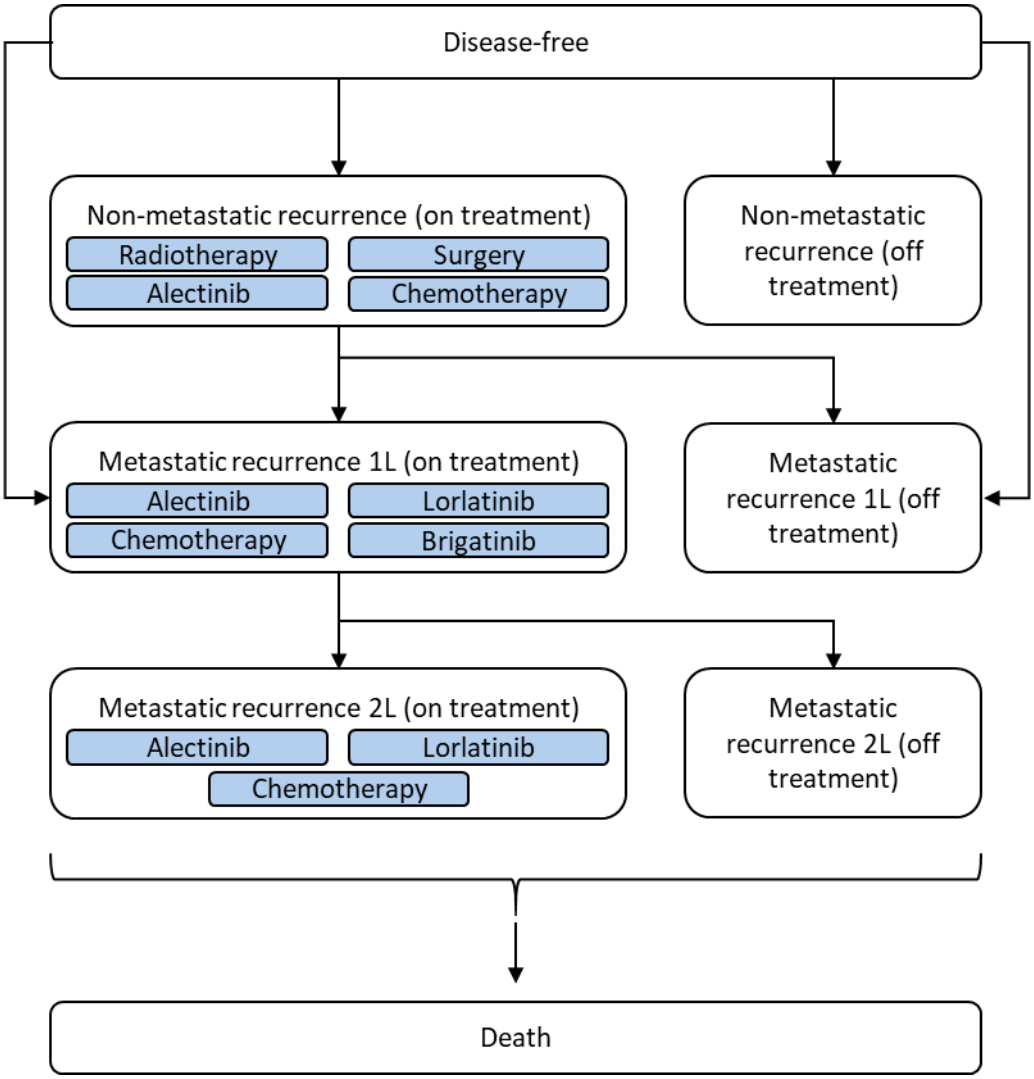
Abbreviations: BNF: British National Formulary; CEM: cost-effectiveness model; CNS: central nervous system; EAG, External Assessment Group; eMIT, electronic market information tool; NHS, national health service; NSCLC, non-small cell lung cancer; PSS, Personal Social Services; PSSRU, Personal Social Services Research Unit; QALY, quality adjusted life year; RCT, randomised controlled trial; SLR, systematic literature review; TLR, targeted literature review.

4.2.2 Modelling approach and model structure

The company's CEM uses a semi-Markov structure (i.e. transition probabilities between health states may vary over time), as illustrated in Figure 7. The model includes health states corresponding to the disease-free state, non-metastatic recurrence, and metastatic recurrence. There are two metastatic recurrence health states, allowing a first and second line of treatment in this setting to be modelled separately.

The non-metastatic and metastatic recurrence health states are divided between patients who receive active treatment following recurrence, and patients who receive no active treatment after disease recurrence or progression. The 'on treatment' health states are also implicitly subdivided by the subsequent treatment received, with up to four treatment options for each health state, each of which may use a different set of transition probabilities. The treatments included were selected based on input from clinicians at the ALINA advisory board conducted on 9 February 2024.[13] Clinicians were asked to report the treatment options in each setting, along with an estimate of the corresponding market shares, and the four treatments with the largest mean estimated market share were included in the CEM. Further details of the subsequent treatments included in the model are given in Section 4.2.5.3. The model also includes the death state, which can be reached from any other health state.

Figure 7. Model structure diagram



Abbreviations: 1L, first line; 2L, second line.

The model structure includes the following assumptions:

- It was assumed that patients would receive at most one line of treatment in the non-metastatic recurrence setting, or two lines of treatment in the metastatic recurrence setting.
- It was assumed that any patient in an off-treatment health state would not receive any subsequent treatment (this was validated by clinical experts at the company's advisory board).[13]
- It was implicitly assumed that patients who do not receive active treatment for non-metastatic recurrence would die prior to developing metastatic recurrence (this was in line with an opinion expressed by one clinical expert at the company's advisory board).
- A fixed proportion of patients entering the recurrence health state was assumed to receive each treatment option; treatments received at earlier lines were not taken into account (with the exception of patients who received alectinib as an adjuvant treatment, who would not be permitted retreatment with alectinib until a user-determined period had elapsed – further details are given in Section 4.2.5.3.3).
- A maximum of four subsequent treatment options were considered in each setting/line of treatment.

4.2.2.1 EAG critique

The EAG considers that the model structure employed by the company is broadly appropriate, capturing the features of disease progression and treatment pathway relevant to patient costs and outcomes in this indication. Very similar model structures were also used in prior appraisals for other adjuvant treatments for NSCLC (TA761 for atezolizumab for adjuvant treatment of resected NSCLC with programmed cell death ligand-1 [PD-L1] expression of at least 50%, and TA823 for adjuvant treatment of epidermal growth factor receptor-positive [EGFR+] resected NSCLC).[33, 34]

However, the EAG also considers that the company provided insufficient justification for some of the assumptions made in the development of the model structure. Firstly, the number of lines of treatment reflected in the model is potentially not reflective of the treatment pathway in clinical practice; one of the EAG's clinical experts stated that patients would be likely to receive more than one line of treatment for non-metastatic recurrence, and more than two lines of treatment for

metastatic recurrence. It is unclear whether the clinicians present at the company's advisory board meeting on 9 February 2024 were explicitly asked to validate the number of lines of treatment reflected in the model structure. During clarification, the company further stated that the number of lines of treatment aligns with the findings of the TLR described in Section 4.1.3; however, the EAG notes that the TLR did not explicitly include data for metastatic recurrence, and none of the studies identified in the TLR including data on treatment options were relevant to the UK context. Overall, while the company's justification for the number of lines of treatment included is unclear, the EAG acknowledges that the addition of further lines of treatment would substantially increase the complexity of the model. Furthermore, the same number of lines of subsequent treatment were included in prior submissions in related disease areas (TA761 and TA823); these models were considered acceptable for decision making. [33, 34] Therefore, the EAG considers that this assumption is acceptable.

Another assumption which may not be reflective of clinical practice is the assumption that patients who do not receive treatment for non-metastatic recurrence would not progress prior to death. Although this is in line with the opinion of one clinician present at the company's advisory board, one of the EAG's clinical experts disagreed with this opinion. In response to the EAG's request for a scenario allowing patients to progress from non-metastatic recurrence (off treatment) to metastatic recurrence (off treatment) during the clarification stage, the company stated that the source used to inform the clinical outcomes of untreated patients (Wong et al. 2016) did not provide evidence on their PFS, only on their OS. While the model structure accommodates these transitions, no appropriate sources for PFS were found. The main impact of allowing these transitions would be to lower the total quality-adjusted life years (QALYs) and increase costs for patients reaching the non-metastatic recurrence (off treatment) health state, since the utility values and resource use of patients with non-metastatic recurrence are currently assigned to these patients until death. This would have a greater impact on the chemotherapy arm, since more patients experience recurrence when treated with chemotherapy compared to alectinib, so the exclusion of these transitions is favourable for alectinib. However, the magnitude of the impact of excluding these transitions is expected to be relatively small, since only a small proportion of patients occupy the non-metastatic recurrence (off treatment) health state over time (Figure 8) – occupancy never exceeds 1.2% of the patient population.

Figure 8. Proportion of patients in the non-metastatic recurrence (off treatment) health state over time – reproduced from company model

Finally, the EAG considers that the set of subsequent treatments included in the model may not be reflective of clinical practice. It should be noted that the model appears to have been arbitrarily designed with a maximum of four active treatments available for each disease stage/treatment line prior to elicitation of clinician opinions on which subsequent treatments would be available; both the clinicians present at the company's advisory board and the EAG's clinical experts suggested that more than four treatment options would be available at each treatment line represented in the model structure.[13] While the EAG accepts that addition of further treatment options to the existing model structure would be technically challenging, the impact of potential other subsequent treatment options, some of which may be relatively expensive, is unknown, and leads to considerable uncertainty in results.

It is also unclear whether combinations of treatments were considered for inclusion in the model; in particular, the EAG's clinical experts stated that chemoradiation would be a commonly used

treatment option for patients in the non-metastatic recurrence health state. As a result, the EAG has developed scenarios exploring alternative efficacy inputs for the model aligning with chemoradiation rather than radiation alone, as well as scenarios exploring alternative market shares for subsequent treatments. Further details of these scenarios are given in Section 4.2.5.3.4.

4.2.3 Comparators

As discussed in Section 2.3.3, while chemotherapy is considered the main relevant comparator for alectinib, some patients who would currently not be expected to receive adjuvant treatment with chemotherapy, and would instead receive only active monitoring, may be considered for treatment with alectinib. Since no direct efficacy data were available to parametrise active monitoring as a comparator, the company presented a conservative scenario reflecting active monitoring as a comparator, which assumed the same efficacy, quality of life and resource use as patients receiving treatment with chemotherapy, but with no treatment or adverse event (AE) costs. The EAG notes that this scenario was implemented incorrectly, since treatment costs for chemotherapy as a subsequent treatment were inadvertently removed. Following corrections by the EAG, the scenario only results in a [redacted] increase in the incremental cost-effectiveness ratio (ICER), so the consideration of active monitoring as a comparator has a limited effect on the cost-effectiveness of alectinib.

4.2.4 Perspective, time horizon and discounting

The CEM was aligned with the UK NHS and Personal Social Services (PSS) perspective. Costs and benefits were both discounted at an annual rate of 3.5%, in alignment with the NICE reference case.

The company base case employs a time horizon of 40 years, which is assumed to reflect a lifetime horizon for patients aged 54.9 years at baseline (in line with the ALINA trial).[37] The model is implemented using a cycle length of one month. A half-cycle correction was not applied in the company's original submitted model, but was introduced as an option during the clarification stage at the EAG's request; since the company's implementation of half-cycle correction did not apply to treatment costs, the EAG updated the model to include this. Ultimately, the half-cycle correction was not applied in the company's base case.

4.2.4.1 EAG critique

The perspective and discounting applied in the CEM are in line with the NICE reference case, and appropriate for this appraisal. As discussed in Section 2.3.1, the EAG has included a scenario with a

baseline age of 70 years (based on Ragd Sami *et al.* 2024) for comparison given there was initially some concern about whether the ALINA trial was fully representative of the ALK+ NSCLC patient population in the UK, which has since reduced based on additional feedback from its clinical experts and peer reviewers as well as additional evidence put forward by the company.[14] This scenario results in a [redacted] reduction in ICER.

The EAG considers that the application of a half-cycle correction is preferable, although ultimately the impact on the resulting ICER is negligible.

4.2.5 Treatment effectiveness

4.2.5.1 Approach to parametrising effectiveness

The transition probabilities included in the model structure are informed by survival data from RCTs and cohort studies. In particular, the transition probabilities from the disease-free state were informed by DFS data from the ALINA trial, while transition probabilities for the recurrence health states were informed by existing literature identified from the SLR of RCTs in advanced or metastatic ALK+ NSCLC, described in Section 4.1.2, and the TLR of cohort studies in locoregional NSCLC, described in Section 4.1.3. PFS data were used for patients receiving active treatment in the non-metastatic recurrence and metastatic recurrence (1L) health states, while OS data were used for patients receiving active treatment in the metastatic recurrence (2L) health state, as well as patients receiving no active treatment at any stage, since it was assumed that these patients would die prior to disease progression (further discussion of this assumption can be found in Section 4.2.2.1). Details of the sources of transition probabilities for the recurrent disease health states are given in Section 4.2.5.3.2.

In order to derive individual transition probabilities corresponding to progression and death, it was assumed that at all time points, a fixed proportion of events DFS/PFS events correspond to death events. These proportions were generally informed by the same source as the DFS/PFS data.

4.2.5.1.1 EAG critique

The EAG considers that the approach taken by the company to parametrise effectiveness is broadly reasonable, especially in light of the extremely immature OS data from the ALINA trial, which would be inappropriate to use directly in the model due to the small number of events. The EAG notes that the assumption that a fixed proportion of patients moves into the death state from each health state is a strong assumption. However, the approach is broadly in line with previous submissions in similar

indications (TA761 and TA823), and introducing time-variant proportions for the proportion of patients moving into each destination health state would considerably increase the complexity of the model.[33, 34] Based on all of these reasons, this assumption was considered reasonable by the EAG with the limited data available and the model structure used.

4.2.5.2 Approach to modelling DFS

4.2.5.2.1 Extrapolation of DFS data

Transition probabilities out of the disease-free health state were informed by the investigator-assessed DFS data from the most recent data cut of the ALINA trial (26 June 2023).

The available data were extrapolated using standard parametric functional forms fitted to individual patient data (IPD), as described in NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14; the gamma distribution was also fitted.[64] It was determined that the proportional hazards assumption was reasonable on the basis of the log-cumulative hazard plot and Schoenfeld residuals test (Figure 9 and Figure 10).

In the company's preferred base case, joint models were fitted to the DFS data for the alectinib and chemotherapy arms. The resulting extrapolations, alongside the corresponding Kaplan-Meier curves, are shown in Figure 11 and Figure 12.

Figure 9. Log-cumulative hazard plot, investigator-assessed DFS, ALINA trial – reproduced from Figure 4 of the CEM technical report

Figure 10. Schoenfeld residuals plot, investigator-assessed DFS, ALINA trial – reproduced from Figure 5 of the CEM technical report

Figure 11. Parametric extrapolations of investigator-assessed DFS, ALINA trial, alectinib arm (joint extrapolation) – reproduced from Figure 13 of the CS

Figure 12. Parametric extrapolations of investigator-assessed DFS, ALINA trial, chemotherapy arm (joint extrapolation) – reproduced from Figure 14 of the CS

The goodness of fit of each extrapolation was assessed by considering the Akaike information criterion (AIC) and Bayesian information criterion (BIC), as shown Table 19. The log-logistic extrapolation was selected for the company's preferred base case since this had both the lowest AIC and lowest BIC value. Further validation of the selected curves by clinical experts was also performed; further details are given in Section 4.2.5.2.4.

Table 19. Goodness of fit statistics for extrapolated DFS data (joint parametrisation)

Distribution	AIC	BIC
Exponential	712.1	719.2
Weibull	709.9	720.5
Log-logistic	**707.8**	**718.5**
Log-normal	711.1	721.7
Gompertz	712.4	723.0
Generalised gamma	710.6	724.8
Gamma	709.2	719.9

The selected model is shown in **bold.**

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; DFS, disease-free survival.

During the clarification stage, the company also added the option to use independently parametrised extrapolations for the two treatment arms. The extrapolations are illustrated in Figure 13 and Figure 14.

Figure 13. Parametric extrapolations of investigator-assessed DFS, ALINA trial, alectinib arm (independent extrapolation) – reproduced from company model

Figure 14. Parametric extrapolations of investigator-assessed DFS, ALINA trial, chemotherapy arm (independent extrapolation) – reproduced from company model

The AIC and BIC values for the independent model fits are presented in Table 20. The company's preferred extrapolations were the exponential fit for the alectinib arm and the log-logistic fit for the chemotherapy arm, on the basis of statistical goodness of fit; the Gompertz extrapolation for the alectinib arm, which displayed a similar goodness of fit to the exponential fit, was excluded since this crossed the corresponding curve for the chemotherapy arm, which was considered clinically implausible. It should be noted that the corresponding scenario was incorrectly implemented by the company, as the choice of extrapolations for the two treatment arms was reversed. As an alternative, the company also considered a scenario with the same distribution for both arms; the log-normal distribution was considered to be the best-fitting joint option for both arms, in which the curves did not cross.

Table 20. Goodness of fit statistics for extrapolated DFS data (alectinib, independent parametrisation)

	Alectinib		Chemotherapy	
Distribution	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	**197.9**	**200.8**	514.2	517.1
Weibull	198.5	204.2	513.3	519.0
Log-logistic	200.8	206.5	**509.8**	**515.4**
Log-normal	200.2	208.8	511.7	520.2
Gompertz	198.8	204.6	510.9	516.6
Generalised gamma	197.2	202.9	515.8	521.5
Gamma	198.7	204.5	512.5	518.2

The selected model is shown in **bold.**

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion.

4.2.5.2.2 Adjustment for cure assumptions and mortality

The extrapolated DFS curves were subsequently adjusted to account for potential cure. Based on discussion with clinicians at the advisory board conducted on 9 February 2024, it was assumed that a fixed proportion of patients would be considered cured at the 10-year timepoint, after which patients would experience no disease progression, and would only experience background rates of mortality.[13] The remaining patients were assumed to experience DFS in alignment with the original extrapolated DFS curve after this time point. The proportion of patients experiencing a cure was based on the mean of the most likely cure proportion estimates at the 10-year timepoint provided by clinicians (92% for the chemotherapy arm and 94% for the alectinib arm). It is notable that the cure assumption was applied as a one-off adjustment at the 10-year time point in the model base case, which differs from the approach taken in some previous appraisals in similar indications (for example, in the original company base case in TA823, and a scenario investigated in TA761), which included a 'ramping-up' period during which the proportion of patients assumed cured increases linearly from 0% over a specified time period; this was used in prior appraisals to avoid an unrealistic sharp slope change in the survival curve at the cure timepoint, but was ultimately not favoured by previous EAGs.[33, 34]

It should be noted that background mortality rates were assumed to be equivalent to age- and sex-adjusted general population mortality, with a standardised mortality ratio (SMR) of 1.25 applied,

informed by Janssen-Heijnen *et al.* 2012; this accounted for potential long-term increases of mortality risk due to treatment, secondary malignancies or other comorbidities.[65]

Finally, the probability of a DFS event was partitioned into a probability of a progression event and the probability of a death event. The probability of a death event was then adjusted to ensure that it did not decrease below the background SMR-adjusted general population mortality risk.

The resulting DFS curves used to parametrise transition probabilities out of the disease-free health state are shown in Figure 15, alongside the associated original log-logistic extrapolation (note that the misalignment between the initial extrapolations and the final curves prior to the cure timepoint is due to the fact that mortality is not bounded in the original extrapolation curves).

Figure 15. Extrapolated investigator-assessed DFS with cure and mortality adjustments – reproduced from Figure 15 of the CS

4.2.5.2.3 Treatment waning scenario

The company also developed a scenario which explores a treatment waning effect; between two user-specified timepoints, the DFS event probability for patients in the alectinib arm is assumed to gradually increase until it is in line with the DFS event probability for the chemotherapy arm, according to the following formula:

$$P_{adjA}(t) = \frac{t - t_1}{t_2 - t_1} \times P_C(t) + \left(1 - \frac{t - t_1}{t_2 - t_1}\right) \times P_A(t)$$

Here, t is the start time of the current cycle, $P_{adjA}(t)$ is the treatment waning-adjusted event probability in the current cycle, $P_C(t)$ and $P_A(t)$ are the unadjusted event probabilities in the current cycle for the chemotherapy and alectinib arms respectively, and t_1 and t_2 are the two user-specified timepoints marking the start and end of the waning period. The application of the treatment waning scenario between 5 and 7 years from baseline increases the ICER for the corrected company base case by [redacted].

4.2.5.2.4 Validation of curve extrapolation

The approach to extrapolating DFS was validated at the company's advisory board conducted on 9 February 2024; the following opinions were elicited from clinicians:

- Most likely estimate, lowest plausible limit and highest plausible limit for mean disease-free survival at 5, 10, 20 and 30 years after initiating treatment with alectinib and chemotherapy;
- Whether each of the joint extrapolations (adjusted for cure assumption and background mortality) was clinically plausible;
- Ranking of extrapolations (adjusted for cure assumption and background mortality) in terms of plausibility.

The validity of the independent extrapolations was not discussed since these were only added to the model during the clarification stage.

The clinicians' feedback broadly supported the choice of the log-logistic joint model fit, with the majority of clinicians considering the log-logistic fit to be clinically plausible for patients receiving either alectinib or chemotherapy, and ranking the log-logistic fit as one of their top two preferred

extrapolations. However, it should be noted that many of the extrapolations were ranked similarly to the log-logistic model (for example, the generalised gamma distribution was considered plausible for patients receiving chemotherapy by more of the clinicians compared to the log-logistic fit, although fewer ranked it as one of their top two extrapolations). Further details are given in Table 21.

Table 21. Clinical expert assessment of DFS model extrapolation plausibility – reproduced from the company's advisory board report

Distribution	Number of experts considering model clinically plausible		Number of experts ranking model 1 or 2 for clinical plausibility	
	Alectinib	Chemotherapy	Alectinib	Chemotherapy
Log-logistic	5/5	4/5	7/7	4/7
Exponential	4/5	4/5	6/7	5/7
Weibull	5/5	3/5	7/7	3/7
Log-normal	5/5	4/5	6/7	4/7
Generalised gamma	5/5	5/5	7/7	3/7
Gompertz	5/5	3/5	7/7	2/7
Gamma	5/5	3/5	6/7	3/7

Reproduced from Table 5 – Table 6, advisory board report.[13]

Note that two experts of the seven present did not comment on the plausibility of individual fitted models, but did present a ranking of the fitted models.

The log-logistic extrapolation tends to give lower DFS estimates at key timepoints than the clinician-preferred point estimates (Table 22 and Table 23); in particular, the survival estimates for patients receiving chemotherapy based on the log-logistic extrapolation are consistently lower than the mean lowest plausible limit for all timepoints. However, similar issues are observed for all model fits provided by the company, suggesting that this problem was shared by all standard joint parametric model fits.

Please note that although the advisory board did not explicitly address the goodness of fit of independently parametrised extrapolations, the resulting DFS estimates at key timepoints are presented alongside clinician estimates in Table 24 and Table 25 for reference. Similar issues are observed with these model fits, although in general the estimates for chemotherapy are slightly more in line with clinician estimates, especially at later timepoints.

Table 22. Clinician estimates and log-logistic extrapolation (joint model) DFS predictions, chemotherapy – reproduced from the company's advisory board report

Timepoint	Clinician opinions			Model results (joint extrapolations)						
	Mean lowest plausible limit	Mean most likely estimate	Mean highest plausible limit	Exponential	Weibull	Log-normal	Generalised gamma	Log-logistic	Gompertz	Gamma
5 years	43%	50%	66%	37%	31%	40%	35%	35%	30%	32%
10 years	28%	38%	51%	14%	6%	22%	12%	16%	2%	8%
20 years	13%	24%	28%	10%	4%	16%	9%	12%	1%	5%
30 years	10%	17%	22%	4%	1%	8%	4%	6%	0%	2%

Clinician estimates reproduced from Table 4, advisory board report.[13]

Estimates which fall outside the mean lowest and highest plausible limits provided by clinicians are shown in red.

Model extrapolations are based on the original version of the model submitted by the company, and incorporate the base case cure assumption.

Abbreviations: DFS, disease-free survival.

Table 23. Clinician estimates and log-logistic extrapolation (joint model) DFS predictions, alectinib – reproduced from the company's advisory board report

Timepoint	Clinician opinions			Model results (joint extrapolations)						
	Mean lowest plausible limit	Mean most likely estimate	Mean highest plausible limit	Exponential	Weibull	Log-normal	Generalised gamma	Log-logistic	Gompertz	Gamma
5 years	58%	69%	83%	76%	73%	73%	73%	72%	73%	73%
10 years	41%	52%	66%	57%	47%	52%	49%	48%	37%	47%
20 years	27%	36%	46%	45%	36%	40%	38%	37%	23%	36%
30 years	18%	26%	34%	23%	17%	20%	19%	19%	3%	18%

Clinician estimates reproduced from Table 4, advisory board report.[13]

Estimates which fall outside the mean lowest and highest plausible limits provided by clinicians are shown in red.

Model extrapolations are based on the original version of the model submitted by the company, and incorporate the base case cure assumption.

Abbreviations: DFS, disease-free survival.

Table 24. Clinician estimates and log-logistic extrapolation (independent model) DFS predictions, chemotherapy – reproduced from the company's advisory board report

Timepoint	Clinician opinions			Model results (joint extrapolations)						
	Mean lowest plausible limit	Mean most likely estimate	Mean highest plausible limit	Exponential	Weibull	Log-normal	Generalised gamma	Log-logistic	Gompertz	Gamma
5 years	43%	50%	66%	37%	31%	37%	0%	35%	34%	31%
10 years	28%	38%	51%	14%	6%	18%	0%	15%	7%	7%
20 years	13%	24%	28%	12%	5%	16%	0%	14%	5%	6%
30 years	10%	17%	22%	10%	4%	13%	0%	12%	3%	5%

Clinician estimates reproduced from Table 4, advisory board report.[13]

Estimates which fall outside the mean lowest and highest plausible limits provided by clinicians are shown in red.

Model extrapolations are based on the original version of the model submitted by the company, and incorporate the base case cure assumption.

Abbreviations: DFS, disease-free survival.

Table 25. Clinician estimates and log-logistic extrapolation (independent model) DFS predictions, alectinib – reproduced from the company's advisory board report

Timepoint	Clinician opinions			Model results (joint extrapolations)						
	Mean lowest plausible limit	Mean most likely estimate	Mean highest plausible limit	Exponential	Weibull	Log-normal	Generalised gamma	Log-logistic	Gompertz	Gamma
5 years	58%	69%	83%	76%	72%	77%	96%	73%	65%	73%
10 years	41%	52%	66%	57%	44%	61%	91%	50%	3%	48%
20 years	27%	36%	46%	52%	39%	55%	84%	45%	1%	43%
30 years	18%	26%	34%	45%	33%	48%	74%	39%	0%	36%

Clinician estimates reproduced from Table 4, advisory board report.[13]

Estimates which fall outside the mean lowest and highest plausible limits provided by clinicians are shown in red.

Model extrapolations are based on the original version of the model submitted by the company, and incorporate the base case cure assumption.

Abbreviations: DFS, disease-free survival.

4.2.5.2.5 Recurrence and death events

The proportion of DFS events corresponding to non-metastatic recurrence, metastatic recurrence and death were informed by the breakdown of DFS events in the ALINA trial, and were assumed to differ between arms.[38] Details of the input values used are given in Table 26. It is notable that 0% of DFS events are considered to be death events in the alectinib arm while 2% of DFS events are considered to be death events in the chemotherapy arm.

Table 26. Proportion of DFS events corresponding to recurrence and death events, ALINA trial

Destination health state	Proportion of events (alectinib arm)	Proportion of events (chemotherapy arm)
Non-metastatic recurrence	64.3%	44.0%
Metastatic recurrence (1L)	35.7%	54.0%
Death	0.0%	2.0%

Abbreviations: 1L, first line.

It should be noted that the proportion of DFS events which were death events was low enough in both arms that the calculated number of death events generally fell below the SMR-adjusted background mortality rate. The number of death events was therefore adjusted upwards, but in the original version of the CEM submitted by the company, no further adjustments were made to transition probabilities to the non-metastatic recurrence and metastatic recurrence (1L) health states. This resulted in the total resulting calculated probability of the leaving the disease-free health state exceeding the observed probability of a DFS event at the same time in the original extrapolated trial data. At the EAG's request, during the clarification stage, the company included an option in the model in which the number of transitions to the non-metastatic and metastatic recurrence health states were scaled down proportionally to account for the increase in the modelled number of death events; although this adjustment was not applied in the company's preferred base case, the EAG considers it to be more methodologically appropriate to apply the adjustment, and therefore the application of this adjustment is considered as a correction to the model.

4.2.5.2.6 EAG critique

Regarding the use of the investigator-assessed data to parametrise treatment efficacy, the EAG notes that DFS as assessed by blinded independent central review (BICR) was substantially different to investigator-assessed DFS in the ALINA trial in the chemotherapy arm (further details are given in Sections 2.3.4 and 3.3.1); therefore, at the request of the EAG during the clarification stage, the company added an additional scenario to the CEM using extrapolated BICR DFS. While the EAG

considers that the use of the investigator-assessed data is appropriate, it should be noted that using the BICR data increases the ICER by [redacted].

However, the EAG notes several concerns with the approach used by the company for using these data to generate transition probabilities out of the disease-free health state.

Firstly, the EAG considers that the choice of extrapolation for the DFS curves has been insufficiently justified. For example, the AIC and BIC values are similar across the model fits explored; although the joint log-logistic model has the lowest AIC and BIC values, the joint Weibull, log-normal and gamma fits all have sufficiently similar AIC and BIC values to suggest no substantial difference in goodness of fit. Similarly, based on clinicians' rankings of the models, there is little to distinguish between the models, and estimates of long-term survival for patients treated with adjuvant alectinib are speculative since no existing long-term data are available. Furthermore, it is unclear why the proportional hazards assumption was used as justification for a joint log-logistic model since this model is not closed under the PH assumption.

More broadly, the EAG notes that the visual fit of all proposed extrapolations for the alectinib arm are reasonably poor (Figure 11, Figure 13). Furthermore, all extrapolations are consistently lower than the estimates proposed by clinicians (Table 22 to Table 25), although once again, it should be noted that clinicians' estimates of survival for patients treated with adjuvant alectinib are speculative.

Overall, the EAG's preferred approach is to use independently parametrised curves, with the Weibull extrapolation for the alectinib curve rather than the exponential extrapolation, since there is no substantial difference in AIC and BIC between these fits (Table 20), and the estimates are more in line with clinician estimates (Table 25). However, the EAG agrees with the company that the independently parametrised log-logistic curve is appropriate for the chemotherapy arm; this is more in line with the clinician estimates than any joint extrapolation models. The company's preferred independent extrapolations were included in a scenario, which decreased the ICER by [redacted].

The EAG also believes that, if joint extrapolations are used, the joint log-normal extrapolation is potentially more appropriate to the joint log-logistic extrapolation, which is used in the company's preferred base case, since again the difference in AIC/BIC value is minimal (Table 19), and the estimates are slightly closer to clinician estimates (Table 22 and Table 23). The EAG included a scenario exploring the use of the joint log-normal distribution, which increased the ICER by [redacted].

It should also be noted that the sum of the AIC/BIC values for the independent extrapolations are directly comparable with the AIC/BIC values for the joint extrapolations, since the independent extrapolation framework assumes that the two datasets are fully independent. The overall AIC values for the company and EAG's preferred extrapolations, for both joint and independent models, are reproduced in Table 27; these are generally comparable, with no substantial difference between the goodness of fit of the selected models.

Table 27. Goodness of fit of preferred extrapolations

Model	AIC	BIC
Joint log-logistic (company base case)	707.8	718.5
Joint log-normal	711.1	721.7
Independent, exponential (alectinib) + log-logistic (chemotherapy)	707.7	716.2
Independent, Weibull (alectinib) + log-logistic (chemotherapy)	708.3	719.6

Abbreviations: Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion.

The EAG considers that the application of a cure assumption is broadly appropriate; the inclusion of a cure assumption was validated by the EAG's clinical experts, and the methodology used is aligned with previous NICE appraisals. However, the parametrisation of the cure approach is potentially misaligned with clinical practice; the EAG's clinical experts stated that most patients who remain disease-free would receive a maximum follow-up of 5 years, after which they could broadly be considered cured; a cure timepoint of 5 years is also aligned with the company's base case in TA761 and TA823 (the EAG proposed a 'pessimistic' cure timepoint of 8 years in TA761).[33, 34] Therefore, it is unclear why a cure timepoint of 10 years was used; however, since comparison of ICERs suggests that this is a conservative assumption compared to a cure timepoint of 5 years, the EAG consider this approach to be acceptable. The EAG notes that the company presented a scenario using a cure timepoint of 5 years, but this used the same cure proportion as the base case, rather than the cure proportions at the 5-year timepoint elicited at the company's advisory board.

The EAG also notes that different cure proportions were used for the alectinib and chemotherapy arms, based on the mean of point estimates elicited from clinicians. Since the cure estimates for alectinib are entirely speculative, the EAG considers that this is insufficient evidence for modelling a benefit in terms of cure for patients receiving alectinib, and prefers to assume the same cure proportion for both treatment arms. This position was supported by the EAG's clinical experts. The

EAG's preferred cure proportion is 91% at 10 years, based on the mean of clinicians' responses from the company's advisory board pooled across both treatments. A scenario with 81% of patients cured at 5 years is also considered, again based on the mean of clinicians' responses from the company's advisory board pooled across both treatments; this scenario results in a [redacted] decrease in the ICER, suggesting that the 10-year cure timepoint remains conservative.

The EAG also questions the appropriateness of the application of the SMR to background mortality. It is notable that the advisory board report states that clinicians believed that cured patients would experience mortality risk in line with age- and sex-adjusted general population rates (i.e., without the application of an SMR).[13] The EAG's clinical experts also held opposing opinions on the appropriateness of applying an SMR. The EAG notes that the source for the SMR proposed by the company is a cohort study which included 12,148 patients diagnosed with stage I-III NSCLC; the statistical analysis to derive the reported SMR was not limited to patients who died while disease-free, or after they were considered cured.[65] Therefore, the SMR reported by this source includes death caused by primary disease, and does not reflect non-disease-specific mortality. However, the EAG was unable to identify any more appropriate alternative sources for an SMR for background mortality. In light of this uncertainty, during clarification the EAG requested that the company include a scenario analysis excluding the SMR from mortality calculations; however, the EAG notes that exclusion of the SMR reduces the ICER by [redacted], suggesting that the inclusion of the SMR has minimal impact on the ICER. Therefore, the SMR is retained in the EAG's preferred base case.

The EAG also considers that, while it is appropriate to bound the probability of death events below background mortality risk, it is also appropriate to down-adjust the probability of recurrence so that the overall DFS does not drop below the DFS extrapolated from trial data; therefore, this adjustment is included as a correction in the EAG's preferred base case.

Finally, although the proportions of patients moving to each destination health state were based on the ALINA trial, the EAG considers that there is insufficient evidence to support a rate of 0% of disease-related death for patients treated with adjuvant alectinib, but a nonzero rate of disease-related death for patients treated with adjuvant chemotherapy. In the ALINA trial, while no deaths were observed for patients treated with alectinib that were not caused by disease recurrence, only three deaths not due to disease recurrence were reported for patients treated with adjuvant chemotherapy, due to bilateral pneumonia, COVID-19 and an unknown cause, respectively (see Section 5.2.1.3 of the clinical study report [CSR]); it is therefore unclear whether these deaths were

disease-related.[38] Furthermore, the EAG's clinical experts stated that it would be appropriate to consider a rate of 0% for disease-related death for all patients in the disease-free state, regardless of treatment received. Therefore, the EAG's preferred base case assume that only deaths in line with background mortality are included for the disease-free health state, regardless of treatment.

The resulting DFS curves using the EAG's preferred assumptions are shown in Figure 16.

Figure 16. DFS extrapolations using EAG's preferred assumptions – reproduced from company model

4.2.5.3 Approach to modelling subsequent treatment efficacy

4.2.5.3.1 Extrapolation of PFS/OS data

The approach to modelling transition probabilities for the recurrent disease health states was similar to the approach used for modelling transition probabilities for the disease-free health states. For patients receiving active treatment, PFS data for the subsequent treatment options outlined in Section 4.2.2 were sourced from existing literature; where IPD were not available (i.e., for all sources except for the ALINA, ALEX and ALUR trials), pseudoIPD were generated by digitising Kaplan-Meier

(KM) curves from relevant publications and applying the Guyot algorithm to estimate pseudoIPD.[66] These were then extrapolated using an exponential distribution; other distributions were not included in the CEM. The probability of a PFS event was then partitioned into a probability of a progression event and the probability of a death event; for all disease stages and lines of treatment, it was assumed that 88.9% of PFS events were progression events, in line with the alectinib arm of the ALEX trial, since relevant treatment-specific data could not be identified.[59]

Similarly to DFS events, the probability of death was bounded below by the SMR-adjusted general population mortality risk; the probability of progression was then adjusted if required, to ensure that the calculated total probability of a PFS event did not exceed the observed probability of a PFS event in the original extrapolated trial data.

A similar approach was used to extrapolate OS data to derive transition probabilities from the metastatic recurrence (2L) and off treatment health states to the death state, although a partition into recurrence and death events was not required in this case.

The company stated that the use of the exponential distribution was a simplifying assumption to allow time-invariant transition probabilities to be used. The EAG requested further justification for this assumption, and implementation of the functionality to use time-variant transition probabilities, during the clarification stage. As a result, the company also fitted the other standard extrapolations specified by TSD14 and presented the resulting extrapolation plots and goodness of fit statistics during the clarification stage, but alternative extrapolations were not ultimately implemented in the model. The extrapolation plots and goodness of fit statistics are provided in Appendix 8.2.

4.2.5.3.2 Sources for transition probabilities

The sources for transition probabilities for recurrent health states are given in Table 28.

Table 28. Sources of PFS/OS data for recurrent disease health states

Health state	Treatment	Source
Non-metastatic recurrence	Radiotherapy	Nakamichi *et al.* 2017[62]
	Surgery	Assumed same efficacy as radiotherapy
	Alectinib	ALINA trial, Roche data on file[38]
	Chemotherapy	ASCEND-4 trial, Soria *et al.* 2017[58]
	No treatment	Wong *et al.* 2016[67]

Metastatic recurrence (1L)	Alectinib	ALEX trial, Roche data on file[59]
	Lorlatinib	CROWN trial, Solomon *et al.* 2023[60]
	Chemotherapy	Assumed same efficacy as chemotherapy in the non-metastatic recurrence state
	Brigatinib	ALTA-1L trial, Camidge *et al.* 2021[61]
	No treatment	Wong *et al.* 2016[67]
Metastatic recurrence (2L)	Alectinib	ALUR trial, Roche data on file[68]
	Lorlatinib	Assumed same efficacy as alectinib
	Chemotherapy	ALUR trial, Roche data on file[68]
	No treatment	Wong *et al.* 2016[67]

Abbreviations: 1L, first line; 2L, second line; OS, overall survival; PFS, progression-free survival.

Transition probabilities for active treatment options the non-metastatic recurrence health state were informed by both the SLR described in Section 4.1.2, and the TLR described in Section 4.1.3, and include a mixture of RCTs specific to the ALK+ NSCLC patient population, and cohort studies in broader NSCLC patient populations. In general, the company favoured the selection of studies with larger sample sizes (at least 50 patients receiving the treatment of interest). The only remaining studies were Wu *et al.* 2017 and Nakamichi *et al.* 2017.[37, 62] Wu *et al.* 2017 was excluded because the presented survival data grouped together patients who received chemotherapy alongside radiation with patients who received radiation alone.[37] The source selected for radiotherapy treatment, Nakamichi *et al.* 2017, was a cohort study of patients with stage I-III NSCLC conducted at a single centre in Japan, including 56 patients receiving radiotherapy treatment in isolation.[62] The efficacy for surgery was assumed equal to the efficacy for radiotherapy, since an appropriate source was not identified. Survival data for alectinib specific to the non-metastatic recurrence setting were also not identified, so it was assumed that PFS for alectinib in this setting was equivalent to DFS reported in the ALINA trial, for the adjuvant setting.

Transition probabilities for active treatment options in the metastatic recurrence health states were informed by the SLR only, and were limited to RCTs specific to the ALK+ NSCLC patient population. No data specific for lorlatinib in the metastatic recurrence (2L) setting were identified, so an equal efficacy to alectinib was assumed. Similarly, no data specific for chemotherapy in the metastatic recurrence (1L) setting were identified, so an equal efficacy to alectinib was assumed.

The source for OS data for patients receiving no active treatment was Wong *et al.* 2016, a USA-based cohort study of patients with stage I-III NSCLC. Transition probabilities for the non-metastatic recurrence health state were aligned with reported OS for patients with loco-regional recurrence, and transitions for both metastatic recurrence health states were aligned with reported OS for patients with distant recurrence.

4.2.5.3.3 Treatment market shares

The proportion of patients assumed to receive each treatment option was based on estimated market shares elicited from clinicians at the company's advisory board meeting on 9 February 2024; details are given in Table 29.[13] The company also assumed that patients may not necessarily be permitted to receive re-treatment with alectinib for recurrent disease if progression had occurred while receiving adjuvant treatment with alectinib; in the base case, it was assumed that patients would not be rechallenged with alectinib until at least two years after initially starting treatment (in line with the maximum treatment duration for alectinib). Different market shares for subsequent treatments were used for the time periods when rechallenge was disallowed and when rechallenge was allowed; the market shares provided for the 'rechallenge disallowed' setting were derived from the 'rechallenge allowed' market shares by setting the alectinib market shares to 0% and rescaling the other market shares proportionally.

Table 29. Market shares for subsequent therapies

Health state	Treatment option	Market share		
		Alectinib arm (rechallenge allowed)	Alectinib arm (rechallenge disallowed)	Chemotherapy arm
Non-metastatic recurrence	Radiotherapy (Conformal 3-dimensional radiotherapy)	32.1%	40.1%	21.1%
	Surgery	14.4%	18.0%	8.5%
	Alectinib	16.9%	0.0%	35.5%
	Chemotherapy (cisplatin + pemetrexed)	21.1%	26.4%	19.4%
	No active treatment	15.5%	15.5%	15.5%
Metastatic recurrence (1L)	Alectinib	19.4%	0.0%	46.1%
	Chemotherapy	11.0%	14.4%	3.3%
	Brigatinib	22.0%	28.7%	33.8%
	Lorlatinib	32.1%	41.4%	1.3%
	No active treatment	15.5%	15.5%	15.5%

Metastatic recurrence (2L)	Alectinib	10.8%	0.0%	26.0%
	Lorlatinib	33.1%	39.4%	31.2%
	Chemotherapy	23.6%	28.1%	10.3%
	No active treatment	32.5%	32.5%	32.5%

Abbreviations: 1L, first line; 2L, second line.

4.2.5.3.4 EAG critique

The EAG notes several concerns with the approach to parametrising treatment market shares. As stated in Section 4.2.2, it is unclear whether combination therapies were considered for inclusion in the CEM. Since the EAG's clinical experts suggested that chemoradiation would be a key treatment option for patients with non-metastatic recurrence, it was considered that it would be more appropriate to reflect chemoradiation as a treatment option in the CEM.

However, even if the same choices of treatment are retained in the CEM, the EAG also notes several concerns with the sources selected to parametrise transition probabilities. There were several limitations with the justification provided for the sources included in the CEM; notably, survival data used to parametrise efficacy for the metastatic recurrence health states were identified using only the SLR described in Section 4.1.2, which was limited to RCTs in ALK+ patient populations. By contrast, transition probabilities for the non-metastatic recurrence health states included sources based on cohort studies, which were not restricted to ALK+ patient populations, which were identified in the TLR described in Section 4.1.3. Therefore, relevant evidence for parametrising transition probabilities for the metastatic recurrence health states may have been overlooked.

Furthermore, the EAG disagrees with the choice of data to parametrise efficacy for several subsequent treatments. Firstly, the EAG considers that it would be more appropriate to parametrise the transition probabilities for alectinib in the non-metastatic recurrence setting based on the ALEX trial rather than the ALINA trial, since the patient population in the ALEX trial is better aligned with this health state; this proposed approach was validated by the EAG's clinical experts. Secondly, the EAG considers that the Nakamichi *et al.* 2017 study used to parametrise transition probabilities is not suitable as a source, since the EAG's clinical experts suggested that both the patient population and standard of care for NSCLC are substantially different in Japan compared to the UK. Furthermore, this study only included 56 patients from a single centre in the analysis used to generate the data parametrising the model; therefore, the generalisability of results may be

limited.[62] The EAG was unable to identify an appropriate alternative data source for patients receiving radiotherapy. However, to explore the impact of using a different data source, the EAG also considered PFS from the Lee *et al.* 2019 study, a multicentre observational study conducted in South Korea, where 127 patients were treated with chemoradiation therapy for loco-regional recurrence for NSCLC.[69] Although clinical practice and expected outcomes in South Korea may also not align with the UK, this study draws on a larger patient cohort than the Nakamichi *et al.* study; furthermore, the use of chemoradiation rather than radiotherapy alone is more aligned with the EAG's clinical experts' opinions.

The assumption of equal efficacy for patients treated with surgery having equal PFS to patients receiving radiotherapy is also a strong assumption; however, neither the company nor the EAG was able to identify any data on progression-free survival following re-operation to treat recurrence of NSCLC.

As a result of the limitations, the EAG has investigated several alternative scenarios for parametrising efficacy in the non-metastatic recurrence health state, as follows:

- A scenario in which surgery is excluded as a treatment option, and other market shares for the non-metastatic recurrence health state are adjusted upward proportionally; this results in a [redacted] decrease in the ICER.
- A scenario in which PFS for patients receiving radiotherapy is informed by Lee *et al.* 2019; this results in a [redacted] decrease in the ICER
- Scenarios in which market shares at each treatment line for subsequent treatments in the alectinib arm are aligned with the chemotherapy arm; these resulted in a [redacted] increase, [redacted] decrease and [redacted] increase in the ICER for the non-metastatic recurrence, metastatic recurrence (1L) and metastatic recurrence (2L) contexts, respectively.

Overall, the scenarios have differing impacts on the ICER, with some scenarios increasing the ICER and others decreasing the ICER. However, the net change in ICER does not exceed £2,000 for any scenario, and all scenarios considered remain below the £20,000/QALY threshold.

More broadly, the EAG notes that the approach taken by the company implicitly assumed that sources for efficacy data for individual treatments within the same health state were directly comparable; no evidence was provided to justify this assumption, or make any attempt to adjust

efficacy estimates to account for differences between studies (for example, via a matching-adjusted indirect comparison [MAIC]). While the EAG appreciates that this was a pragmatic approach given the limited availability of IPD, and such analyses were not pursued in previous appraisals in the same indication (TA761 and TA823), this remains a key area of uncertainty in the CEM.[33, 34]

Regardless of the sources for efficacy data included in the CEM, another key consideration is that only exponential extrapolations were considered for inclusion in the CEM. The company's reasoning was that introducing time-variant transition probabilities would increase the complexity of the model; however, since tunnel states are included in the model to account for duration of treatment for subsequent therapies, the EAG does not consider that this would unduly increase the complexity of the current approach employed. Furthermore, all standard parametric extrapolations were explored for subsequent treatments in the CEM presented in TA761, which employs an almost identical model structure.[33] The extrapolation plots and goodness of fit statistics presented during the clarification stage also suggest that exponential extrapolations provide a relatively poor fit compared to other parametric distributions, with a substantial difference in AIC and BIC between the exponential compared to the best-fitting extrapolations for each subsequent treatment option. As a result, the EAG implemented the functionality to use alternative standard parametric fits for subsequent treatment survival data, with a slight simplification assuming that patients would not remain in any subsequent health state beyond 60 cycles (5 years), due to the existing structure of the CEM; a summary of the EAG's preferred extrapolations, selected based on visual goodness of fit and AIC and BIC values, is given in Table 30. It should be noted that the EAG's preferred approach of using time-variant transition probabilities for subsequent treatments is incorporated into the EAG's preferred base case, since it is considered to be a substantially better reflection of the input data than using time-invariant transition probabilities. The EAG's preferred extrapolations result in a decrease in the ICER of £1149 compared to the company's preferred approach; however, the ICER is particularly sensitive to the choice of extrapolation for brigatinib and lorlatinib in the metastatic recurrence (1L) setting, and selecting alternative plausible extrapolations for these curves. In particular, using the Gompertz extrapolation for brigatinib and the log-normal extrapolation for lorlatinib) results in an overall increase of [redacted] in the ICER compared to the company's preferred approach; both extrapolations do not have a substantial difference in AIC and BIC compared to the best-fitting extrapolations. As a result, the long-term effectiveness of subsequent treatments is a key area of uncertainty in the model. The EAG considers the use of these extrapolation choices as a plausible but more pessimistic scenario.

Table 30. EAG preferred extrapolations for subsequent treatment survival data

Health state	Treatment option	Preferred extrapolation
Non-metastatic recurrence	Radiotherapy/surgery	Generalised gamma
	Chemotherapy	Log-normal
	Alectinib (using ALEX trial data)	Log-normal
	No treatment	Log-normal
Metastatic recurrence (1L)	Alectinib	Assumed same as non-metastatic recurrence efficacy
	Brigatinib	Generalised gamma
	Lorlatinib	Gompertz
	Chemotherapy	Assumed same as non-metastatic recurrence efficacy
	No treatment	Log-normal
Metastatic recurrence (2L)	Alectinib/lorlatinib	Log-logistic
	Chemotherapy	Gompertz
	No treatment	Log-normal

Abbreviations: 1L, first line; 2L, second line; EAG, External Assessment Group.

The EAG also noted that for all treatments in the non-metastatic recurrence and metastatic recurrence (1L) health states, the proportion of events which were progression events was aligned with the ALEX trial. However, the ALEX trial was conducted in patients with previously untreated advanced NSCLC, and therefore may not be representative of patients with metastatic disease.[59] Furthermore, the data used in the model were relevant for the alectinib arm of the trial, which may not be applicable to other treatments. However, since no alternative data sources could be identified, the impact of this assumption was explored in a series of scenarios varying the proportion of progression events occurring across health states; assuming 100% of PFS events are progression events (excluding background mortality) leads to an decrease of [redacted] in the ICER, while reducing the proportion of progression events to 80% increases the ICER by [redacted]. Therefore, this assumption has a relatively minimal impact on the ICER.

Finally, the EAG notes that the approach taken to account for restrictions in rechallenging patients with alectinib may not fully reflect clinical practice. One of the EAG's clinical experts suggested that patients would not be rechallenged with alectinib if they experience recurrence within six months of discontinuing initial treatment with alectinib. However, the implementation of this assumption in the CEM applies a restriction on rechallenge based on time from baseline rather than time from treatment discontinuation. While the EAG acknowledges that this choice was made to avoid the introduction of additional tunnel states to account for time from discontinuation, it should be noted

that this is an area of uncertainty in the model. Furthermore, there is some uncertainty in the duration of the 'rechallenge disallowed' period, since one of the EAG's clinical experts stated that rechallenge would only be disallowed if patients experienced recurrence while still receiving treatment with alectinib. In order to investigate the impact of these assumptions, the EAG investigated several scenarios around the duration of the 'rechallenge disallowed' phase in the model; removing all restrictions on the time to rechallenge (i.e. the rechallenge disallowed phase has a duration of 0 months) results in a [redacted] decrease in ICER, while extending the time to rechallenge by six months (i.e. the rechallenge disallowed phase has a duration of 30 months) results in a [redacted] increase in the ICER, suggesting that the impact of this assumption is limited.

4.2.6 Health-related quality of life

4.2.6.1 Health state utility values

Health state utility values used in the company's economic model were derived from both HRQoL data collected in the ALINA clinical trial and published literature estimates. Further detail on the methods and sources used are provided below.

4.2.6.1.1 Disease-free health state utilities

For the disease-free (DF) health state, HRQoL data collected in the ALINA trial (June 2023 data cut-off) using the EQ-5D-5L were used to estimate utility values. Based on the NICE methods guide,[70] EQ-5D-5L data was mapped to EQ-5D-3L index scores using Hernández Alava *et al.* 2017.[71] EQ-5D-5L data was collected at the following timepoints, outlined below:

- At baseline;
- Every three weeks up to week 12;
- Every 12 weeks thereafter until disease recurrence, withdrawal of consent, death or week 96 (alectinib arm only);
- During safety and disease follow-up visits.

Although stated in the CS that HRQoL was collected every 12 weeks after the initial 12 weeks for the alectinib treatment arm only, patients in both treatment arms completed EQ-5D questionnaires at disease follow up visits, which according to the CSR, occurred every 12 weeks for the first two years. Safety follow up visits were scheduled for after treatment completion and therefore occurred earlier

for patients in the chemotherapy arm. Figure 17 shows a graphical display of utility values collected during the ALINA trial for each treatment arm.

Figure 17. Individual patient utility values from the ALINA clinical trial for each treatment arm – reproduced from Figure 1 of the company's UK supplementary information technical report document

Minimal details regarding the derivation of utility values from the trial data were included in the company's submission. During clarification, the EAG requested further details on the regression model used, including details of model structure and inclusion of relevant covariates. The company used a linear mixed effects model, using a normal random subject effect. Regression output of the mixed effects model conducted by the company are shown in Table 31. Plots of the standardised residuals and fitted vs observed values are given in Figure 18 and Figure 19; the residuals are generally evenly distributed around 0, suggesting a reasonable fit of the model to observed data; it should be noted that the straight line of observations in the upper right quadrants arise from the

bounding of utility values at 1. During clarification, the company stated that p-values obtained using the lme4 package in R can be difficult to interpret and therefore were not provided.

Table 31. Linear mixed effects regression model outputs – reproduced from Table 40 of the company's CQ response

Fixed effects	Estimate	Standard error	t-value
Intercept	0.487	0.04201	11.59
Baseline utility	0.3912	0.0494	7.918
Alectinib	0.01735	0.01487	1.167
Off-treatment	0.04729	0.005986	7.9
Alectinib*Off-treatment	-0.01194	0.01216	-0.982

Figure 18. Standardised residuals for linear mixed effects regression model – reproduced from Figure 1 of the company's additional clarification response

Figure 19. Fitted vs observed values for linear mixed effects regression model – reproduced from Figure 1 of the company's additional clarification response

The company stated that inclusion of model variables was based on the health states included in the economic model and differences in treatment schedules. Therefore, the company's mixed effects regression model separately controlled for treatment arm and patients' on/off treatment status. As such, the company applied separate utility values in the DF health state for patients receiving adjuvant alectinib (on treatment versus off treatment) and chemotherapy (on treatment versus off treatment), shown below in Table 32.

Table 32. Utility values applied in the company's base case economic model in the disease-free health states, dependent on treatment status

Disease-free treatment status	Utility value	Standard error
Alectinib - On-treatment	0.828	0.010
Alectinib - Off-treatment	0.863	0.014
Chemotherapy - On-treatment	0.811	0.011

Chemotherapy - Off-treatment	0.858	0.011

4.2.6.1.2 Disease recurrence health states

As HRQoL data was not collected in the ALINA trial following disease progression, the company applied utility values sourced from the literature for disease recurrence health states. As the company's HRQoL SLR excluded studies focused on progressed/metastatic disease, discussed previously in Section 4.1.1, it was unclear how the company identified the most appropriate study (Chouaid *et al.* 2013)[72] for use in the economic model and if any relevant studies may have been missed. In response to clarification, the company stated that this study was identified via an additional burden of illness (BOI) SLR of patients with locally advanced and metastatic NSCLC. However, the EAG was unable to identify any reference to HRQoL or the Chouaid *et al.* study in the BOI report provided by the company.

Chouaid *et al.*[72] estimated EQ-5D(-3L) utility values for adult patients with stage IIIB and stage IV NSCLC across 25 multinational sites, including the UK. At the time, the EQ-5D survey was completed, the majority of patients were stage IV (82.1%).

The CS originally stated that a value of 0.77 was applied to all disease recurrence health states, regardless of if this was local or metastatic recurrence. However, following a clarification question, the company confirmed that a value of 0.77 was applied only to patients with non-metastatic recurrence and a value of 0.70 for patients with metastatic recurrence. These values were obtained by using the coefficients for the intercept and stage IV disease from the linear regression model published in Chouaid *et al.*.,[72] shown below in Table 33.

Table 33. Regression coefficients used to estimate utility values for recurrence disease health states – reproduced from Table 3 of Chouaid *et al.* 2013[72]

Covariate	*Parameter estimate*	*Standard error*	*P-value*
Intercept	0.77	0.03	<0.0001
Stage IV	-0.07	0.04	0.0290
HS 1: first-line PF*	0.00	NA	NA
HS 2: first-line PD	-0.04	0.04	0.4067
HS 3: second-line PF	0.03	0.04	0.4697
HS 4: second-line PD	-0.11	0.08	0.1836

HS 5: third/fourth-line PF	-0.10	0.06	0.0920
HS 6: third/fourth-line PD	-0.26	0.08	0.0022

*reference category
Abbreviations: HS, health state; SE, standard error; PD, progressive disease; PF, progression-free; NA, not available

4.2.6.2 Adverse events disutility

As previously noted, the company did not separately account for disutility associated with treatment-related AEs, despite providing data on the monthly probability of AEs. The company stated that the reason for excluding disutilities for adverse events since this may lead to double counting given that differences between treatment were accounted for in the regression model fitted to utilities from the ALINA trial. In addition, no disutility associated with subsequent treatments with included in the economic model, despite costs of managing these being included (see Section 4.2.7.5)

4.2.6.3 Age-adjustment of utility values

The company's original submitted model used Ara and Brazier 2010[73] to apply age-related utility decrement. As a result of a clarification request, the company updated the model to use the Health Survey for England (HSE) 2014 dataset, as recommended by the NICE DSU (Hernández Alava *et al.* 2022).[71] The EAG notes that the company's application of age-adjustment was applied by bounding the utility value by the age-sex matched general population utility. The EAG consider a more appropriate technique is to multiply the health state utility values by general population utility at the age of interest divided by general population utility at the baseline age. Following clarification, the company updated the model to use this approach in their updated base case.

The EAG identified an error in the implementation of the age-adjustment of utility values which did not account for the cure fraction. This was amended in the EAG's preferred base-case, detailed in Section 6.

4.2.6.4 EAG critique

The EAG agrees with the company's use of EQ-5D-5L data collected from the key trial to inform health state utility values for the disease-free health state. However, the EAG considers there to be a number of limitations related to the following points which are discussed in further detail below:

- Implausibly high utility values for DF health states;
- Limitations of the regression analysis used to derive utility values in the DF health state;
- Implausibly high utility values in metastatic recurrence health states, which are independent of line of treatment;
- Exclusion of disutility associated with AEs.

Implausibly high utility values for DF health states

The utility values applied in the DF health state for patients no longer receiving adjuvant treatment in both treatment arms are higher than the mean age and sex matched general population. Clinical experts to the EAG noted that for DF patients who are no receiving treatment they would expect patients HRQoL to be similar to that of the general population, once recovered from surgery. The EAG considers the use of utility values higher than the general population to be implausible considering the long-term consequences that can occur related to receiving invasive treatments. Although the model accounts for general population age adjustment, the EAG consider it to highlight the limitations of the value used.

Limitations of the regression analysis used to derive utility values

The EAG notes that minimal detail was provided on the approach used for including predictors and it is unclear how the final model specification was chosen, e.g. if AIC and BIC statistics for several potential models were considered.

As previously discussed, the company noted that p-values obtained using the lme4 package in R can be difficult to interpret and therefore were omitted. The EAG notes that based on the standard errors and the provided t-values, it can be inferred that the coefficients for the alectinib treatment arm and interaction term of alectinib and treatment status are unlikely to be significant at $p < 0.05$. The EAG acknowledges that a finding not being statistically significance does not equate to no effect, and further notes the analysis was unlikely to be powered to detect meaningful increases of utility values for alectinib versus chemotherapy. In an additional clarification response, the company provided bootstrapped 95% confidence intervals for each parameter in the mixed effects model. The EAG notes that in the table provided by the company, the regression estimates do not match up with those previously provided as it appears that the values are offset by one row, with the final row of the table duplicated. This made it difficult for the EAG to correctly interpret but based on comparison with the previous results, the bootstrapped confidence intervals for both the alectinib

term and the alectinib*off treatment term cross zero, implying that they are not significant. The EAG considers there to be a large degree of uncertainty of the resulting utility values used in the economic model, especially concerning the presence and/or magnitude of the treatment specific utility assigned to alectinib.

The EAG's clinical experts considered it a reasonable assumption that patients receiving chemotherapy in the disease-free health state would have a lower HRQoL than patients receiving adjuvant alectinib due to more burdensome AEs with chemotherapy. Rather than applying separate utility values associated with treatment arm, the EAG considers that it would have been more appropriate to control for AEs in the regression analysis and apply separate disutility values associated with those experienced. During clarification (B24), the company stated that due to the need to estimate utility values for 'on treatment' for both alectinib and chemotherapy, it is expected that this will already account for any treatment related disutility and including a separate AE covariate may introduce issues, such as multicollinearity. The EAG notes that while this may be true, the inclusion of an AE covariate should have been explored. As previously noted, the regression coefficient for both alectinib and the interaction terms for alectinib*off treatment were both non-significant. Therefore, it is uncertain if separate utilities between treatment arms and treatment status is appropriate and therefore the 'need' to have separate utility values may not have been required. Overall, due to the limited justification for the approach used by the company, the EAG's preferred approach is to align utility values in the disease-free health state with age- and sex-adjusted utility values for the general population, with a one-off adjustment at baseline accounting for AEs.

Implausibly high utility values in metastatic recurrence health states, which are independent of line of treatment

Utility values for non-metastatic (0.77) and metastatic recurrence (0.70) health states were based on values obtained from a regression analyses by Chouaid *et al*. 2013.[72] It is noted in the CS that clinical experts considered the value of 0.77 too high for patients with metastatic disease; this input was therefore varied in scenario analyses. On examination of the company's clinical advisory board report it is reported that clinicians also considered a utility value of 0.70 to be too high for patients with metastatic disease recurrence. Based on the feedback from clinical experts in the advisory board meeting, it is unclear to the EAG as to why the company did not look to source alternative values for use in the economic model. The EAG notes that the company included a scenario analysis

in which the utility value after recurrence is stated to be 0.60. However, no details on the source of this value or whether this was applied to all recurrence health states is provided. During clarification, the company noted that this value was used to show the impact on the ICER when a conservative value is applied, as the true value is expected to be higher.

Instead of using an arbitrary value for the scenario analysis, it would have been more appropriate to examine alternative values available in the literature and used in previous appraisals. As utility values for metastatic/advanced NSCLC were excluded from the company's SLR, alternative values for use were not discussed. The EAG explored the utility values considered in the NICE TA for alectinib at advanced stage NSCLC (TA536). The company used utility values for progression based on the ALEX trial (0.725). As committee had concerns this value may be too high, a scenario analysis was included which used alternative values based on Roughley *et al.*[74] which reports a utility of 0.65 for progressed disease in the advanced setting. The EAG in TA536 preferred the use of utility values that accounted for both the site of progression (central nervous system [CNS] versus not) and weighted to reflect the distribution of subsequent treatment in each arm. Therefore, separate utility values were applied based on treatment arm of the model (alectinib versus crizotinib), type of progression and subsequent treatment used for second line metastases. As the subsequent treatments used in the appraisal are not entirely reflective of those used in the current appraisal, these values may not be directly comparable. However, the values applied for progressed disease by the EAG, and preferred by committee, ranged from 0.470 to 0.649; lower than those used in the current appraisal.

The EAG also explored the utility values used for recurrence in previous NICE TAs for adjuvant treatment of NSCLC, although none are specifically available for the ALK+ population. In TA761 for adjuvant osimertinib, the committee concluded that although there was concern that values may be too high, the company's utility values were acceptable for decision making. In TA823, the EAG was generally satisfied with the utility values applied by the company and these were ultimately used in decision making. Table 34 below shows utility values used in both the osimertinib and atezolizumab appraisals.

Table 34. Utility values used in previous NICE technology appraisals for adjuvant treatment of NSCLC

Health state	Current appraisal – adjuvant alectinib		TA823 – adjuvant atezolizumab		TA761 – adjuvant osimertinib	
	Utility value	Source	Utility value	Source	Utility value	Source
Disease-free survival	Alectinib on-treatment: 0.828 Alectinib off-treatment: 0.863 Chemotherapy on treatment: 0.811 Chemotherapy off treatment: 0.858	ALINA trial	Stage II: 0.78 Stage III: 0.73	Jang *et al.* 2010[75]	0.81	Mean utility for age-and sex-matched general population. Ara and Brazier *et al.* 2010[73]
Locoregional recurrence	0.77	Chouaid *et al.* 2013[72]	0.77	Chouaid *et al.* 2013[72]	0.81	Mean utility for age-and sex-matched general population. Ara and Brazier *et al*. 2010[73]
Metastatic recurrence (first line)	0.70	Chouaid *et al.* 2013[72]	0.71	Impower150 trial	0.794	FLAURA trial (EORTC QLQ-C30 mapped to EQ-5D-3L).
Metastatic recurrence (second line)			0.69	Impower150 trial	0.640	Labbé et al. 2017[76] (reported UK EQ-5D estimate)
No treatment in all recurrence states	NA	NA	0.62	Van den Hout *et al.* 2006[77]	NA	NA

Abbreviations: EORTC QLQ, European Organisation for Research and Treatment of Cancer - Quality of Life questionnaire; EQ-5D, EuroQol 5 dimension; NA, not applicable; NICE, National Institute for Health and Care Excellence; NSCLC, non-small cell lung cancer; TA, technology appraisal

Clinical experts to the EAG also noted that you may expect to see a difference in HRQoL based on the line of treatment patients are receiving in the metastatic stage, with HRQoL reducing due to the cumulative impact of treatments. This was not considered in the company's economic model, despite Chouaid *et al.* accounting for the impact of line of treatment in the advanced/metastatic setting.

As shown in Table 34, previous appraisals in adjuvant treatment for NSCLC applied separate utility estimates dependent on the line of treatment for metastatic recurrence, both of which are lower than that used in the current appraisal. However, values are not consistent across the two appraisals presented and although the EAG considers there to be uncertainty in the values, they are within the same range as those previously used. In addition, as more patients in the comparator arm are expected to progress to second line in the metastatic health state, applying a lower utility value for 2nd line treatment is expected to reduce the ICER.

While the EAG considers the values used in the current appraisal to be unreflective of the HRQoL of patients in the metastatic setting, an issue also observed in previous TAs, it is noted that the company's scenario using a value of 0.60 had a minimal impact on the ICER ([redacted] reduction). Therefore, despite the EAG's concerns about the validity of the utility values used, as they could be considered to result in a conservative ICER, the EAG considers them to not to be unreasonable for decision making.

Exclusion of disutility associated with adverse events

The EAG consider the exclusion of AE disutilities to be inappropriate and may underestimate the impact of treatment on HRQoL. As previously discussed, the company did not control for AEs in the regression model used to inform DF utility values and instead implicitly assumes that any differences between treatment arms is a result of AEs. The EAG considers that applying disutility values from the published literature for the AEs observed may have been a more appropriate method. The EAG notes that six grade 3-4 AEs occurred with a difference in incidence rate of at least 2% between treatment arms in the ALINA trial (see Section 3.3.4); neutrophil count decreased, blood creatine phosphokinase increase, white blood cell count decrease, neutropenia, nausea and asthenia. Nafees *et al*. 2008 is commonly used in previous appraisals for NSCLC as a source of estimates of disutility associated with regularly experienced AEs for NSCLC patients. Therefore, the EAG considers the implementation of a disutility associated with AEs to be appropriate to use in the model, and

explored the implementation of this in the CEM. Neutrophil count decreased, blood creatine phosphokinase increase and white blood cell count decrease are assumed to have no impact on patients HRQoL. The table below provides the disutility values sourced from Nafees *et al.* for the remaining AEs included in the model. Data on average duration of AEs was not available to the EAG and previous technology appraisals in NSCLC examined by the EAG either did not specify the AE duration used in disutility calculations or used a range of values, often based on assumption. Therefore, for simplicity, in the EAG's approach, it is assumed that AEs last for one model cycle (one month). This resulted in a one-off disutility in the chemotherapy arm of -0.00094, which had a negligible impact on the ICER (see Section 6). As none of the three included AEs were experienced in the alectinib arm, no disutility was applied.

Table 35. Adverse event disutilities applied by the EAG

Adverse event	Disutility value	Source
Neutropenia	-0.08973	Nafees *et al.* 2008
Nausea	-0.04802	Nafees *et al.* 2008
Asthenia	-0.07346	Nafees *et al.* 2008, assumed equal to fatigue

Abbreviations: EAG, External Assessment Group.

4.2.7 Resource use and costs

The company's model includes costs related to drug acquisition for adjuvant and subsequent treatments, drug administration, disease management costs, AEs, ALK mutation testing and end-of-life care. These are detailed further in the following subsections. Costs used in the model represent the most recent prices available.

4.2.7.1 Treatment acquisition costs

A PAS discount is in place for adjuvant alectinib, detailed below. Confidential PAS discounts/Commercial Medicines Unit (CMU) prices are also available for a number of subsequent treatments included in the economic model. As such, the EAG has produced a confidential appendix to the EAG report. Analyses included in the confidential appendix include the company base case results, scenario analyses and EAG base case and scenario analyses. Please refer to Appendix 8.1 for details on the source of the confidential price for each treatment.

Adjuvant alectinib has a list price of £5,032 per pack of 150mg tablets (224 tablets per pack) and is administered at a dose of 600mg daily, as stated in the summary of product characteristics (SmPC).[36]

A simple PAS discount is available for alectinib, resulting in a pack per price of [redacted]. All results presented in this report include the PAS price.

Patients were assumed to receive alectinib until disease progression, unacceptable toxicity or a maximum of two years, based on the SmPC and in line with the treatment schedule in the ALINA trial.[36, 37] The proportion of patients remaining on treatment at the beginning of each monthly cycle, based on clinical data from the ALINA trial, was used to inform alectinib drug acquisition costs. In the original CEM submitted by the company, a weekly treatment cost was calculated and applied in the estimation of monthly acquisition costs, as opposed to applying the cost of a full pack at the beginning of each cycle, which would be more reflective of treatment in clinical practice. Following clarification, the company provided a scenario analysis in which the cost of a full pack was applied at the beginning of each cycle. The company's base case analysis assumed a relative dose intensity (RDI) of 100%.

Adjuvant treatment in the comparator arm was platinum-based chemotherapy (PBC), administered for a total of four 21-day cycles. Patients received one of six possible PBCs in the model, based on treatments received in ALINA. The PBC treatment regimens included in the economic model are shown in Table 36, alongside the proportion of patients receiving each treatment and cost per administration. The company originally costed all PBC treatments using the British National Formulary (BNF); however, following clarification these were updated to use the latest prices available in the drugs and pharmaceutical electronic market information tool (eMIT) (see Table 35 of the CS for list prices).[78, 79] When different prices were available for different vial sizes, the company used the minimum cost based on dosage required. In the company's base case analysis, vial sharing was permitted.

To account for patients discontinuing treatment, the proportion of patients remaining on treatment at the beginning of each model cycle was informed from the ALINA trial for each PBC treatment regimen.

For any treatment doses based on weight or body surface area (BSA), the company used the average patient data from the ALINA trial: 69.63kg and 1.77m^2 respectively.[37] Dosing used for drug acquisition costs of carboplatin was informed by the Calvert formula, shown below, with average glomerular filtration rate (GFR) informed by patients in the ALINA trial (125ml/min).[80]

*Total dose (mg)= target area under the concentration [AUC] * (GRF + 25)*

Table 36. Dosage and treatment acquisition costs for adjuvant chemotherapy

Treatment regimen	Proportion receiving regimen	Individual regimen component	Administration per cycle	Dose per administration (mg)	Drug acquisition cost per administration	Total cost of treatment regimen per cycle
Cisplatin plus vinorelbine	17.50%	Cisplatin	Day 1: 75mg/m^2	133	£38.86	£344.30
		Vinorelbine	Day 1 and 8: 25mg/m^2	44	£152.72	
Cisplatin plus gemcitabine	0.80%	Cisplatin	Day 1: 75mg/m^2	133	£38.86	£119.28
		Gemcitabine	Day 1 and 8: 1250mg/m^2	2213	£40.21	
Cisplatin plus pemetrexed	70.00%	Cisplatin	Day 1: 75mg/m^2	133	£38.86	£255.87
		Pemetrexed	Day 1: 500mg/m^2	885	£217.00	
Carboplatin plus vinorelbine	1.70%	Carboplatin	Day 1: target AUC 5mg/ml/min	750	£89.30	£394.74
		Vinorelbine	Day 1 and 8: 25mg/m^2	44	£152.72	
Carboplatin plus pemetrexed	10.00%	Carboplatin	Day 1: target AUC 5mg/ml/min	750	£89.30	£306.61
		Pemetrexed	Day 1: 500mg/m^2	885	£217.00	

Abbreviations: AUC, area under curve; mg, milligrams.

4.2.7.1.1 EAG critique

As previously noted, the company's base-case analysis calculated a weekly treatment cost and applied this in the estimation of monthly acquisition costs, as opposed to applying the cost of a full pack at the beginning of each cycle. As treatment with alectinib would not be prescribed on a weekly basis, the EAG considers that the approach used by the company would lead to incorrect discounting of the true costs and underestimate the costs of alectinib if patients progress or die. Therefore, the EAG's preferred approach is to apply the cost of a full pack at the start of each cycle (see Section 6). The EAG notes that the company's scenario analysis implementing this was applied incorrectly. The EAG corrected this error; there was a minimal impact on the ICER as a result.

When updating the costs applied for chemotherapy treatments to use the latest eMIT prices following a clarification request, the EAG notes that the company made some minor errors. A lower price is available for the pemetrexed large vial size used in the model (£40.70 instead of £172.56). In addition, a more appropriate size for a large vial of gemcitabine is available (2g instead of 1g), resulting in a lower price. The EAG amended these in their preferred base case (See Section 6.1 for further details.)

As previously noted, the company assumed perfect vial sharing of chemotherapy treatments in their base-case analysis. The EAG consider this to be unreflective of clinical practice and therefore prefer the assumption of no vial sharing in the economic model in the calculation of chemotherapy costs.

4.2.7.2 Subsequent treatment acquisition costs

The costs for subsequent treatments were calculated by applying costs per month until treatment discontinuation, with the exception of costs for radiotherapy and surgery in the non-metastatic recurrence health state, which were applied as one-off costs. The company used a cost of £588.30 for surgery in their preferred base case; the source given was the NHS reference costs 2021-2022 (DZ02K- Complex Thoracic Procedures, 19 years and over, with CC Score 0-2);[81] however, the EAG has been unable to identify this cost in the stated source. The cost per radiotherapy fraction was based on a weighted average of NHS reference costs SSC22Z (Deliver a Fraction of Treatment on a Megavoltage Machine), SC31Z (Deliver a Fraction of Adaptive Radiotherapy on a Megavoltage Machine), and SC52Z (Preparation for Complex Conformal Radiotherapy, with Technical Support).[81] This cost was applied for a total of 33 fractions, in line with the Royal College of Radiologists' dose fractionation guidelines on radiotherapy for treatment of NSCLC.[82] However, the EAG notes that due

to an error in the model, no costs for radiotherapy were incorporated into the model results in the company's base case.

Costs for pharmacological treatments incorporated both treatment acquisition and administration costs; treatment acquisition costs were sourced from eMIT where possible, and BNF otherwise. Chemotherapy as a subsequent treatment was costed as a combination of cisplatin and pemetrexed for all health states; costs per treatment cycle for chemotherapy and alectinib were the same as the cost per cycle for adjuvant treatment (see Section 4.2.7.1). Costs did not account for RDI or vial wastage. Full details of the costs used for pharmacological treatments not including discounts are given in Table 37*;* details of the same costs including confidential discounts are presented in the confidential appendix.

Table 37. Dosage and treatment acquisition costs for subsequent treatments

Treatment regimen	Dosing schedule	Drug acquisition cost per administration	Total cost of treatment regimen per week
Brigatinib	180 mg once daily	£175.00	£1,225.00
Lorlatinib	100 mg once daily	£176.10	£1,232.70
Abbreviations: mg, milligrams.			

The approach for costing subsequent treatments did not explicitly incorporate time to discontinuation data in the CEM, but an option was included to allow the user to specify a maximum treatment duration. The maximum treatment durations and associated sources used in the company's base case are summarised in Table 38. In general, the company has used the maximum allowed treatment duration, median treatment duration or duration of response (DOR) reported for a corresponding treatment arm in a relevant trial; the latter is generally used for treatments which are received until disease progression. Please note, for some of these parameter values the EAG has been unable to identify the source used by the company.

Table 38. Maximum treatment duration for subsequent treatments

Health state	Treatment	Maximum treatment duration	Source
Non-metastatic recurrence	Alectinib	27 months	Median treatment duration, alectinib, ALEX trial (Camidge *et al.* 2019)[59]
	Chemotherapy	3 months	Maximum treatment duration, platinum-based chemotherapy,

			ASCEND-4 trial (Soria *et al.* 2017)[58]
Metastatic recurrence (1L)	Alectinib	27 months	Median treatment duration, alectinib, ALEX trial (Camidge *et al.* 2019)[59]
	Lorlatinib	33 months	Median treatment duration, lorlatinib, CROWN trial (Solomon *et al.* 2023)[60]
	Chemotherapy	10 months	Could not be identified
	Brigatinib	35 months	Mean DOR, brigatinib, ALTA-1L trial (Camidge *et al.* 2021)[61]
Metastatic recurrence (2L)	Alectinib	20 weeks	Median treatment duration, alectinib, ALUR trial (Novello *et al.* 2018)[83]
	Lorlatinib	33 weeks	Could not be identified
	Chemotherapy	6 weeks	Median treatment duration, chemotherapy, ALUR trial (Novello *et al.* 2018)[83]

Abbreviations: 1L, first line; 2L, second line; DOR, duration of response.

It should be noted that, due to the approach used for implementing subsequent treatments, the company's version of the CEM could only implement a maximum of 60 months of treatment with alectinib and 6 months of treatment with chemotherapy in the non-metastatic recurrence health state. Treatment costs were then applied using tunnel states to track the amount of time elapsed since a patient has started receiving treatment.

4.2.7.2.1 EAG critique

The EAG considers that the approach to calculating the cost per dose for subsequent treatments is broadly acceptable; however, the EAG's preferred base case incorporates an alternative cost of £9,201 for surgery based on DZ02K (Complex Thoracic Procedures, 19 years and over, with CC Score 0-2), elective procedures, NHS reference costs 2021-2022.[81] The EAG also considers that it would be more appropriate to assume vial wastage.

The EAG also has several concerns with the approach used to calculate subsequent treatment duration, as follows:

- The approach to costing chemotherapy is unlikely to be reflective of clinical practice; according to the EAG's clinical experts, patients would be likely to receive platinum-based chemotherapy for a limited number of cycles, alongside a maintenance pemetrexed component which would be received until disease progression.
- The sources for maximum treatment duration parameters for chemotherapy in the metastatic recurrence (1L) health state and lorlatinib in the metastatic recurrence (2L) heath state could not be identified by the EAG.
- In many cases, the maximum treatment duration has been parametrised using an average treatment duration or DOR. However, the approach to implementing tunnel states allows patients to progress prior to the average treatment duration being reached. Therefore, the subsequent treatment costs will consistently underestimate true costs.
- In the company's preferred base case, the sources for maximum treatment duration do not consistently align with the sources used to parametrise efficacy for each treatment; for example, in the non-metastatic recurrence health state, the maximum treatment duration for alectinib is parametrised based on the ALEX trial, while the efficacy for alectinib in this context is based on the ALINA trial. However, this is not a major consideration for the EAG's preferred base case, since the EAG prefers the use of the ALEX trial in this context.

Therefore, the EAG considers that the company's preferred base case does not accurately reflect the true costs for subsequent treatments. At the request of the EAG, during the clarification stage, the company produced a scenario in which the maximum treatment duration is not restricted; however, due to restrictions in the structure of the model (in particular, the limited number of tunnel states used to calculate treatment costs), this does not fully represent treatment to progression. As a result, the EAG has implemented an alternative approach to costing subsequent treatments, in which a one-off cost corresponding to the average duration of treatment is applied upon progression. Since other alternative data could not be identified, the duration of treatment for chemotherapy in the metastatic recurrence (1L) health state is aligned with the ASCEND-4 trial, while duration of treatment with lorlatinib in the metastatic recurrence (2L) health state is assumed to align with the duration of treatment with alectinib in the same context. The EAG also incorporates additional pemetrexed costs, reflecting maintenance treatment. The duration of the maintenance treatment is aligned with the median PFS reported in the corresponding source for efficacy data, i.e. 8.1 months for chemotherapy in the non-metastatic recurrence and metastatic recurrence (1L)

context, as reported in the ASCEND-4 trial, and 1.6 months for chemotherapy in the metastatic recurrence (2L) context, in line with the ALUR trial.[58]

As discussed in Section 4.2.2.1, it is the view of the EAG's clinical experts that patients are more likely to receive chemoradiation therapy rather than radiation alone; therefore, the EAG has included a scenario in the model in which the cost for six cycles of platinum doublet chemotherapy is added to the cost for radiotherapy, in line with Lee *et al.* 2019.[69] This scenario results in a [redacted] reduction in the ICER.

4.2.7.3 Administration costs

The company applied administration costs for both oral and IV treatments used in the model. For oral treatments, this was assumed to be equivalent to 12 minutes of pharmacist time every 4 weeks, sourced from the Personal Social Services Research Unit (PSSRU) 2023. The EAG notes that administration costs for alectinib were not applied correctly in the original submitted CEM, as administration costs were applied on a weekly basis. Following clarification, this was updated and implemented in the company's updated base case.

For intravenous (IV) chemotherapy treatments, the company applied an administration cost based on the SB14Z cost code from NHS Reference Costs 2021/22 (delivery of complex chemotherapy, including prolonged infusional treatment, at first attendance). This is equal to £475.94. Following clarification, at the request of the EAG, the company applied separate administration costs for all subsequent administrations (i.e. after the first administration), based on the SB15Z cost code (Deliver subsequent elements of a chemotherapy cycle), with an associated cost of £368.44. This was incorporated into the company's updated base case.

Table 36 of the CS summarises the costs and sources used for treatment administration, applied in the company's updated base case analysis.

4.2.7.4 Disease management costs

Disease management associated with each health state was informed by healthcare resource use (HCRU) reported in TA823 (atezolizumab)[33] and TA761 (adjuvant osimertinib)[34] and clinical expert opinion, obtained during the company's clinical advisory board meeting. All annual resource use rates were converted to monthly rates, in line with the model cycle length.

HCRU was combined with unit costs associated with each resource, sourced from either NHS Reference Costs 2021/22 or PSSRU 2023, to give a per cycle cost for each health state.

Table 39 shows annual resource use applied in the company's base case analysis, alongside the corresponding unit costs for each resource. Although not stated in the CS, resource use for outpatient visits was assumed to be related to treatment status in the metastatic recurrence health states. However, no further details were provided on the data informing these differences.

Table 39. Unit costs and annual resource use applied in each state

Resource Use	Unit cost	Source	Health state resource use					
			Disease-free	Non-metastatic recurrence	Metastatic recurrence (1st line)		Metastatic recurrence (2nd line)	
					On treatment	Off treatment	On treatment	Off treatment
Chest Radiography	£38.28	NHS reference costs 2021/2022: DAPF	1.00	1.00	1.00	1.00	1.00	1.00
Outpatient Visit	£194.71	NHS Reference costs 2021/22: Code 370 outpatient medical oncology	1.40	4.00	4.00	12.00	12.00	1.40
Community Nurse Visit	£82.00	PSSRU 2023: Band 8a, cost per hour	1.18	1.18	1.18	1.18	1.18	1.18
Clinical Nurse Specialist	£94.00	PSSRU 2023: Band 8b, cost per hour	1.70	1.70	1.70	1.70	1.70	1.70
GP Surgery Visit	£50.50	PSSRU 2023: Average cost per surgery consultation lasting 10 minutes	2.80	2.80	2.80	2.80	2.80	2.80
Echocardiogram	£363.09	NHS Reference costs 2021/22: EY50Z	0.00	0.00	2.50	2.50	2.50	2.50
MRI scans	£223.00	NHS Reference costs 2021/22: RD05Z - Magnetic Resonance Imaging Scan of Two or Three Areas, with Contrast	1.00	1.00	1.00	2.00	2.00	2.00
Complete blood count	£2.96	NHS Reference costs 2021/22: DAPS05 – Haematology	4.00	4.00	12.00	12.00	12.00	12.00
Liver Function test	£1.55	NHS Reference costs 2021/22: DAPS04 – Clinical biochemistry	4.00	4.00	12.00	12.00	12.00	12.00
Renal function test	£1.55	NHS Reference costs 2021/22: DAPS04 – Clinical biochemistry	4.00	4.00	12.00	12.00	12.00	12.00

Abbreviations: GP, general practitioner; MRI, magnetic resonance imaging.

The per-cycle disease management costs applied in the company's base case model are provided in Table 40.

Table 40. Disease management costs as applied in company's base case

Health state	Per cycle cost
Disease-free	£79.67
Non-metastatic recurrence	£121.86
Metastatic recurrence (1st line), on treatment	£201.54
Metastatic recurrence (1st line), off treatment	£349.93
Metastatic recurrence (2nd line), on treatment	£349.93
Metastatic recurrence (2nd line), off treatment	£177.93

In addition to disease management resource use costs applied each model cycle, the company also applied separate costs related to computed tomography (CT) scans, with frequency differing between health states, as shown in Table 41.

Table 41. Frequency of CT scans in each health state applied in company's base case

Time point of CT scan	Frequency
Disease-free health state	
First 24 months (2 years) after surgery	Every six months
Between 25 to 60 months (5 years) after surgery	Every 12 months
Month at which CT scans cease	60 months after surgery
Non-metastatic recurrence	
All time points	Every three months
Metastatic recurrence *(patients on 1L treatment only)*	
All time points	Every three months
Abbreviations: 1L, first-line; CT, computed tomography.	

4.2.7.4.1 EAG critique

During clarification, the EAG noted a number of misalignments of the resource use assumptions applied in the economic model with the advice obtained from the company's clinical experts. In the company's clinical advisory board report it was noted that all experts suggested that patients in the metastatic setting would receive CT scans every three months. However, in the company's economic model, patients with metastatic recurrence on second line treatment were assumed to have zero CT

scans. The company provided a scenario analysis with CT scans for patients in the metastatic recurrence (2L) health state included during clarification; however, they did not update the base case. As more patients in the chemotherapy arm of the model enter the metastatic recurrence (2L) health state, this scenario reduces the ICER, albeit by a minimal amount [redacted] Regardless, the EAG considers it more appropriate to include CT scans for patients in the metastatic recurrence (2L) health state, in line with clinical expert advice, and incorporates this amendment as a correction. In addition, clinical experts to the EAG also stated that patients would be required to attend an outpatient appointment every time a CT scan was required, as was also noted by one of the company's clinical experts. As such, the EAG considers it appropriate to apply additional outpatient visits to those already included for each CT scan.

The company's clinical advisory board report also suggested that patients with metastatic disease would receive magnetic resonance imaging (MRI) scans once every six months; however, the economic model assumed that patients in the metastatic recurrence (1L) health state have only one MRI per year. Despite noting that this was incorrectly incorporated in the economic model, the company did not update their base case. The EAG notes that this correction resulted in a small decrease in the ICER and is incorporated in the EAG's preferred analysis.

The EAG also considers that the costs used for community nurse visits and clinical nurse specialist attendance are too high, since the bands used to derive costs (8a and 8b respectively) are not representative of clinical practice; as a correction, the EAG updated the costs used to £53.00 for a community nurse visit (Band 5) and £74.00 for a clinical specialist nurse visit (Band 7). The GP cost used in the model (£50.50) also does not align with the stated source; the EAG has updated this cost to £56.

The company's clinical experts all agreed that 1.18 community nurse visits per year was higher than they would expect to see in clinical practice. This was also noted by clinical experts to the EAG who stated that this is not a resource that they routinely see provided on an annual basis. During clarification, the company provided an alternative scenario in which the number of annual community nurse visits was assumed to be 0.5 in all health states. This had a minimal increase in the ICER. Based on the clinical expert advice from both the company's and the EAG's clinical experts, the EAG consider it more appropriate to remove this resource use from the routine monthly disease management costs.

The EAG's clinical experts noted that all patients receiving alectinib and any chemotherapy treatment would require blood tests prior to each cycle of treatment as part of routine monitoring. While the company's disease management resource use includes full blood counts in the disease-free health state, this does not account for the increased requirement suggested by the clinical experts related to treatment. During clarification, the company provided a scenario in which all patients receiving alectinib and any chemotherapy treatment receive blood tests prior to each cycle of treatment. However, this scenario was implemented incorrectly, since the costs for additional blood tests were only applied to patients receiving treatment with cisplatin. However, a corrected version of this scenario was implemented in the EAG's preferred model (see Section 6).

Resource use estimates applied in the model are based on previous technology appraisals and clinical experts' opinions. The EAG notes that across previous appraisals in similar areas,[33, 34] there are often small discrepancies in the resource use applied for each health state. As was seen in the company's clinical advisory board meeting report, there are often differences in opinion from clinical experts, highlighting how routine practice in disease management may differ between centres. Therefore, the EAG considers there to be some uncertainty in the resource use applied in each health state. However, based on the results of the requested scenario analyses during clarification, the EAG does not expect this uncertainty to result in large changes in the ICER.

4.2.7.5 Adverse event costs

The company applied costs associated with the management of AEs for both adjuvant and subsequent treatments. Data on frequency of AEs for adjuvant treatments was informed by the ALINA trial, as discussed in Section 3.3.4. Details on the source of AE data for subsequent treatments was not provided in the CS and is unclear from the data presented in the CEM. In general, the source of the AE data appears to be based on the same sources used for effectiveness, although this is not true for all cases (see Section 4.2.7.5.1 for further detail).

The company based the costs of managing AEs included in the economic model on previous NICE technology appraisals and assumptions. The unit costs used for those included is shown in Table 42.

Table 42. Unit costs of adverse events included in the company's economic model for both adjuvant and subsequent treatments

Adverse event	Unit cost	Source
Neutrophil count decreased	£0.00	NICE TA428

Blood creatine phosphokinase increased	£0.00	NICE TA531
Alanine aminotransferase increased	£0.00	Assumption
Glutamyltransferase increased	£0.00	Assumption
White blood cell count decreased	£0.00	NICE TA428
Neutropenia	£747.24	Inflated from NICE TA812
Nausea	£1266.62	Inflated from NICE TA812
Asthenia	£0.00	NICE TA531
Appendicitis	£4,376.75	NHS reference costs 2021/22 - FF37D
Febrile neutropenia	£0.00	NICE TA531
Hypercholesterolaemia	£0.00	Assumption
Hypertriglyceridaemia	£0.00	Assumption
Weight increased	£0.00	Assumption
Hypertension	£770.10	NHS Reference costs 2021/22 - EB04Z
Lipase increased	£0.00	Assumption

Abbreviations: NICE, National Institute for Health and Care Excellence; TA, technology appraisal.

The company calculated a monthly probability of AEs occurring and applied a per month cost in each model cycle. The monthly cost of managing AEs applied in the company's economic model for both adjuvant and subsequent treatments are shown below in Table 43. To note, the EAG found a number of errors and discrepancies in the costs applied, discussed further in Section 4.2.7.5.1.

Table 43. Monthly cost of AE management for adjuvant and subsequent treatments applied in the company's base case

Health state	Treatment	Monthly costs of managing AEs
Disease-free	Alectinib	£1.07
	Chemotherapy	£3.59
Non-metastatic recurrence	Radiotherapy	£1.94
	Surgery	£0.00
	Alectinib	£0.00
	Chemotherapy	£0.00
Metastatic recurrence (1L)	Alectinib	£0.00
	Chemotherapy	£0.19
	Brigatinib	£2.66
	Lorlatinib	£2.39
Metastatic recurrence (2L)	Alectinib	£0.00
	Lorlatinib	£0.00
	Chemotherapy	£0.00

Abbreviations: 1L, first line; 2L, second line; AE, adverse event.

4.2.7.5.1 EAG critique

During clarification, the EAG noted a number of errors and discrepancies with the application and write up of the AEs costs described in the economic model and CS. While some of these concerns were addressed during the clarification stage, the EAG notes that a number of issues remain, relating to the following points:

- Incorrect calculation of monthly probability of AEs;
- Inclusion of appendicitis cost despite not meeting the stated inclusion criteria for AEs in the CEM;
- Inconsistent and unclear use of data used for subsequent treatments AEs;
- Clinically implausible costs used for subsequent treatment AEs (e.g. febrile neutropenia).

Although not clearly reported, the company appear to use the entire follow up duration for the calculation of the monthly probability of an AE as opposed to the safety follow up period in each treatment arm. The EAG incorporated a correction to address this issue in which the follow up period for the alectinib arm is assumed to be 25 months and 5 months in the chemotherapy arm. The company's approach underestimates the costs of management of AEs in the chemotherapy arm of the model and therefore amending this reduces the ICER, albeit by a minimal amount.

The company stated that only Grade 3 to 5 treatment-related AEs with a difference in incidence rate of at least 2% between treatment arms were included in the economic model. However, treatment-related appendicitis did not have a difference in incidence rates between the treatment arms of 2% or more. The difference in incidence rate of 2% or greater is only applicable when considering appendicitis as "all Grade 3-5 AEs", as opposed to treatment-related, therefore, the EAG does not consider it appropriate to include. The EAG considers this to be an error and has removed the cost related to appendicitis in the EAG preferred base case (see Section 6).

The company used the cost for both neutropenia and nausea directly from NICE TA812. During clarification, the EAG highlighted that TA812 referenced TA531 as the original cost source and inflated costs to the appropriate year. The EAG noted that the company had not accounted for the fact that TA812 uses a different cost year to the current appraisal. During clarification, the EAG requested that the company inflated the costs from the original source (Brown *et al.* 2013)[84] to the current price year. The company instead inflated from TA812, however, it was unclear to the EAG if

this was done appropriately as it appeared to have only been inflated from the previous cost year, whereas TA812 used costs from 2019/20. In addition, the EAG notes that in the original cost source, Brown *et al.* 2013,[84] the cost for nausea is reported to be £443.54 (2009/10 prices) per episode, but the study assumes that patients will require two hospital admissions during chemotherapy. Due to this, previous TAs have assumed the cost of nausea is double. This price has then regularly been inflated, including in the current TA, without accounting for the data in the original source. Therefore, the EAG considers it more appropriate to apply the cost for managing nausea equal to the per episode cost reported in Brown *et al.*[84] and inflated to current prices.[85] This has been incorporated into the model as a correction.

As previously noted, the company did not provide any detail on the source of AEs used for subsequent treatments. In response to clarification, the company stated that "… *AEs that occurred with a difference in incidence rate of at least 2% between treatment arms were included in the model in line with the disease-free health state*". However, it is unclear to the EAG the exact trial data used to inform this, although for metastatic recurrence health states, the model appears to have used data from the same trials used to inform effectiveness data. In the non-metastatic recurrence health state, the company applied the same AE frequency data from the alectinib arm of the ALINA trial for patients receiving alectinib, as for adjuvant alectinib. However, the chemotherapy arm AEs of the ALINA trial were applied to patients receiving radiotherapy for non-metastatic recurrence, whereas those receiving surgery or chemotherapy are assumed to have no AEs. It is unclear to the EAG why these data were used to parametrise these model inputs. The EAG also notes that despite applying the same AE frequency data used in the disease-free health state for alectinib to those in non-metastatic recurrence, the overall monthly costs differs (as seen in Table 43) as the company assumed that only neutropenia has an associated cost in the non-metastatic health state and all other costs are set to zero. It is unclear to the EAG why the company used this inconsistent approach.

The company assumed the cost associated with the management of febrile neutropenia to be zero, based on previous NICE TA531. However, The EAG notes that the cost of managing neutropenia in the company's model is £747 and therefore the EAG does not consider it clinically plausible that the management of febrile neutropenia would be lower than the cost for managing neutropenia, and especially not zero. Despite the EAG considering this to be incorrect, febrile neutropenia does not appear to occur in greater than 2% of patients in any of the included treatments modelled and

therefore this cost is not actually applied in the economic model. Therefore, the EAG is unsure why this was reported.

Due to the aforementioned reasons, there is considerable uncertainty in the modelling of AEs for subsequent treatments in the economic model. Therefore, the EAG considers it to be more appropriate to remove costs of managing all AEs associated with subsequent treatments. While this will underestimate the costs in both treatment arms, the EAG does not consider AEs to be a key driver of the ICER and considers it more appropriate than using inconsistent methods.

As the included Grade 3-5 AEs are expected to require a hospital attendance, the EAG considers it inappropriate to apply zero costs for their management. Therefore, for AEs observed in ALINA for adjuvant alectinib and chemotherapy included in the DF health state, the EAG considers it more appropriate to include a cost associated with outpatient visit. The unit costs applied in the EAG's preferred base case are shown below in Table 44. This includes the costs of neutropenia and nausea inflated from the original source by the EAG, based on previous discussion.

Table 44. Unit costs for adverse event management applied in the EAG preferred base case

Adverse event	Unit cost	Source
Neutrophil count decreased	£205.78	NHS Reference Costs 2021/22: Total outpatient attendances, Medical oncology service.[81]
Blood creatine phosphokinase increased	£205.78	NHS Reference Costs 2021/22: Total outpatient attendances, Medical oncology service.[81]
White blood cell count decreased	£205.78	NHS Reference Costs 2021/22: Total outpatient attendances, Medical oncology service.[81]
Neutropenia	£717.26	Brown *et al.* 2013.[84] Cost per episode to treat non-febrile neutropenia (£537.52), inflated by the EAG from 2009/10 prices to 2023 using NHSCII pay and prices index 2022/23[85]
Nausea	£591.86	Brown *et al.* 2013. Cost per episode to treat non-nausea (£443.54),[84] inflated by the EAG from 2009/10 prices to 2023 using NHSCII pay and prices index 2022/23[85]
Asthenia	£205.78	NHS Reference Costs 2021/22: Total outpatient attendances, Medical oncology service.[81]

Abbreviations: EAG, External Assessment Group; NHSCII, National Health Service Cost Inflation Index; NICE, National Institute for Health and Care Excellence; TA, technology appraisal.

4.2.7.6 ALK mutation testing

The company's model assumed that all patients receiving adjuvant alectinib or chemotherapy would require an ALK mutation test prior to starting treatment, which was applied as a one-off cost to all patients at the beginning of the model. The cost of immunohistochemistry (IHC) testing was assumed to be £50, sourced from the adult immunohistochemistry laboratory based within Manchester University NHS trust.[86]

4.2.7.7 End of life costs

The company applied a cost associated with end-of-life care to all disease-related deaths occurring in the model. Based on the trial evidence, the company assumed that deaths occurring from the disease-free health state are not disease-related and therefore did not apply any costs to deaths from occurring from this health state. While the EAG considers that some deaths in the DF health state may be related to NSCLC, as the number modelled is extremely small, the EAG considers the approach used to be acceptable.

Following clarification, the company updated the cost used for disease related deaths to use the end-of-life costs associated with cancer available in the PSSRU 2023.[85] However, the EAG notes that the company incorrectly used the number of patients informing the average cost (19,934) as the input parameter, as opposed to the actual cost reported. Therefore, the EAG updated this error in model corrections (Section 6.1) to £13,314 (hospital and social care cost).

5 Cost effectiveness results

5.1 Company's cost effectiveness results

The results of the company's base case deterministic cost-effectiveness analysis are presented in Table 45. The deterministic analysis gives incremental costs of [redacted] for an increase of 3.30 quality-adjusted life years (QALYs), leading to an overall incremental cost-effectiveness ratio (ICER) of [redacted]/QALY. Please note that since active monitoring was not considered a key comparator, fully incremental analyses are not presented; however, individual results for the conservative scenario for active monitoring described in Section 4.2.3 are given as a scenario analysis in Section 5.3 below.

Table 45. Company's base case results: deterministic

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Alectinib	[redacted]	12.40	9.90	-	-	-	-
PBC	[redacted]	8.51	6.60	[redacted]	3.89	3.30	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; PBC, platinum-based chemotherapy; QALY, quality-adjusted life-year

5.2 Company's sensitivity analyses

5.2.1 Probabilistic sensitivity analyses

A probabilistic sensitivity analysis (PSA) was conducted to assess the combined parameter uncertainty; a Monte Carlo simulation with 1,000 simulations was run in order to generate results. The PSA gave an average of 3.23 incremental QALYs for alectinib compared to chemotherapy, at an additional cost of [redacted], giving an ICER of [redacted]/QALY; this is generally well aligned with the deterministic results. Further details are given in Table 46.

Table 46. Company's base case results: probabilistic

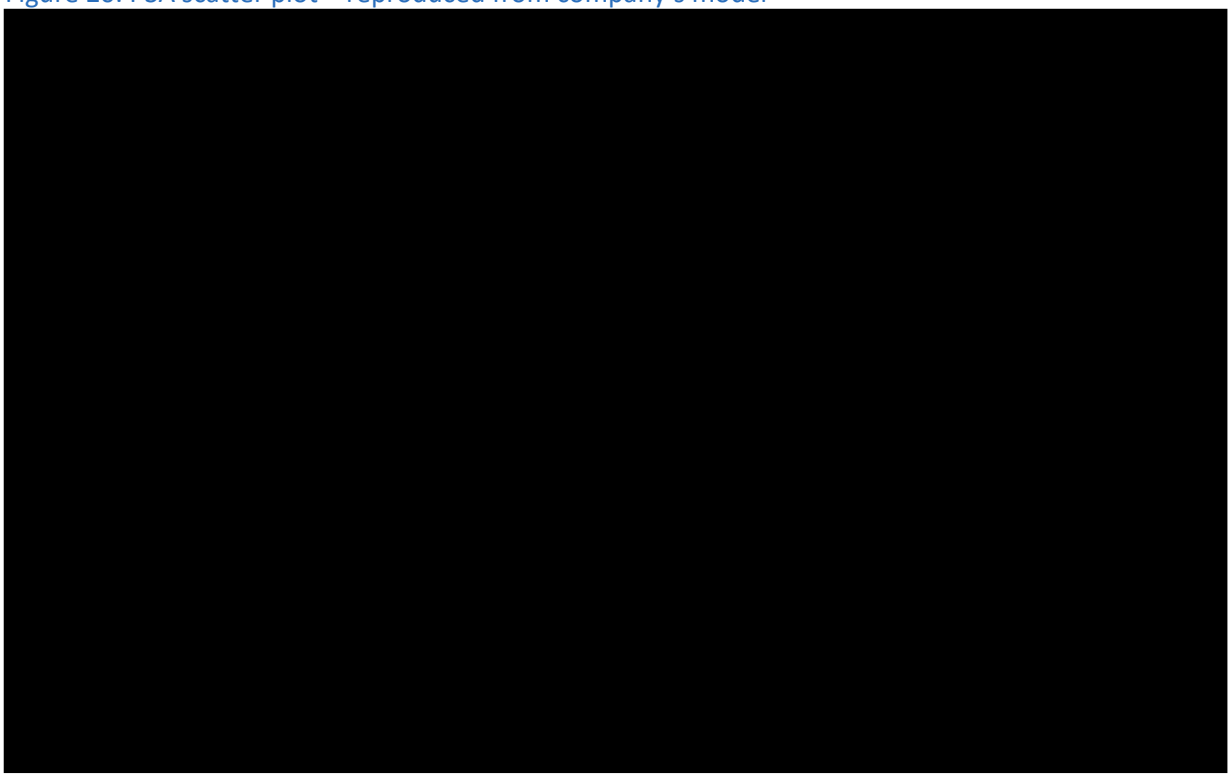
Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Alectinib	[redacted]	12.35	9.87	-	-	-	-
PBC	[redacted]	8.53	6.64	[redacted]	3.82	3.23	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; PBC, platinum-based chemotherapy; QALY, quality-adjusted life-year

Results of individual runs in the PSA are illustrated in the cost-effectiveness plane scatterplot below (Figure 20), and the cost-effectiveness acceptability curve (CEAC) is shown in Figure 21; both have

been produced using the company's updated model. Using the company's base case assumptions, the ICER for alectinib lies below the £20,000/QALY and £30,000/QALY thresholds with probabilities of 99% and 100%, respectively.

Figure 20. PSA scatter plot – reproduced from company's model



5.2.2 *One-way sensitivity analysis*

The company also conducted a one-way sensitivity analysis (OWSA); the results from the company's updated model are displayed in the tornado plot below. Notably, the parameters which have the greatest impact on the overall ICER tend to be treatment market shares for subsequent treatments.

Figure 22. One-way sensitivity analysis tornado plot, company base case – reproduced from company's model

Abbreviations: 1L, first line; 2L, second line; ALE, alectinib; CHT, chemotherapy; DFS, disease-free survival; inc., incremental; PFS, progression-free survival; QALY, quality-adjusted life year.

5.3 Company's scenario analyses

The company conducted a range of scenario analyses to explore the impact of specific alternative assumptions. The deterministic results based on the company's updated model are presented in Table 47. It is notable that the choice of disease-free survival (DFS) extrapolation can have a considerable impact on the ICER (varying the extrapolation chosen gives ICERs between [redacted] for the exponential extrapolation, and [redacted] for the Gompertz extrapolation). It is also notable that the ICER is particularly sensitive to the cure timepoint and cure proportion.

Table 47. Company scenario analyses

Scenario	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Base case	[redacted]	3.89	3.30	[redacted]
Time horizon: 10 years	[redacted]	1.12	1.10	[redacted]
Time horizon: 20 years	[redacted]	2.80	2.48	[redacted]
Time horizon: 30 years	[redacted]	3.68	3.15	[redacted]
DFS extrapolated using joint exponential distribution	[redacted]	4.77	4.06	[redacted]
DFS extrapolated using joint Weibull distribution	[redacted]	4.65	3.94	[redacted]
DFS extrapolated using joint log-normal distribution	[redacted]	3.59	3.05	[redacted]
DFS extrapolated using joint generalised gamma distribution	[redacted]	4.25	3.60	[redacted]
DFS extrapolated using joint Gompertz distribution	[redacted]	3.96	3.34	[redacted]
DFS extrapolated using joint gamma distribution	[redacted]	4.51	3.82	[redacted]
Cure proportion: 0%	[redacted]	3.43	2.89	[redacted]
Cure proportion: 30%	[redacted]	3.55	3.00	[redacted]
Cure proportion: 70%	[redacted]	3.75	3.17	[redacted]

Cure proportion: 100%	[redacted]	3.92	3.32	[redacted]
Cure timepoint: 5 years	[redacted]	4.12	3.51	[redacted]
Cure timepoint: 20 years	[redacted]	3.48	2.94	[redacted]
ALINA trial data pooled between arms to estimate split of recurrence types	[redacted]	3.92	3.32	[redacted]
Treatment effect waning included	[redacted]	2.65	2.23	[redacted]
SMR: 1.7	[redacted]	3.52	3.02	[redacted]
SMR: 2.3	[redacted]	3.14	2.72	[redacted]
Cost of ALK+ testing excluded	[redacted]	3.89	3.30	[redacted]
Utility value post-recurrence: 0.60	[redacted]	3.89	3.45	[redacted]
Active monitoring as comparator	[redacted]	3.89	3.30	[redacted]

Abbreviations: ALK+, anaplastic lymphoma kinase positive; DFS, disease-free survival; SMR, standardised mortality ratio.

5.4 Model validation and face validity check

The company submission (CS) states that the modelling approach and inputs were validated by UK clinicians at the company's advisory board meeting, and results from the cost-effectiveness model (CEM) were validated. Validation of the implementation of the model was conducted by an external consultancy; the CS states that a cell-by-cell verification of the model was performed, alongside 'pressure tests' based on extreme input values. Further details of the tests performed were not given, and it was not stated whether a standard checklist was used to validate the model functionality.

The External Assessment Group (EAG) notes that a large number of avoidable errors were included in the original CEM submitted by the company. While many of these were corrected at the EAG's request during the clarification stage, further errors were also introduced, which have subsequently been corrected by the EAG (further details are given in Section 6.1). Many of the errors identified by the EAG should have been picked up by standard face validity checks or pressure tests (for example, the inadvertent use of Canadian costs for adverse events (AEs) in the submitted version of the CEM,

or the exclusion of administration costs for adjuvant alectinib). This suggests that the company's approach to model validation was limited.

5.4.1 Validation of derived overall survival against ALINA trial

At the EAG's request, the company provided a comparison of the derived overall survival (OS) data from the CEM with the observed OS from the ALINA trial. The results for the corrected company base case are shown in Figure 23. It is notable that the OS observed in the ALINA trial is consistently higher than the OS results from the CEM in both cases. Since fewer deaths occurred over the ALINA trial than expected for the age- and sex-matched general population, this may account for the discrepancy. Therefore, no robust conclusions can be drawn from this comparison.

Figure 23. Comparison of OS derived from model with Kaplan-Meier data from ALINA trial: corrected company base case

Abbreviations: ALE, alectinib; CHT, chemotherapy; OS, overall survival.

Figure 24. Comparison of OS derived from model with Kaplan-Meier data from ALINA trial: EAG base case

6 Additional economic analysis undertaken by the EAG

6.1 Model corrections

The External Assessment Group (EAG) has corrected the following errors in the cost-effectiveness model (CEM) provided by the company:

- Transition probabilities for the disease-free health state had not been adjusted to account for the bounding by background mortality (further details are given in Section 4.2.5.2.6).
- The updated approach for age-adjustment of utility values did not account for the cure fraction (further details are given in Section 4.2.6.3).
- Radiotherapy costs had been inadvertently excluded from subsequent treatment cost calculations.
- The cost for some treatments was incorrect (further details are given in Section 4.2.7.1.1).
- The cost for surgery as a subsequent treatment was incorrect (further details are given in Section 4.2.7.2.1).
- The cost for a General Practitioner (GP) appointment, community nurse visit and clinical nurse specialist were incorrect (further details are given in Section 4.2.7.4.1).
- The cost for computed tomography (CT) scans in the metastatic recurrence (2L) health state had been inadvertently excluded (further details are given in Section 4.2.7.4.1).
- The frequence of magnetic resonance imaging (MRI) scans in the metastatic recurrence (1L) health state was set to once a year instead of twice a year (further details are given in Section 4.2.7.4.1).
- Appendicitis was included as an AE, although the stated inclusion criteria were not met (further details are given in Section 4.2.7.5.1).
- Some AE costs were incorrect (further details are given in Section 4.2.7.5.1).
- The incorrect follow-up period was used to calculate the monthly probability of AEs (further details are given in Section 4.2.7.5.1).
- The end-of-life cost applied by the company was incorrect (further details are given in Section 4.2.7.7).
- Half-cycle correction had not been applied to treatment costs calculated using tunnel states.

- The company's active monitoring scenario was incorrect, since all treatment costs for chemotherapy were removed, including costs for chemotherapy as a subsequent treatment as well as an adjuvant treatment.
- The company's scenario applying full pack costs for alectinib at the start of each month was implemented incorrectly, since the administration costs had inadvertently been multiplied by 4.
- The company's scenario incorporating additional costs for one blood test per treatment cycle while on treatment was implemented incorrectly, as the additional cost was applied only to patients receiving cisplatin.

The impact of these corrections on the company base case is illustrated in Table 48.

Table 48. Corrected company base case

Intervention	Total Costs	Total LY	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Company base case							
Alectinib	[redacted]	12.40	[redacted]	-	-	-	-
PBC	[redacted]	8.51	[redacted]	[redacted]	3.89	3.30	[redacted]
Corrected company base case							
Alectinib	[redacted]	12.82	[redacted]	-	-	-	-
PBC	[redacted]	8.60	[redacted]	[redacted]	4.22	3.56	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; PBC, platinum-based chemotherapy; QALY, quality-adjusted life-year

6.2 EAG scenario analyses

The EAG conducted additional scenario analyses to explore the effects of parameter uncertainty in the model; deterministic results including the patient access scheme (PAS) discount for alectinib are presented in Table 49 below. Probabilistic results were not generated, as the probabilistic results were found to align well with deterministic results. Scenario results including additional confidential prices for subsequent treatments are provided in the confidential appendix.

For all scenarios explored, patients treated with alectinib accumulated both more quality-adjusted life years (QALYs) and more costs than patients treated with platinum-based chemotherapy (PBC); in all cases, the resulting incremental cost-effectiveness ratio (ICER) was below the £20,000/QALY threshold.

Table 49. Results of the EAG's scenario analyses

	Results per patient	Alectinib	PBC	Incremental value
0	Corrected company base case			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	10.24	6.67	3.56
	ICER (£/QALY)	-	-	[redacted]
1	Scenario with active monitoring as the comparator			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	10.24	6.67	3.56
	ICER (£/QALY)	-	-	[redacted]
2	BICR DFS data is used			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	10.46	7.48	2.98
	ICER (£/QALY)	-	-	[redacted]
3	Patients' age at baseline is assumed to be 70 years			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	7.74	5.74	2.01
	ICER (£/QALY)	-	-	[redacted]
4	Alternative joint DFS extrapolations are used (joint log-normal)			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	10.46	7.17	3.29
	ICER (£/QALY)	-	-	[redacted]
5	Alternative independent DFS extrapolations are used (exponential extrapolation for alectinib, log-logistic extrapolation for chemotherapy)			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	10.92	6.63	4.29
	ICER (£/QALY)	-	-	[redacted]
6	Pessimistic but plausible PFS extrapolations for subsequent treatments are used (Gompertz extrapolation for brigatinib and log-normal extrapolation for lorlatinib in the metastatic recurrence (1L) setting)			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	9.91	6.38	3.54
	ICER (£/QALY)	-	-	[redacted]
7	PFS for patients treated with radiation therapy in the non-metastatic recurrence setting is aligned with Lee *et al.* 2019, reflecting treatment with chemoradiation (base case: PFS is aligned with Nakamichi *et al.* 2017)			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	9.88	6.51	3.37
	ICER (£/QALY)	-	-	[redacted]
8	Treatment market shares in the non-metastatic recurrence setting are reweighted to exclude surgery			

	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	9.85	6.50	3.34
	ICER (£/QALY)	-	-	[redacted]
9	Treatment market shares for alectinib in the non-metastatic recurrence setting are set equal to PBC			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	10.26	6.67	3.59
	ICER (£/QALY)	-	-	[redacted]
10	Treatment market shares for alectinib in the metastatic recurrence (1L) setting are set equal to PBC			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	10.15	6.67	3.47
	ICER (£/QALY)	-	-	[redacted]
11	Treatment market shares for alectinib in the metastatic recurrence (2L) setting are set equal to PBC			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	10.27	6.67	3.59
	ICER (£/QALY)	-	-	[redacted]
12	Alternative cure assumption is used (81% cure in both arms at 5-year timepoint)			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	11.04	7.43	3.61
	ICER (£/QALY)	-	-	[redacted]
13	SMR for background mortality is removed			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	10.48	6.76	3.72
	ICER (£/QALY)	-	-	[redacted]
14	Treatment waning effect is applied from 5 years to 7 years after commencing treatment			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	9.08	6.67	2.41
	ICER (£/QALY)	-	-	[redacted]
15	Proportion of progression events per PFS event in the non-metastatic recurrence and metastatic recurrence (1L) settings is assumed to be 100% (base case value = 88.9%)			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	10.30	6.79	3.51
	ICER (£/QALY)	-	-	[redacted]
16	Proportion of progression events per PFS event in the non-metastatic recurrence and metastatic recurrence (1L) settings is assumed to be 80% (base case value = 88.9%)			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	10.17	6.56	3.61
	ICER (£/QALY)	-	-	[redacted]
17	No restrictions on time to rechallenge with alectinib (base case: rechallenge only permitted 2 years from starting treatment)			
	Total costs (£)	[redacted]	[redacted]	[redacted]

	QALYs	10.24	6.67	3.56
	ICER (£/QALY)	-	-	[redacted]
18	Rechallenge with alectinib only permitted 2.5 years from starting treatment			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	10.24	6.67	3.56
	ICER (£/QALY)	-	-	[redacted]
19	Additional treatment costs for chemoradiation are applied to patients receiving radiation therapy in the non-metastatic recurrence health state			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	10.24	6.67	3.56
	ICER (£/QALY)	-	-	[redacted]

Abbreviations: 1L, first line; 2L, second line; BICR, blinded independent central review; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; PBC, platinum-based chemotherapy; PFS, progression-free survival; QALY, quality adjusted life year; SMR, standardised mortality ratio.

6.3 EAG preferred assumptions

The EAG's preferred base case analysis incorporates the following assumptions:

- No disease-related deaths occur in the disease-free health state;
- Disease-free survival (DFS) is modelled using independent extrapolations, with the Weibull extrapolation for the alectinib arm, and the log-logistic extrapolation for the chemotherapy arm;
- Transition probabilities for subsequent treatment are time-variant, with extrapolations based on the standard extrapolations with best statistical fit;
- Progression-free survival (PFS) for patients receiving alectinib as a treatment for non-metastatic recurrence is aligned with the ALEX trial;
- The cure fraction is assumed to be 91% in both treatment arms;
- Health-related quality of life (HRQoL) for the disease-free health state is assumed equal to age- and sex-adjusted general population norms, with a one-off disutility for adverse events (AEs) applied at baseline;
- Treatment acquisition and administration costs for subsequent treatments are applied as one-off costs upon progression; costs for maintenance pemetrexed as a component of chemotherapy as a subsequent treatment are incorporated;
- The EAG-preferred approach is used for treatment costs:

    - The cost for alectinib is applied as a one-off pack cost at the start of each cycle, rather than on a per-cycle basis;
    - Vial sharing is not assumed.
- The EAG's preferred approach is used for resource use:
    - Costs for community nurse visits are excluded from the model;
    - An additional outpatient visit is incorporated for every CT scan performed;
    - An additional blood test is carried out for each cycle on treatment;
- AE costs for subsequent treatments are excluded;
- A half-cycle correction is applied.

The effect of each of these assumptions on the corrected company base case is presented in Table 50, while the deterministic EAG base case results are presented in more detail in Table 53.

Table 50. EAG's preferred modelling assumptions

EAG-preferred assumption	Section in EAG report	Individual ICER compared to company base case £/QALY	Cumulative ICER £/QALY
Corrected company base case	N/A	[redacted]	N/A
No disease-related deaths occur in the disease-free health state	4.2.5.2.6	[redacted]	[redacted]
EAG-preferred extrapolations for DFS	4.2.5.2.6	[redacted]	[redacted]
EAG-preferred approach for deriving transition probabilities for subsequent treatments	4.2.5.3.4	[redacted]	[redacted]
PFS for patients receiving alectinib as a treatment for non-metastatic recurrence is aligned with the ALEX trial	4.2.5.3.4	[redacted]	[redacted]
No difference in assumed cure fraction for alectinib and chemotherapy	4.2.5.2.6	[redacted]	[redacted]
HRQoL for the disease-free health state is assumed equal to age- and sex-adjusted general population norms, with a one-off disutility for adverse events applied at baseline	4.2.6.4	[redacted]	[redacted]
Treatment acquisition and administration costs for subsequent treatments are applied as one-off costs upon progression; costs for maintenance pemetrexed as a component of chemotherapy as a subsequent treatment are incorporated	4.2.7.2.1	[redacted]	[redacted]
EAG-preferred approach for treatment acquisition costs	4.2.7.1.1	[redacted]	[redacted]
EAG-preferred assumptions for resource use	4.2.7.4.1	[redacted]	[redacted]

Adverse event costs for subsequent treatments are excluded	4.2.7.5.1	[redacted]	[redacted]
Application of half-cycle correction	4.2.4.1	[redacted]	[redacted]

Abbreviations: DFS, disease-free survival; EAG, External Assessment Group; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; N/A, not applicable; PFS, progression-free survival; QALY, quality-adjusted life-year.

Table 51. EAG's base case results: deterministic

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Alectinib	[redacted]	11.71	9.46	-	-	-	-
PBC	[redacted]	8.08	6.32	[redacted]	3.63	3.15	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; LY, life year; PBC, platinum-based chemotherapy; QALY, quality-adjusted life-year

6.4 Sensitivity analyses undertaken by the EAG

6.4.1 Probabilistic sensitivity analyses

The probabilistic sensitivity analysis (PSA) was rerun over 2,000 iterations using the EAG's preferred assumptions, since the incremental net monetary benefit (NMB) plot suggested that 1,000 iterations was insufficient to achieve convergence. This gave an average of 3.10 incremental QALYs for alectinib compared to chemotherapy, at an additional cost of [redacted], giving an ICER of [redacted]/QALY; this is reasonably well aligned with the deterministic results. Further details are given in Table 52.

Table 52. EAG's base case results: probabilistic

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Alectinib	[redacted]	11.67	9.44	-	-	-	-
PBC	[redacted]	8.08	6.34	[redacted]	3.59	3.10	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; LY, life year; PBC, platinum-based chemotherapy; QALY, quality-adjusted life-year

Results of individual runs in the PSA are illustrated in the cost-effectiveness plane scatterplot below (Figure 25), and the cost-effectiveness acceptability curve (CEAC) is shown in Figure 26. The ICER for alectinib lies below the £20,000/QALY threshold with a probability of 85%, and below the £30,000/QALY threshold with a probability of 89%.

Figure 25. PSA scatter plot – EAG base case

Figure 26. Cost-effectiveness acceptability curve – EAG base case

Abbreviations: ALE, alectinib; CHT, chemotherapy.

6.4.2 One-way sensitivity analysis

The EAG also reran the one-way sensitivity analysis (OWSA) included in the model using the EAG's preferred assumptions; the results are displayed in the tornado plot below. Similarly to the company's base case, the parameters which have the greatest impact on the overall ICER tend to be treatment market shares for subsequent treatments.

Figure 27. One-way sensitivity analysis tornado plot, EAG base case

Abbreviations: 1L, first line; 2L, second line; ALE, alectinib; CHT, chemotherapy; DFS, disease-free survival; inc., incremental; PFS, progression-free survival; QALY, quality-adjusted life year.

6.5 Conclusions of the cost effectiveness sections

In conclusion, the EAG considers that the cost-effectiveness analysis presented by the company broadly captures the key disease milestones, aligns with the National Institute for Health and Care Excellence (NICE) reference case, and appropriately addresses the decision problem. However, there are several key areas of uncertainty in the modelling approach.

The lack of mature DFS or overall survival (OS) data is a key contributor to uncertainty, requiring long-term assumptions to be made regarding survival. The EAG acknowledges that it is highly unlikely that more mature data from the ALINA trial will become available during the timeframe of this appraisal, and neither the EAG nor the company have been able to identify any suitable alternative data sources from the existing literature. However, the lack of mature data results in a reliance on extrapolating DFS data from the ALINA trial, and survival data for subsequent treatment from other sources; the choice of extrapolation can have a substantial proportional impact on the ICER (for example, using the EAG's preferred extrapolations for DFS curves results in a 37% increase of the ICER compared to the company's preferred base case). While the company has justified their approach as far as possible through opinions elicited from their expert clinicians, the EAG notes that there is still considerable uncertainty in these estimates; there was naturally some variation of opinion between clinicians, and furthermore any opinions on long-term survival for alectinib in the adjuvant context are necessarily speculative.

The lack of availability of OS data also necessitates the use of a complex model structure to indirectly estimate OS. If alternative OS data were available, a significantly simpler model structure (for example, a partitioned survival model) may have been sufficient to capture relevant outcomes. The complexity of the model structure has resulted in the company making numerous simplifications, for example, the use of time-invariant transition probabilities for subsequent treatment health states. While the EAG acknowledges that the company has focused on taking a pragmatic approach, the EAG also considers that the company has not always sufficiently justified the simplifications made, or considered the impact that these simplifications would have on the model outcomes. The EAG has investigated the impact of removing these simplifications as far as possible, and suggested more robust alternative approaches, but in some cases, this would not be feasible without fundamentally changing the model implementation (for example, limiting the included subsequent treatments to four options per treatment line).

The EAG also notes that key parameters in the model, for example, treatment market shares for subsequent treatments, are entirely based on clinical expert opinions from a single advisory board. Given that these market shares are key drivers of the ICER, as can be seen from the results of the OWSA, it would be preferable to inform these inputs from a more robust source.

On the other hand, while substantial areas of uncertainty remain, the EAG notes that all scenarios considered result in an increase in both costs and QALYs compared to the current standard of care, with an ICER lying considerably under the £20,000 threshold. Although the impact of some areas of uncertainty, such as market shares for subsequent treatment, is unknown, it should also be noted that a key benefit of alectinib (i.e. reduction in central nervous system [CNS] metastases) cannot be captured within the existing model structure. In this respect, the cost-effectiveness analysis may underestimate the improvements in quality of life, and overrepresent the increase in cost.

7 References

1. European Medicines Agency (EMA). Alecensa - opinion on variation to marketing authorisation, 2024. Available from: https://www.ema.europa.eu/en/medicines/human/variation/alecensa. Date accessed: Jun 24.
2. National Institute for Health and Care Excellence (NICE). Alectinib for untreated ALK-positive advanced non-small-cell lung cancer: Technology appraisal guidance [TA536], 2018. Available from: https://www.nice.org.uk/guidance/ta536. Date accessed: Jun 24.
3. Cancer Research UK. Lung cancer statistics, 2023. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer. Date accessed: Apr 24.
4. National Lung Cancer Audit (NCLA) - Royal College of Surgeons of England. State of the Nation Report 2023, 2023. Available from: https://www.lungcanceraudit.org.uk/wp-content/uploads/2024/03/NLCA-Patient-Summary_SotN-report-2023_final-12.04.23.pdf. Date accessed: Apr 24.
5. International Agency for Research on Cancer (IARC) WHO. International Cancer Benchmarking Partnership (ICBP), Cancer Survival in High-Income Countries (SURVMARK-2). Available from: https://gco.iarc.fr/survival/survmark/. Date accessed: Apr 24.
6. American Cancer Society. Lung Cancer Survival Rates, 2024. Available from: https://www.cancer.org/cancer/types/lung-cancer/detection-diagnosis-staging/survival-rates.html. Date accessed: Apr 24.
7. Chevallier M, Borgeaud M, Addeo A, Friedlaender A. Oncogenic driver mutations in non-small cell lung cancer: Past, present and future. *World J Clin Oncol* 2021; **12**: 217-37.
8. Ravdin PM, Davis G. Prognosis of patients with resected non-small cell lung cancer: impact of clinical and pathologic variables. *Lung cancer (Amsterdam, Netherlands)* 2006; **52**: 207-12.
9. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol* 2010; **17**: 1471-4.
10. UyBico SJ, Wu CC, Suh RD, Le NH, Brown K, Krishnam MS. Lung cancer staging essentials: the new TNM staging system and potential imaging pitfalls. *Radiographics* 2010; **30**: 1163-81.
11. Choi YL, Soda M, Yamashita Y, Ueno T, Takashima J, Nakajima T, et al. EML4-ALK mutations in lung cancer that confer resistance to ALK inhibitors. *The New England journal of medicine* 2010; **363**: 1734-9.
12. Ou SH, Bartlett CH, Mino-Kenudson M, Cui J, Iafrate AJ. Crizotinib for the treatment of ALK-rearranged non-small cell lung cancer: a success story to usher in the second decade of molecular targeted therapy in oncology. *The oncologist* 2012; **17**: 1351-75.
13. Roche. ALINA Advisory Board - Discussion of the Clinical Data and Health Technology Assessment (HTA) Submission for Adjuvant Alectinib for ALK+ Stage IB–IIIA NSCLC [Data on File]. 2024.
14. Ragd Sami E, Sabeshan P, Datta I, Jha A, Abdelkhalek H, Ahmed S, et al. 84 National Real World Study of Adjuvant Osimertinib in Resected EGFR Mutated Lung Cancer. *Lung cancer (Amsterdam, Netherlands)* 2024; **190**.
15. Johung KL, Yeh N, Desai NB, Williams TM, Lautenschlaeger T, Arvold ND, et al. Extended Survival and Prognostic Factors for Patients With ALK-Rearranged Non-Small-Cell Lung Cancer and Brain Metastasis. *J Clin Oncol* 2016; **34**: 123-9.
16. Tian HX, Zhang XC, Yang JJ, Guo WB, Chen ZH, Wang Z, et al. Clinical characteristics and sequence complexity of anaplastic lymphoma kinase gene fusions in Chinese lung cancer patients. *Lung cancer (Amsterdam, Netherlands)* 2017; **114**: 90-5.
17. Guérin A, Sasane M, Zhang J, Culver KW, Dea K, Nitulescu R, et al. Brain metastases in patients with ALK+ non-small cell lung cancer: clinical symptoms, treatment patterns and economic burden. *Journal of medical economics* 2015; **18**: 312-22.

18. Roy Castle Lung Cancer Foundation. Lung cancer and brain metastases. Available from: https://roycastle.org/about-lung-cancer/advanced-lung-cancer/brain-metastases/. Date accessed: Apr 24.
19. National Lung Cancer Audit (NCLA) Royal College of Surgeons of England. State of the Nation Report 2024. Available from: https://www.lungcanceraudit.org.uk/reports-publications/nlca-state-of-the-nation-2024/. Date accessed: Jun 24.
20. Martin J, Ginsberg RJ, Venkatraman ES, Bains MS, Downey RJ, Korst RJ, et al. Long-term results of combined-modality therapy in resectable non-small-cell lung cancer. *J Clin Oncol* 2002; **20**: 1989-95.
21. Sugimura H, Nichols FC, Yang P, Allen MS, Cassivi SD, Deschamps C, et al. Survival after recurrent nonsmall-cell lung cancer after complete pulmonary resection. *Ann Thorac Surg* 2007; **83**: 409-17; discussioin 17-8.
22. Group NM-aC. Preoperative chemotherapy for non-small-cell lung cancer: a systematic review and meta-analysis of individual participant data. *Lancet* 2014; **383**: 1561-71.
23. Williams BA, Sugimura H, Endo C, Nichols FC, Cassivi SD, Allen MS, et al. Predicting postrecurrence survival among completely resected nonsmall-cell lung cancer patients. *Ann Thorac Surg* 2006; **81**: 1021-7.
24. Lim JU. Update on Adjuvant Treatment in Resectable Non-Small Cell Lung Cancer and Potential Biomarkers Predicting Postoperative Relapse. *Tuberc Respir Dis (Seoul)* 2023; **86**: 14-22.
25. National Institute for Health and Care Excellence (NICE). Treatment for lung cancer, 2019. Available from: https://www.nice.org.uk/about/what-we-do/into-practice/measuring-the-use-of-nice-guidance/impact-of-our-guidance/niceimpact-lung-cancer/ch4-treatment-for-lung-cancer#:~:text=Treatment%20for%20lung%20cancer%20includes,well%20as%20their%20general%20health. Date accessed: Apr 24.
26. Tsuboi M, Herbst RS, John T, Kato T, Majem M, Grohé C, et al. Overall Survival with Osimertinib in Resected EGFR-Mutated NSCLC. *The New England journal of medicine* 2023; **389**: 137-47.
27. Tang WF, Ye HY, Tang X, Su JW, Xu KM, Zhong WZ, et al. Adjuvant immunotherapy in early-stage resectable non-small cell lung cancer: A new milestone. *Front Oncol* 2023; **13**: 1063183.
28. Bowes K, Jovanoski N, Brown AE, Di Maio D, Belleli R, Chadda S, et al. Treatment patterns and survival of patients with locoregional recurrence in early-stage NSCLC: a literature review of real-world evidence. *Med Oncol* 2022; **40**: 4.
29. Chouaid C, Danson S, Andreas S, Siakpere O, Benjamin L, Ehness R, et al. Adjuvant treatment patterns and outcomes in patients with stage IB-IIIA non-small cell lung cancer in France, Germany, and the United Kingdom based on the LuCaBIS burden of illness study. *Lung cancer (Amsterdam, Netherlands)* 2018; **124**: 310-6.
30. Burdett S, Pignon JP, Tierney J, Tribodet H, Stewart L, Le Pechoux C, et al. Adjuvant chemotherapy for resected early-stage non-small cell lung cancer. *Cochrane Database Syst Rev* 2015; **2015**: Cd011430.
31. West H, Hu X, Zhang S, Song Y, Chirovsky D, Gao C, et al. Treatment Patterns and Outcomes in Resected Early-stage Non-small Cell Lung Cancer: An Analysis of the SEER-Medicare Data. *Clinical lung cancer* 2023; **24**: 260-8.
32. Artal Cortés Á, Calera Urquizu L, Hernando Cubero J. Adjuvant chemotherapy in non-small cell lung cancer: state-of-the-art. *Transl Lung Cancer Res* 2015; **4**: 191-7.
33. National Institute for Health and Care Excellence (NICE). Atezolizumab for adjuvant treatment of resected non-small-cell lung cancer: Technology appraisal guidance [TA823], 2022. Available from: https://www.nice.org.uk/guidance/ta823. Date accessed: Jun 24.
34. National Institute for Health and Care Excellence (NICE). Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection: Technology

appraisal guidance [TA761], 2022. Available from: https://www.nice.org.uk/guidance/ta761. Date accessed: Jun 24.
35. Friedlaender A, Banna G, Patel S, Addeo A. Diagnosis and Treatment of ALK Aberrations in Metastatic NSCLC. *Current treatment options in oncology* 2019; **20**: 79.
36. Electronic Medicines Compendium (EMC). Alecensa 150 mg Hard Capsules - Summary of Product Characteristics (SmPC), 2024. Available from: https://www.medicines.org.uk/emc/product/2438/smpc#gref. Date accessed: Aug 24.
37. Wu YL, Dziadziuszko R, Ahn JS, Barlesi F, Nishio M, Lee DH, et al. Alectinib in Resected ALK-Positive Non-Small-Cell Lung Cancer. *The New England journal of medicine* 2024; **390**: 1265-76.
38. Roche. Primary CSR Clinical Report: Study BO40336 (ALINA): A Phase III, open-label, randomised study to evaluate the efficacy and safety of adjuvant alectinib versus adjuvant platinum-based chemotherapy in patients with completely resected Stage IB to Stage IIIA ALK+ NSCLC [Data on File]. 2023.
39. National Institute for Health and Care Excellence (NICE). Alectinib for adjuvant treatment of ALK-positive non-small-cell lung cancer [ID6368]: Final scope, 2024. Available from: https://www.nice.org.uk/guidance/gid-ta11436/documents/final-scope. Date accessed: Jun 24.
40. Hendriks LE, Kerr KM, Menis J, Mok TS, Nestle U, Passaro A, et al. Oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol* 2023; **34**: 339-57.
41. Mazieres J, Drilon A, Lusque A, Mhanna L, Cortot AB, Mezquita L, et al. Immune checkpoint inhibitors for patients with advanced lung cancer and oncogenic driver alterations: results from the IMMUNOTARGET registry. *Ann Oncol* 2019; **30**: 1321-8.
42. O'Brien M, Paz-Ares L, Marreaud S, Dafni U, Oselin K, Havel L, et al. Pembrolizumab versus placebo as adjuvant therapy for completely resected stage IB–IIIA non-small-cell lung cancer (PEARLS/KEYNOTE-091): an interim analysis of a randomised, triple-blind, phase 3 trial. *The Lancet Oncology* 2022; **23**: 1274-86.
43. Montague D. P39.04 ALK Positive UK: 42% of UK Patients do not Receive Regular Brain MRI Scans Despite Data Showing up to 70% of Patients Develop Brain Metastases. *Journal of Thoracic Oncology* 2021; **16**: S467.
44. Lucas T, Hassan H, Sattar A, So A, Buckley T, Hunter S, et al. 95 Lorlatinib in advanced ALK-rearranged NSCLC - real-world experience in a UK population. *Lung cancer (Amsterdam, Netherlands)* 2024; **190**.
45. Gomes F, Yip K, Tokaca N, Greystoke A, Escriu C, Conibear J, et al. The ALK project: a real-world national network and database. 2019.
46. Le Pechoux C, Pourel N, Barlesi F, Lerouge D, Antoni D, Lamezec B, et al. Postoperative radiotherapy versus no postoperative radiotherapy in patients with completely resected non-small-cell lung cancer and proven mediastinal N2 involvement (Lung ART, IFCT 0503): an open-label, randomised, phase 3 trial. *The Lancet Oncology* 2022; **23**: 104-14.
47. Serrano J, Crespo PC, Taboada B, Gonzalez AA, García RG, Caamaño AG, et al. Postoperative radiotherapy in resected non-small cell lung cancer: The never-ending story. *World J Clin Oncol* 2021; **12**: 833-44.
48. Postmus PE, Kerr KM, Oudkerk M, Senan S, Waller DA, Vansteenkiste J, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up[†]. *Annals of Oncology* 2017; **28**: iv1-iv21.
49. Rodrigues G, Choy H, Bradley J, Rosenzweig KE, Bogart J, Curran WJ, Jr., et al. Adjuvant radiation therapy in locally advanced non-small cell lung cancer: Executive summary of an American Society for Radiation Oncology (ASTRO) evidence-based clinical practice guideline. *Practical Radiation Oncology* 2015; **5**: 149-55.

50. Kris MG, Gaspar LE, Chaft JE, Kennedy EB, Azzoli CG, Ellis PM, et al. Adjuvant Systemic Therapy and Adjuvant Radiation Therapy for Stage I to IIIA Completely Resected Non-Small-Cell Lung Cancers: American Society of Clinical Oncology/Cancer Care Ontario Clinical Practice Guideline Update. *J Clin Oncol* 2017; **35**: 2960-74.
51. National Institute for Health and Care Excellence (NICE). Pembrolizumab for adjuvant treatment of resected non-small-cell lung cancer [ID3907]: In development [GID-TA10784], 2024. Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10784. Date accessed: Jun 24.
52. National Institute for Health and Care Excellence (NICE). Alectinib for adjuvant treatment of ALK-positive non-small-cell lung cancer [ID6368] - NICE's response to comments on the draft scope and provisional stakeholder list, 2024. Available from: https://www.nice.org.uk/guidance/gid-ta11436/documents/scope-consultation-comments-and-responses. Date accessed: Jun 24.
53. O'Brien M, Paz-Ares L, Marreaud S, Dafni U, Oselin K, Havel L, et al. Pembrolizumab versus placebo as adjuvant therapy for completely resected stage IB-IIIA non-small-cell lung cancer (PEARLS/KEYNOTE-091): an interim analysis of a randomised, triple-blind, phase 3 trial. *Lancet Oncol* 2022; **23**: 1274-86.
54. Solomon BJ, Ahn JS, Dziadziuszko R, Barlesi F, Nishio M, H. LD, et al. LBA2 ALINA: Efficacy and safety of adjuvant alectinib versus chemotherapy in patients with early-stage ALK+ non-small cell lung cancer (NSCLC). *Annals of Oncology* 2023; **34**: S1295-S6.
55. Higgins Jpt SJPMJERGSJAC. Chapter 8: Assessing risk of bias in a randomized trial. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). Cochrane, 2023. Available from www.training.cochrane.org/handbook.
56. Molinier L, Bauvin E, Combescure C, Castelli C, Rebillard X, Soulié M, et al. Methodological considerations in cost of prostate cancer studies: a systematic review. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research* 2008; **11**: 878-85.
57. National Institute for Health and Care Excellence (NICE). Nivolumab with chemotherapy for neoadjuvant treatment of resectable non-small-cell lung cancer [TA876], 2023. Available from: https://www.nice.org.uk/guidance/ta876. Date accessed: Jun 24.
58. Soria JC, Tan DSW, Chiari R, Wu YL, Paz-Ares L, Wolf J, et al. First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study. *Lancet* 2017; **389**: 917-29.
59. 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.
60. Solomon BJ, Bauer TM, Mok TSK, Liu G, Mazieres J, de Marinis F, et al. Efficacy and safety of first-line lorlatinib versus crizotinib in patients with advanced, ALK-positive non-small-cell lung cancer: updated analysis of data from the phase 3, randomised, open-label CROWN study. *Lancet Respir Med* 2023; **11**: 354-66.
61. Camidge DR, Kim HR, Ahn MJ, Yang JCH, Han JY, Hochmair MJ, 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 : official publication of the International Association for the Study of Lung Cancer* 2021; **16**: 2091-108.
62. 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 Surgery. *Clinical lung cancer* 2017; **18**: e441-e8.
63. Grutters JP, Joore MA, Wiegman EM, Langendijk JA, de Ruysscher D, Hochstenbag M, et al. Health-related quality of life in patients surviving non-small cell lung cancer. *Thorax* 2010; **65**: 903-7.

64. Latimer N. NICE DSU Technical Support Document 14: Undertaking survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. 2011.
65. Janssen-Heijnen ML, van Steenbergen LN, Steyerberg E, Visser O, De Ruysscher DK, Groen HJ. Long-term excess mortality for survivors of non-small cell lung cancer in the Netherlands. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer* 2012; **7**: 496-502.
66. Guyot P, Ades AE, Ouwens MJNM, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. *BMC medical research methodology* 2012; **12**: 9.
67. Wong ML, McMurry TL, Stukenborg GJ, Francescatti AB, Amato-Martz C, Schumacher JR, et al. Impact of age and comorbidity on treatment of non-small cell lung cancer recurrence following complete resection: A nationally representative cohort study. *Lung cancer (Amsterdam, Netherlands)* 2016; **102**: 108-17.
68. Roche. Final CSR Study − MO29750 (ALUR) − Randomized, Multicenter, Phase III, Open-Label Study of Alectinib versus Pemetrexed or Docetaxel in Anaplastic Lymphoma Kinase-Positive Advanced Non-Small Cell Lung Cancer Patients Previously treated with Platinum Based Chemotherapy and Crizotinib [Data on File]. 2019.
69. Lee KH, Ahn YC, Pyo H, Noh JM, Park SG, Kim TG, et al. Salvage Concurrent Chemo-radiation Therapy for Loco-regional Recurrence Following Curative Surgery of Non-small Cell Lung Cancer. *Cancer Res Treat* 2019; **51**: 769-76.
70. National Institute for H, Care E. NICE health technology evaluations: the manual [PMG36].
71. Hernández Alava M, Pudney S, Wailoo A. Estimating EQ-5D by Age and Sex for the UK. NICE DSU Report. 2022.
72. Chouaid C, Agulnik J, Goker E, Herder GJM, Lester JF, Vansteenkiste J, 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. *Journal of Thoracic Oncology* 2013; **8**: 997-1003.
73. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research* 2010; **13**: 509-18.
74. Roughley A, Damonte E, Taylor-Stokes G, Rider A, Munk VC. Impact of Brain Metastases on Quality of Life and Estimated Life Expectancy in Patients with Advanced Non-Small Cell Lung Cancer. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research* 2014; **17**: A650.
75. Jang RW, Isogai PK, Mittmann N, Bradbury PA, Shepherd FA, Feld R, et al. Derivation of utility values from European Organization for Research and Treatment of Cancer Quality of Life-Core 30 questionnaire values in lung cancer. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer* 2010; **5**: 1953-7.
76. Labbé C, Leung Y, Silva Lemes JG, Stewart E, Brown C, Cosio AP, et al. Real-World EQ5D Health Utility Scores for Patients With Metastatic Lung Cancer by Molecular Alteration and Response to Therapy. *Clinical lung cancer* 2017; **18**: 388-95.e4.
77. van den Hout WB, Kramer GW, Noordijk EM, Leer JW. Cost-utility analysis of short- versus long-course palliative radiotherapy in patients with non-small-cell lung cancer. *Journal of the National Cancer Institute* 2006; **98**: 1786-94.
78. National Institute for Health and Care Excellence (NICE). NICE British National Formulary (BNF) 2024. Available from: https://bnf.nice.org.uk/. Date accessed: Apr 24.
79. Department of Health and Social Care. Drugs and pharmaceutical electronic market information tool (eMIT), 2024. Available from: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit. Date accessed: Apr 24.

80. van Warmerdam LJ, Rodenhuis S, ten Bokkel Huinink WW, Maes RA, Beijnen JH. The use of the Calvert formula to determine the optimal carboplatin dosage. *J Cancer Res Clin Oncol* 1995; **121**: 478-86.
81. NHS England. 2021/22 National Cost Collection Data Publication. 2023.
82. The Royal College of Radiologists. Radiotherapy dose fractionation, fourth edition. 2024.
83. 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.
84. Brown T, Pilkington G, Bagust A, Boland A, Oyee J, Tudur-Smith C, et al. Clinical effectiveness and cost-effectiveness of first-line chemotherapy for adult patients with locally advanced or metastatic non-small cell lung cancer: a systematic review and economic evaluation. *Health Technol Assess* 2013; **17**: 1-278.
85. Personal Social Services Research Unit (PSSRU). Unit Costs of Health and Social Care programme (2022 – 2027). 2023.
86. Manchester University NHS Foundation Trust. Immuno-histochemistry and Research, 2017. Available from: https://mft.nhs.uk/the-trust/other-departments/laboratory-medicine/histopathology/immunohistochemistry-and-research/#:~:text=IHC%20tests%20are%20charged%20at,are%20charged%20at%20%C2%A330. Date accessed: Apr 24.

8 Appendices

8.1 Price sources for treatments included in the confidential appendix

The table below shows the source of confidential prices used in the comparator patient access scheme (cPAS) appendix.

Table 53. Source of the confidential prices used in the confidential appendix

Treatment	Source of price/type of commercial arrangement
Crizotinib	CAA
Brigatinib	CAA
Loratinib	CAA
Certinib	CAA
Pemetrexed	CMU

Abbreviations: CAA, commercial access arrangement; CMU, Commercial Medicines Unit.

8.2 Subsequent treatment survival extrapolations

The extrapolation plots and goodness of fit statistics for progression-free survival (PFS) and overall survival (OS) data for subsequent treatment are presented in the figures and tables below. In general, the standard parametric extrapolations (as per NICE DSU TSD 14) are used; however, in some cases, the generalised gamma model fits did not converge.

8.2.1 Radiotherapy PFS, Nakamichi et al. *2017*

These data were used to model PFS for patients receiving radiotherapy or surgery in the non-metastatic recurrence health state in the company's base case.

Figure 28. Radiotherapy PFS extrapolations, Nakamichi *et al.* 2017 – reproduced from Figure 3 of the company's additional CQ responses

Abbreviations: CQ, clarification question; KM, Kaplan-Meier; PFS, progression-free survival.

Table 54. Radiotherapy PFS extrapolations, Nakamichi *et al.* 2017, goodness of fit statistics

Distribution	AIC	BIC
Exponential	400.8	402.8
Weibull	402.8	406.8
Log-normal	389.7	393.8
Generalised gamma	**384.6**	**390.6**
Log-logistic	390.9	394.9
Gompertz	399.5	403.6

The EAG's preferred extrapolation is shown in **bold**

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; EAG, External Assessment Group; PFS, progression-free survival.

8.2.2 Chemotherapy PFS, ASCEND-4

These data were used to model PFS for patients receiving chemotherapy in the non-metastatic recurrence health state.

Figure 29. Chemotherapy PFS extrapolations, ASCEND-4 – reproduced from Figure 4 of the company's additional CQ responses

Abbreviations: CQ, clarification question; KM, Kaplan-Meier; PFS, progression-free survival.

Table 55. Chemotherapy PFS extrapolations, ASCEND-4, goodness of fit statistics

Distribution	AIC	BIC
Exponential	787.1	790.3
Weibull	787.3	793.8
Log-normal	**777.8**	**784.2**
Generalised gamma	779.8	789.5
Log-logistic	781.1	787.6
Gompertz	789.1	795.6

The EAG's preferred extrapolation is shown in **bold**

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; EAG, External Assessment Group; PFS, progression-free survival.

8.2.3 No treatment OS, Wong et al. *2016 (non-metastatic recurrence)*

These data were used to model OS for patients receiving no active treatment in the non-metastatic recurrence health state.

Figure 30. No treatment OS extrapolations, Wong *et al.* 2016 (non-metastatic recurrence) – reproduced from Figure 5 of the company's additional CQ responses

Abbreviations: CQ, clarification question; KM, Kaplan-Meier; OS, overall survival.

Table 56. No treatment OS extrapolations, Wong *et al.* 2016 (non-metastatic recurrence), goodness of fit statistics

Distribution	AIC	BIC
Exponential	1167.8	1171.2
Weibull	1124.5	1131.2
Log-normal	**1085.4**	**1092.1**
Generalised gamma	Did not converge	Did not converge
Log-logistic	1094.9	1101.6
Gompertz	1102.5	1109.1

The EAG's preferred extrapolation is shown in **bold**

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; EAG, External Assessment Group; OS, overall survival.

8.2.4 Alectinib PFS, ALEX trial

These data were used to model PFS for patients receiving chemotherapy in the metastatic recurrence (1L) health state in the company's base case, and additionally in the non-metastatic recurrence health state in the External Assessment Group (EAG)'s preferred base case.

Figure 31. Alectinib PFS extrapolations, ALEX trial – reproduced from Figure 6 of the company's additional CQ responses

Abbreviations: CQ, clarification question; KM, Kaplan-Meier; PFS, progression-free survival.

Table 57. Alectinib PFS extrapolations, ALEX trial, goodness of fit statistics

Distribution	AIC	BIC
Exponential	459.1	462.1
Weibull	448.9	455.0
Log-normal	439.6	445.7
Generalised gamma	**438.8**	**447.8**
Log-logistic	444.0	450.0
Gompertz	442.0	448.0

The EAG's preferred extrapolation is shown in **bold**

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; EAG, External Assessment Group; PFS, progression-free survival.

8.2.5 Brigatinib PFS, ALTA-1L trial

These data were used to model progression-free survival for patients receiving brigatinib in the metastatic recurrence (1L) health state.

Figure 32. Brigatinib PFS extrapolations, ALTA-1L trial – reproduced from Figure 9 of the company's CQ responses

Abbreviations: CQ, clarification question; KM, Kaplan-Meier; PFS, progression-free survival.

Table 58. Brigatinib PFS extrapolations, ALTA-1L trial – reproduced from the company's CQ responses, goodness of fit statistics

Distribution	AIC	BIC
Exponential	727.9	730.8
Weibull	729.1	734.9
Log-normal	722.3	728.2
Generalised gamma	**722.3**	**731.0**
Log-logistic	727.7	732.6
Gompertz	727.9	733.7

The EAG's preferred extrapolation is shown in **bold**

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; EAG, External Assessment Group; PFS, progression-free survival.

8.2.6 Lorlatinib PFS, CROWN trial

These data were used to model progression-free survival for patients receiving lorlatinib in the metastatic recurrence (1L) health state.

Figure 33. Loratinib PFS extrapolations, CROWN trial – reproduced from Figure 10 of the company's CQ responses

Abbreviations: CQ, clarification question; KM, Kaplan-Meier; PFS, progression-free survival.

Table 59. Loratinib PFS extrapolations, CROWN trial, goodness of fit statistics

Distribution	AIC	BIC
Exponential	511.3	514.3
Weibull	505.5	511.5
Log-normal	497.6	503.6
Generalised gamma	Did not converge	Did not converge
Log-logistic	502.5	508.5
Gompertz	**494.5**	**500.5**

The EAG's preferred extrapolation is shown in **bold**

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; EAG, External Assessment Group; PFS, progression-free survival.

8.2.7 Alectinib OS, ALUR trial

These data were used to model OS for patients receiving alectinib and lorlatinib in the metastatic recurrence (2L) health state.

Figure 34. Alectinib OS extrapolations, ALUR trial – reproduced from Figure 12 of the company's CQ responses

Abbreviations: CQ, clarification question; KM, Kaplan-Meier; OS, overall survival.

Table 60. Alectinib OS extrapolations, ALUR trial, goodness of fit statistics

Distribution	AIC	BIC
Exponential	202.6	205.0
Weibull	201.2	206.0
Log-normal	201.0	205.8
Generalised gamma	202.8	209.9
Log-logistic	**201.0**	**205.7**
Gompertz	201.5	206.3

The EAG's preferred extrapolation is shown in **bold**

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; EAG, External Assessment Group; OS, overall survival.

8.2.8 Chemotherapy OS, ALUR trial

These data were used to model OS for patients receiving chemotherapy in the metastatic recurrence (2L) health state.

Figure 35. Chemotherapy OS extrapolations, ALUR trial – reproduced from Figure 13 of the company's CQ responses

Abbreviations: CQ, clarification question; KM, Kaplan-Meier; OS, overall survival.

Table 61. Chemotherapy OS extrapolations, ALUR trial, goodness of fit statistics

Distribution	AIC	BIC
Exponential	103.9	105.5
Weibull	102.3	105.7
Log-normal	100.1	103.5
Generalised gamma	100.8	105.8
Log-logistic	101.2	104.6
Gompertz	**99.3**	**102.7**

The EAG's preferred extrapolation is shown in **bold**

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; EAG, External Assessment Group; OS, overall survival.

8.2.9 No treatment OS, Wong et al. *2016 (metastatic recurrence)*

These data were used to model OS for patients receiving no active treatment in both metastatic recurrence health states.

Figure 36. No treatment OS extrapolations, Wong *et al.* 2016 (metastatic recurrence) – reproduced from Figure 11 of the company's CQ responses

Abbreviations: CQ, clarification question; KM, Kaplan-Meier; OS, overall survival.

Table 62. No treatment OS extrapolations, Wong *et al.* 2016 (metastatic recurrence), goodness of fit statistics

Distribution	AIC	BIC
Exponential	2093.4	2097.3
Weibull	2016.9	2024.8
Log-normal	**1964.6**	**1972.5**
Generalised gamma	1964.3	1976.2
Log-logistic	1968.1	1975.9
Gompertz	1972.6	1980.5

The EAG's preferred extrapolation is shown in **bold**

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; EAG, External Assessment Group; OS, overall survival.

Single Technology Appraisal

Alectinib for adjuvant treatment of ALK-positive non-small-cell lung cancer [ID6368]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 30 July 2024** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.2.1 EAG critique, Page 84, “It is unclear whether the clinicians present at the company’s advisory board meeting on 9 February 2024 were explicitly asked to validate the number of lines of treatment reflected in the model structure”	The model structure including lines of treatment was validated during the advisory board and the clinical experts stated that the proposed structure (including lines of treatment) is appropriate.	This wording reflects that the number of treatment lines were validated.	Not a factual inaccuracy, no change required. The advisory board summary report provided by the company states that clinicians were asked to validate the model structure, but it is not stated whether clinicians were explicitly asked about whether the number of lines of treatment reflected UK clinical practice.

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In Section 4.2.5.3.3, Table 29 on Page 107, the market shares for subsequent therapies are incorrect.	The market shares should match Table 41 on Page 114 of the updated company submission. These market shares in the CS align with the CEM.	The values are incorrect in the EAG report however, the values are correct in the model therefore this discrepancy will have no impact on the results.	Not a factual inaccuracy, no change required. The market shares presented in Table 29 reflect market shares for the whole patient population, including

			patients receiving no treatment, whereas Table 41 of the CS and the model inputs are applicable only to the patient population receiving active treatment.

Issue 3

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.6.1.2, Page 116, Disease recurrence health states, “the EAG was unable to identify any reference to HRQoL or the Chouaid et al. study in the BOI report provided by the company.”	References to HRQoL and the Chouaid et al. study were identified in the “Adjuvant/Neoadjuvant Treatment Of Early Non-Small Cell Lung Cancer (NSCLC): Systematic Literature Review (SLR) To Identify Economic Evaluations, 2023” This report was provided as a reference, therefore the company suggests that this sentence is removed.	Incorrect reference is stated in report.	Not a factual inaccuracy, no change required. The BOI report referred to here was provided to the EAG in response to clarification question B26 as a source for HRQoL data; however, no HRQoL data could be identified from this source. The EAG has not been provided with any materials related to the SLR mentioned in the company’s proposed amendment.

Issue 4

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.4. Perspective, time horizon and discounting, Page 87, “Ultimately, the half-cycle correction was not applied in the company’s base case.”	The half-cycle correction was applied in the company's base case however this correction was only applied to efficacy inputs and not to treatment costs.	This wording reflects what was updated in the company’s base case.	Not a factual inaccuracy, no change required. The half-cycle correction was implemented as a scenario in the company’s updated model provided during the clarification stage, but was not applied in the company’s base case.

Issue 5

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.6.2. Adverse events disutility, Page 117. “No justification was provided in the CS as to why these were not	Disutilities associated with adverse events were not included to avoid double counting, as impact on utilities from adverse events may have already	A justification was provided in company submission. The proposed wording reflects this.	The EAG thanks the company for identifying the factual inaccuracy, and has updated the report using the following wording: ‘The

included in the economic model.”	been accounted for in the ALINA trial and the identified utility source.		company stated that the reason for excluding disutilities for adverse events since this may lead to double counting given that differences between treatments were accounted for in the regression model fitted to utilities from the ALINA trial.’

Issue 6

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.1.3, Targeted review of real world evidence for clinical burden and treatment patterns in early NSCLC, page 78,“The EAG requested that the company rerun the searches during the clarification stage, but the company was unable to	During the clarification meeting, the Company explained that this would be a time-consuming process and is highly unlikely that any new relevant literature would be found in the updated search. The Company then proposed to run a scenario analysis to vary the input used for radiotherapy efficacy, which the EAG accepted as a reasonable alternative. The scenario analysis was provided in the clarification response.	This wording provides additional detail.	Not a factual inaccuracy, no change required.

do this in the time available”			

Issue 7

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 6.1, page 149, “Transition probabilities for the disease-free health state had not been adjusted to account for the bounding by background mortality”	Company suggest removing this sentence	This is not an error, this is an alternative approach that can be used.	Not a factual inaccuracy, no change required. The EAG considers that the issue described is an error, since the calculated survival data distort the original input data, and the approach taken is inconsistent with the handling of other lines of treatment.

Issue 8

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 6.1, Page 149 “Half-cycle correction had not been applied to	Company suggests removing this sentence	The EAG confirmed in our call that it would be sufficient to only apply the half-cycle adjustments to	Not a factual inaccuracy, no change required. The EAG considers that the issue described is an error, since

treatment costs calculated using tunnel states.”		the Markov trace. Therefore this is not an error.	while half-cycle correction need not be applied to tunnel state occupancy calculations, the resulting treatment costs should be half-cycle corrected when pulled through to the Markov trace, for consistency with other cost calculations.

Issue 9

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 6.1, Page 149, “The updated approach for age-adjustment of utility values did not account for the cure fraction.”	Company suggests removing this sentence	This is not an error, this is an alternative approach that can be used.	Not a factual inaccuracy, no change required. The EAG considers that the issue described is an error, since the utility values of cured patients were not accurately calculated in line with the company’s stated assumptions.

Issue 10

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.2.1, Page 84, "During clarification, the company further stated that the number of lines of treatment aligns with the findings of the TLR described in Section 4.1.3; however, the EAG notes that the TLR did not explicitly include data for metastatic recurrence, and none of the studies identified in the TLR including data on treatment options were relevant to the UK context."	"During clarification, the company explained that a pragmatic literature search was conducted during the conceptualisation phase of the CEM to determine the proportion of patients advancing to 3L+ metastatic treatment. The findings from the literature search revealed a significant decline in the proportion of patients moving to 3L+ metastatic treatment. This initial finding informed the model structure. To verify whether this simplification was appropriate, the CEM structure was reviewed by UK clinical experts in February 2024. These experts confirmed that the proposed model structure accurately represents the treatment pathways for eNSCLC."	The proposed wording aligns with the company's clarification response to question B6.	Not a factual inaccuracy, no change required.

Issue 11

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.1.1, Page 85, "In response to the EAG's request for a scenario allowing patients to progress from non-metastatic recurrence (off treatment) to metastatic recurrence (off treatment) during the clarification stage, the company stated that this could not be implemented within the current model structure."	"In response to the EAG's request for a scenario allowing patients to progress from non-metastatic recurrence (off treatment) to metastatic recurrence (off treatment) during the clarification stage, the company stated that the source used to inform the clinical outcomes of untreated patients (Wong et al. 2016) did not provide evidence on their PFS, only on their OS. While the model structure accommodates these transitions, no appropriate sources for PFS were found."	The proposed wording aligns with the company's clarification response	The EAG thanks the company for identifying the factual inaccuracy, and has updated the report accordingly.

Incorrect Marking

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Section 2.1 Introduction. Page 25	Anticipated marketing authorisation (MA). MA has been granted on the 11th of July 2024.	The marketing authorisation for alectinib in this indication was granted in July 2024.	The EAG thanks the company for identifying this inaccuracy and has amended all references to the anticipated marketing authorisation accordingly.
Section 2.1 Introduction. Page 25	Confidential marking of indication can be removed as this has now been approved by the MHRA. This is only applicable to Great Britain. Northern Ireland will follow the EMA approved indication.	No requirement for confidential marking.	The EAG thanks the company for identifying this inaccuracy and has amended the report accordingly.
Section 2.2 Background/ Current treatment pathway. Page 27	Indication for Great Britain has now been approved by the MHRA, therefore confidential marking is not required.	No requirement for confidential marking.	The EAG thanks the company for identifying this inaccuracy and has amended the report accordingly.
Section 2.2 Background/ Critique of company's definition of the decision	As MA has been approved and a new SmPC has been published, please remove the wording on "anticipated" in first row and "draft" in second row.	First row: "[...] the marketing authorisation [...]"	The EAG thanks the company for identifying this inaccuracy and has

problem. Table 7, page 31		Second row: “[...] and SmPC [...]”	amended all references to the draft SmPC accordingly.
	“from ALINA and” does not require confidential marking.	No requirement for confidential marking.	The EAG thanks the company for identifying this inaccuracy and has amended the report accordingly.
Section 2.2 Background/ Population. Page 40	Confidential marking of the population is no longer required as this has now been approved by the MHRA.	No requirement for confidential marking.	The EAG thanks the company for identifying this inaccuracy and has amended Page 39, Section 2.3.1 of the report accordingly.
	As MA has been approved, please remove the wording on “anticipated”	“[...] in line with the marketing authorisation [...]	The EAG thanks the company for identifying this inaccuracy and has amended Page 39, Section 2.3.1 of the report accordingly.
Section 2.2 Background/ Population. Page 41	Confidential marking of the population is no longer required as this has now been approved by the MHRA.	No requirement for confidential marking.	The EAG thanks the company for identifying this inaccuracy and has amended Page 40, Section 2.3.1 of the report accordingly.

	As a new SmPC has been published, please remove the wording “draft”.	“[...]” wording in the Summary of [...]	The EAG thanks the company for identifying this inaccuracy and has amended Page 40, Section 2.3.1 of the report accordingly.
Section 2.2 Background/ Intervention. Page 43	As a new SmPC has been published, please remove the wording “draft”.	“[described in the SmPC [...]”	The EAG thanks the company for identifying this inaccuracy and has amended Page 41, Section 2.3.1 of the report accordingly.
	Confidential marking of the duration of treatment is no longer required as this has now been approved by the MHRA.	No requirement for confidential marking.	The EAG thanks the company for identifying this inaccuracy and has amended Page 42, Section 2.3.1 of the report accordingly.
Section 2.2 Background/ Subgroups. Page 48	Confidential marking of Asian vs Non-Asion subgroups is no longer required as this is published in the Wu et al NEJM 2024 paper (figure 2).	No requirement for confidential marking.	The EAG thanks the company for identifying this inaccuracy and has amended Page 46, Section 2.3.5 of the report accordingly.

Section 3 Critique of ALINA. Table 9, page 55	% of never smoker in the chemotherapy arm is 55.1%, not 55.5%	(64.6% vs 55.1%)	The EAG thanks the company for identifying this inaccuracy and has amended Page 53, Section 3.2 of the report accordingly.
Section 3 Critique of ALINA. Table 9, page 56	Wu et al NEJM 2024, protocol is publicly available in the supplementary information, and therefore 255 and 191 patients confidential marking is not required.	No requirement for confidential marking.	The EAG thanks the company for identifying this inaccuracy and has amended Page 55, Section 3.2 of the report accordingly.
Section 3 Critique of the clinical effectiveness analysis and interpretation. Page 58	Data is incorrect when defining the calculation of treatment duration. This should read “date”.	Date	The EAG thanks the company for identifying this inaccuracy and has amended Page 56, Section 3.2 of the report accordingly.
Section 3 Critique of the clinical effectiveness analysis and interpretation/ Subgroups. Page 70	Confidential marking of Asian vs Non-Asian, ECOG 0-1 and regional lymph node stage subgroups is no longer required as this is published in the Wu et al NEJM 2024 paper (figure 2).	No requirement for confidential marking.	The EAG thanks the company for identifying this inaccuracy and has amended Page 68, Section 3.3.5 of the report accordingly.

Section 3 Critique of ALINA/ Conclusions of the clinical effectiveness section. Page 72 and 74	As MA has been approved and a new SmPC has been published, please remove the wording on “anticipated” and “draft”.	“[...] final scope being in line with the marketing authorisation for [...]” “[...] AEs mentioned in the SmPC [...]”	The EAG thanks the company for identifying this inaccuracy and has amended Pages 70 and 71, Section 3.4 of the report accordingly.
Section 3.1 EAG comment on the company’s review of cost effectiveness evidence. Page 78	Incorrect reference to TA838, it should be TA823 instead.	“NICE technology appraisals (TA761 – adjuvant osimertinib, TA823 – atezolizumab, TA876 – nivolumab).”	The EAG thanks the company for identifying this inaccuracy and has amended Page 75, Section 4.1.1 of the report accordingly.
Section 4.1.4. Targeted review of real-world evidence for clinical burden and treatment patterns in early NSCLC. Page 79	Incorrect reference to SLR, it should be TLR	“Although the TLR identified some sources”	The EAG thanks the company for identifying this inaccuracy and has amended Page 79, Section 4.1.3 of the report accordingly.
4.2.6.1.1 Disease-free health state utilities. Page 113	There is a typo in this sentence, “The company used al linear mixed effects model.”	“The company used a linear mixed effects model”	The EAG thanks the company for identifying this inaccuracy and has amended the report accordingly.