NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Alectinib for untreated anaplastic lymphoma kinase positive advanced non-small-cell lung cancer [ID925]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Alectinib for untreated anaplastic lymphoma kinase positive advanced non-small-cell lung cancer [ID925]

The final scope and matrix of consultees and commentators are available on the NICE website for this appraisal.

Contents:

Any information supplied to NICE which has been marked as confidential has been redacted

Pre-meeting briefing

Alectinib for untreated anaplastic lymphoma kinase-positive advanced non-small cell lung cancer [ID925]

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting

Key issues

Clinical effectiveness:

- Can conclusions be drawn about overall survival given the immaturity of the data?
- What are the committee's conclusions on the ALEX clinical trial that compared alectinib with crizotinib in terms of quality, risk of bias and generalisability given:
  - Different measurements of progression-free survival and CNS- progression-free survival (investigator, IRC RECIST or IRC RECIST & CNS-RECIST)?
  - Treatment of asymptomatic disease after progression?
  - Missing data on subsequent treatment distribution?

Cost effectiveness:

- Are assumptions about post-progression subsequent treatment distribution plausible?
- Company chose 18 month Kaplan-Meier data cut-off point for progression-free survival extrapolation → is this appropriate?
- Company extrapolated overall survival using exponential distribution, ERG preferred KM + exponential tail → which is most appropriate?
- Management of CNS events: in company base-case 100% patients have stereotactic radiosurgery (SRS) & steroids; in company scenario analysis 23% have SRS, 77% have whole brain radiotherapy (WBRT) & all have steroids → are either appropriate?

Non-small cell lung cancer (NSCLC)

- Usually no early signs, presents in advanced stages III/IV (75%)
- Symptoms include cough, breathlessness, blood in sputum, weight loss
- 2 histological types: non-small-cell (85–90%) and small cell
- Approximately 40% to 50% of patients with NSCLC develop central nervous system (CNS) metastases which are associated with poor median survival (4 to 9 months with chemotherapy, 2 months if untreated)
- Anaplastic lymphoma kinase (ALK) fusion genes are chromosomal alterations believed to be involved in tumour growth, and occur most commonly in tumours with adenocarcinoma histology (non-squamous)
- ~5% people with advanced NSCLC have ALK mutation (1170 people in England)

ERG comment:

- ALK variant: younger, female, less associated with smoking history
- As a result, may not be picked up by ‘high risk’ screening programs

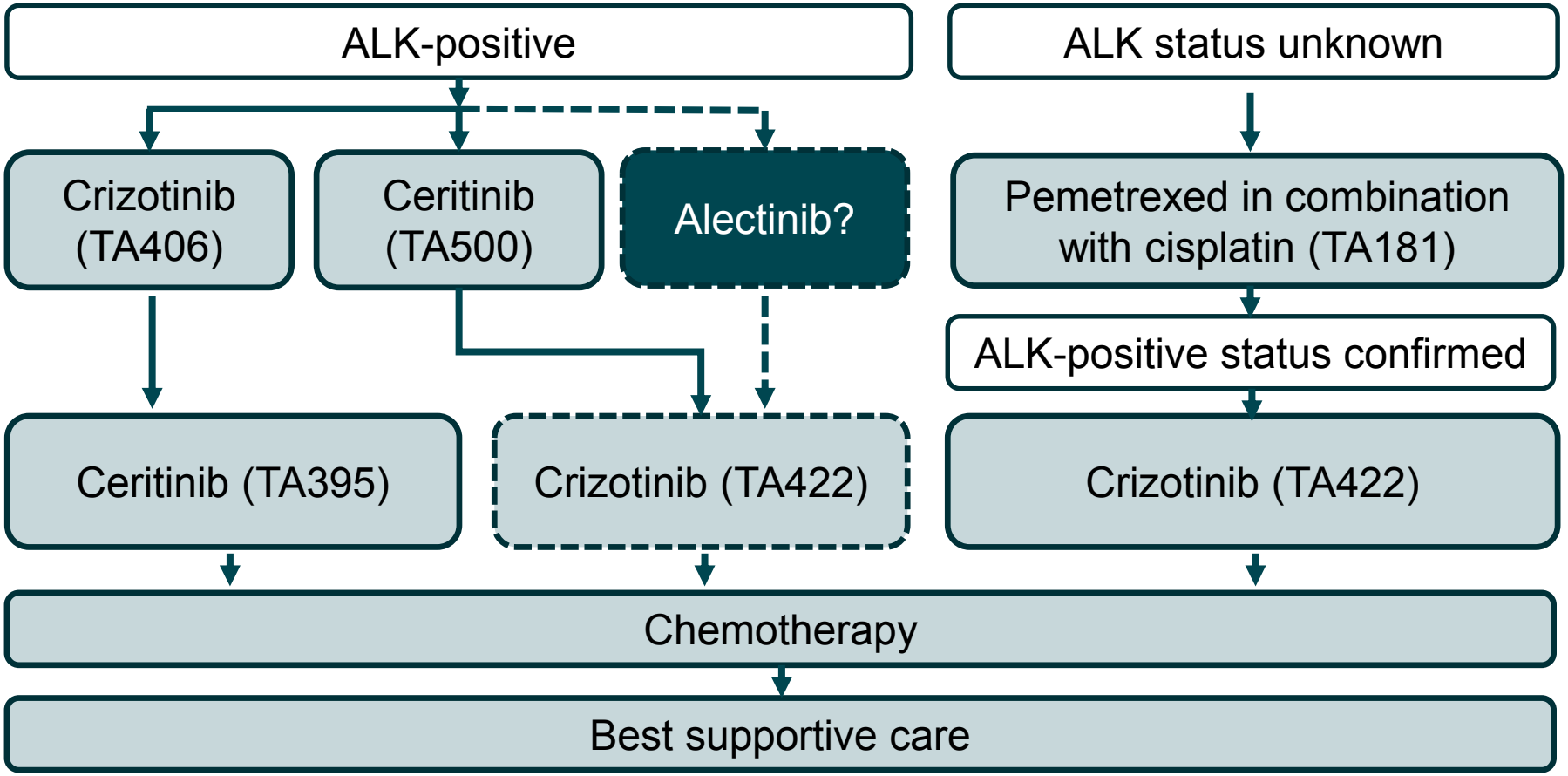
Patient perspectives

- Submission from Roy Castle Lung Cancer Foundation
- Non-small cell lung cancer (NSCLC) is a disease with no cure that can lead to physical and psychological distress
- Anaplastic Lymphoma Kinase (ALK) gene rearrangement found in a very few lung cancer patients
- New target therapies offer much better therapy options for these patients
- Compared with Crizotinib, Alectinib has superior efficacy and lower toxicity

Clinician perspectives

- Submissions: British Thoracic Oncology Group, and 3 clinical experts
- “Brain metastases are uniquely difficult to treat and palliate”
- ALEX trial:
  - Only 1% UK population (45% Asian)
  - Sample may be healthier than UK → may over-estimate survival gains
  - But survival gains expected given brain disease control
- Compared to Crizotinib, Alectinib:
  - Is better tolerated (so reduced resources)
  - Has better intracranial disease control and progression-free survival
  - Enables better quality of life
  - Leads to fewer neurological investigations and interventions
  - “Paradigm shift”
- Stopping rule: “when radiological and clinical progression on treatment”
- Same oral administration as Crizotinib – minimal new resources/ education

Current treatment for advanced NSCLC



ERG comment:

- Treatment pathway in line with NICE pathway for NSCLC
- Ceritinib now available for first line use (TA500) → uncertainty about effect on treatment pathway

Alectinib (Alecensa)
Roche

Mechanism of action	2nd generation tyrosine kinase inhibitor (TKI)
Marketing authorisation	Alectinib as a monotherapy is indicated for the first line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).
Administration	Oral
Dose	600 mg (4x 150 mg capsules) twice daily
Duration of treatment	Continued until disease progression or unacceptable toxicity
Cost (list price)	£5,032 per 224 capsule pack (28 day supply) Patient access scheme has been accepted by Department of Health. This provides a simple discount to list price.

Decision problem

	Scope	Company?
Population	Adults with untreated anaplastic lymphoma kinase-positive (ALK-positive) advanced non-small-cell lung cancer (NSCLC)	✓
Intervention	Alectinib	✓
Comparators	Crizotinib	✓
Outcomes	• Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health-related quality of life	✓

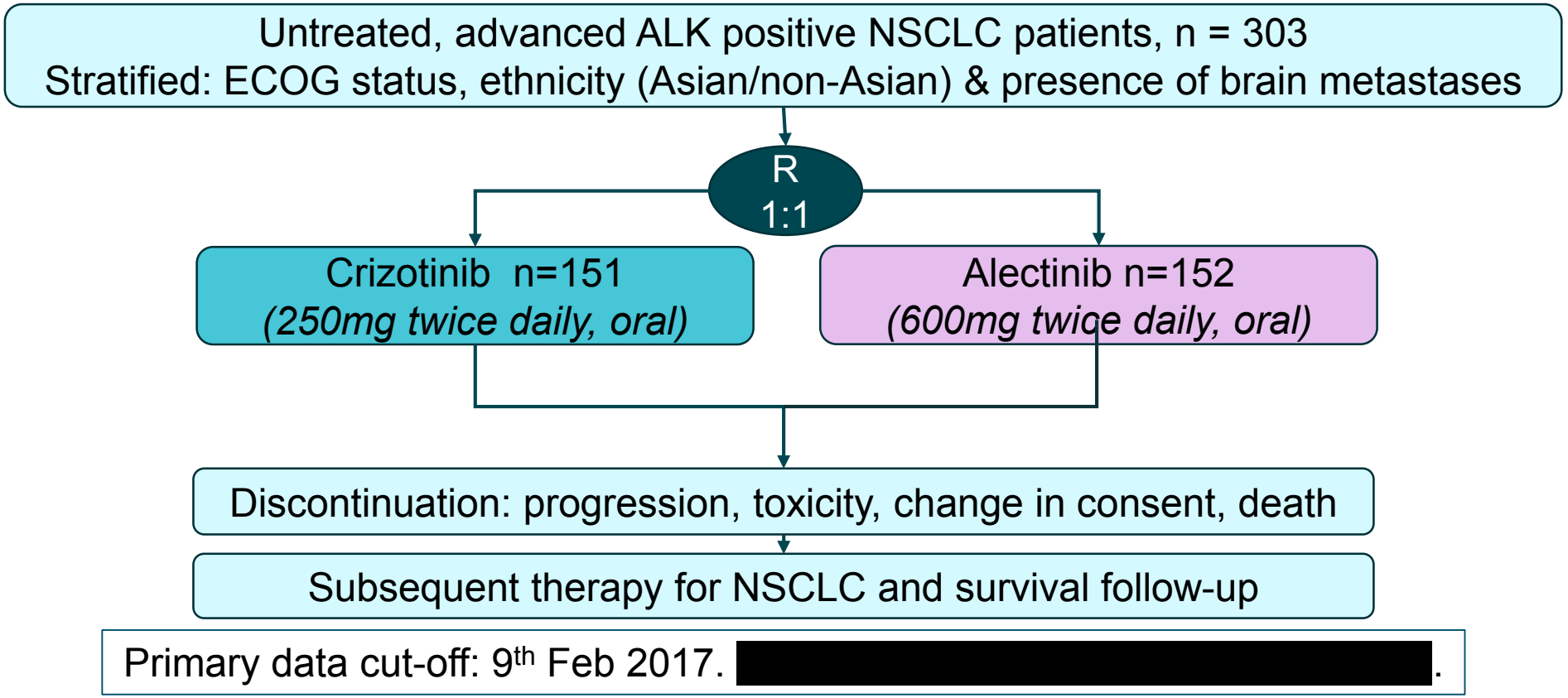
Key trial: ALEX

Design	Phase III, open-label, multi-centre randomised controlled trial
Population	Patients with previously untreated advanced ALK-positive NSCLC, n=303
Intervention	Alectinib, 600 mg twice daily, n=152
Comparator	Crizotinib, 250 mg, twice daily, n=151
1◦ outcome	Progression-free survival (investigator assessed)
Secondary outcomes	• Overall response rate • Duration of response • Time-to-central nervous system (CNS) progression • Progression-free survival (independent review committee; IRC) • Overall survival • Safety endpoints • Patient-reported outcomes

ERG comment: Well conducted and provides high quality evidence

- ALEX *'closely matches the decision problem… in the NICE final scope'*

ALEX: study design



- ALEX did not have protocol defined crossover
- However, some sites were in countries where study medications already available
- Some patients switched between treatments after discontinuing study treatment
- Crizotinib → alectinib = 10 patients; alectinib → crizotinib = 9 patients

Trial outcomes

Endpoint	Outcome	Measurement
Primary	Progression-free survival	Investigator assessed using RECIST
Secondary	Objective response rate	• % patients with complete or partial response • Investigator assessed, RECIST
	Duration of response	
	→ CNS progression rate → CNS objective response rate → CNS duration of response	• IRC assessed using RECIST • IRC assessed using CNS-RECIST
	Progression-free survival	• IRC assessed using RECIST • IRC assessed using CNS-RECIST
	Overall survival	

CNS = central nervous system; IRC = independent review committee; RECIST = Response Evaluation Criteria in Solid Tumours, v1.1; CNS-RECIST = adapted RECIST criteria designed to evaluate CNS progression

ALEX: key baseline characteristics

Baseline intention-to-treat population		Alectinib (n=152)	Crizotinib (n=151)
Age	Mean (range)	56.3 (25–88)	53.8 (18–91)
Gender	Male, n (%)	68 (45)	64 (42)
Race	Asian, n (%)	69 (45)	69 (46)
	Non-Asian, n (%)	83 (55)	82 (54)
ECOG PS	0 or 1, n (%)	142 (93)	141 (93)
	2, n (%)	10 (7)	10 (7)
CNS metastases	IRC, n (%)	64 (42)	58 (38)
Stage of disease	IIIB	4 (3)	6 (4)
	IV	148 (97)	145 (96)
Prior brain radiation, n (%)		26 (17)	21 (14)
CNS metastases treatment	Brain surgery	1 (4)	1 (5)
	Radiosurgery	5 (19)	4 (18)
	WBRT	17 (63)	16 (73)
	Other	4 (15)	1 (5)

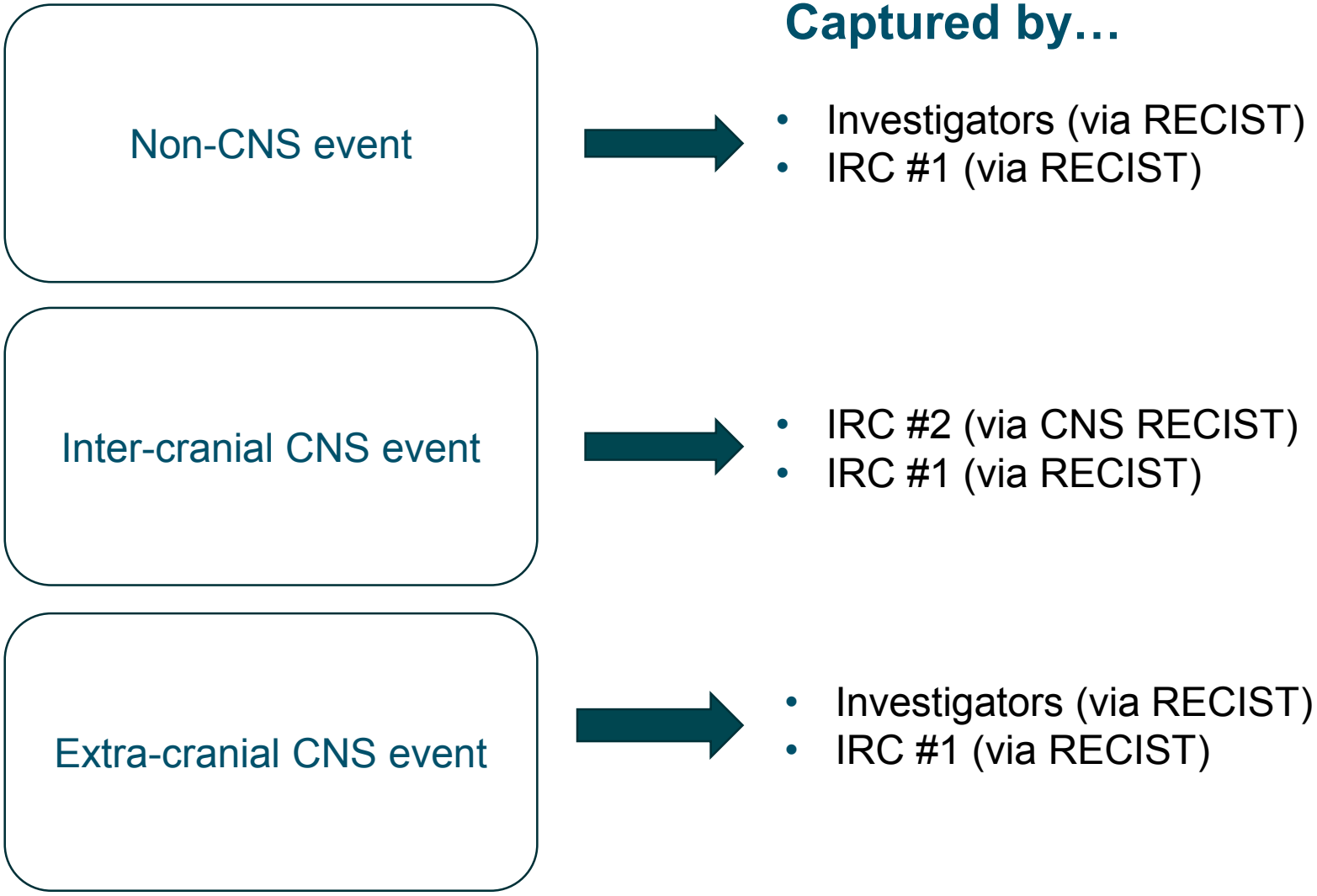
ERG comment on trial conduct

- In general, ALEX well conducted and provides high quality evidence
- Additional clinical effectiveness evidence from systematic review/ indirect comparison not needed because ALEX matches decision problem
- Open-label study design → ERG prefer IRC measurements to investigator as likely to be less biased
- Alectinib arm may have had slightly worse prognosis at baseline than crizotinib (older, ↑ baseline brain metastases, ↑ ECOG PS 1 vs 0); however, no statistical comparisons presented
- ALEX population younger with ↑ proportion women & non-smokers compared with wider lung cancer population → characteristic of ALK+ NSCLC population
- ↓ proportion ECOG PS 2 than UK population in both treatment arms → ALEX population may be healthier than population eligible for alectinib if approved
- Only 1% patients from UK centres; baseline characteristics reflective but may have implications for subsequent treatment distributions
- Statistical approach *'mostly appropriate'* although prefer analyses to be based on IRC RECIST measurements

Progression events in ALEX

- One independent review committee (IRC #1) assessed systemic progression events using RECIST criteria
- A separate independent review committee (IRC #2) assessed inter-cranial CNS progression events using CNS-RECIST criteria
- Investigators assessed all 3 types of progression events using RECIST tumour evaluation and brain imaging
- Relevant progression events in ALEX were:
  - Systemic progression
  - Symptomatic CNS progression
  - Asymptomatic CNS progression (investigator assessed only)
- Events captured by chosen measurement (ie. IRC CNS-RECIST & RECIST, IRC RECIST only or investigator assessed by RECIST) were counted as progression-free survival events

Measurement of CNS events



Progression-free survival and CNS progression events

- One of alectinib's potential benefits is delaying/preventing CNS progression → important to capture benefit in this area
- During clarification process, company restructured model to better demonstrate role of alectinib in CNS progression → adapted their progression-free survival to incorporate CNS events
- Progression-free survival = survival without any progression events
- CNS-progression-free survival = survival without any CNS progression events
- PFS and CNS-PFS need to be based on same measurement of events to ensure internal consistency of the economic model

Options for analysis:

Option 1: Add CNS RECIST outcomes to PFS data, so that PFS and CNS-PFS are both assessed by CNS-RECIST and RECIST

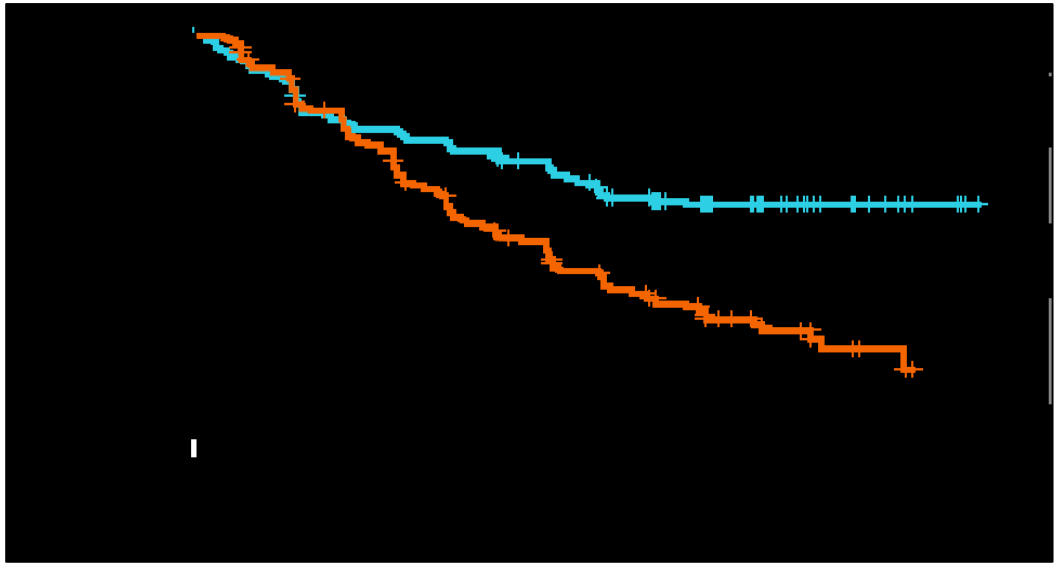
Option 2: Use RECIST data as the only measure of CNS outcomes, so that PFS and CNS-PFS are both assessed by RECIST only

Progression-free survival and CNS progression events

- Company's original base-case used investigator assessed PFS
- Company's **new base-case** based on Option 1 (PFS and CNS-PFS both based on IRC assessments using RECIST and CNS-RECIST)
- Company argues this is the *'most complete and robust analysis of the impact of CNS metastases'*

- ERG does not consider Option 1 to be a robust method:
  - CNS-RECIST not routinely used in UK clinical practice
  - CNS-RECIST may be more sensitive than RECIST and may detect events earlier than clinical practice
  - Unclear how CNS-RECIST outcomes 'added' to PFS data
- Could not validate information about sequence in patients (e.g. number of CNS progression events identified by CNS-RECIST before being identified by RECIST) to ensure that double counting is avoided
- ERG's preferred base-case based on Option 2 (PFS and CNS-PFS based on IRC assessments using RECIST only)

Primary outcome results: Progression-free survival (investigator)



Investigator assessed (RECIST); ITT	Alectinib n=152	Crizotinib n=151
Patients with events n (%)	62 (41)	102 (68)
Hazard ratio (95% CI)	0.47 (0.34, 0.65)	
Median duration of follow-up (months)	18.6	17.6
Median PFS (months; 95% CI)	Not met (17.7, NE)	11.1 (9.1, 13.1)
12-month event free survival (95% CI)	68.4% (61.0, 75.9)	48.7% (40.4, 56.9)

Secondary outcome results: Progression-free survival (IRC: RECIST)

IRC-assessed (using RECIST) progression-free survival:

IRC assessed; ITT	Alectinib	Crizotinib
Hazard ratio (95% confidence interval)	0.50 (0.36, 0.70)	
Median progression-free survival (months; 95% confidence interval)	25.7 (19.9, NE)	10.4 (7.7, 14.6)

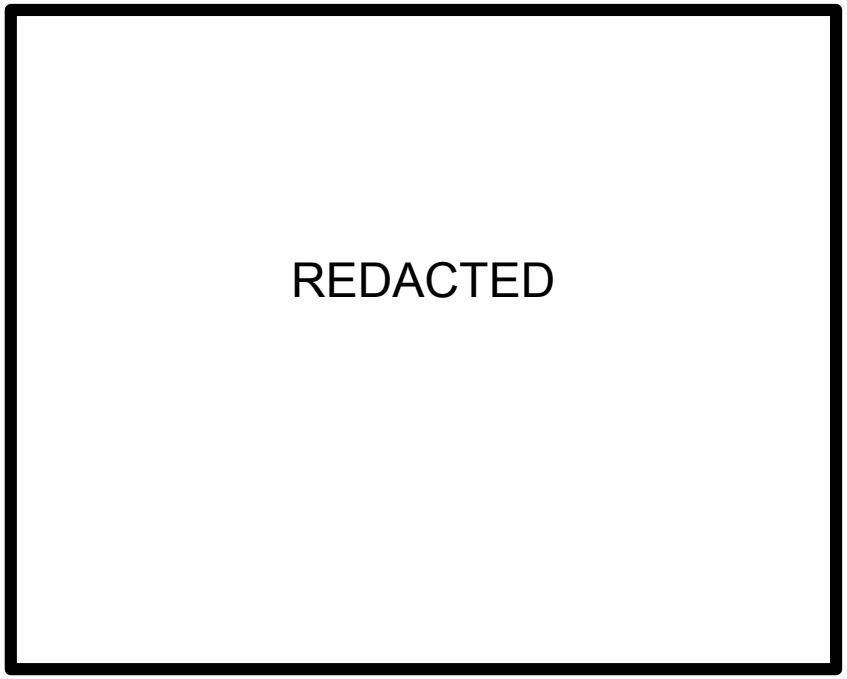
REDACTED

- ERG's preferred measure of progression-free survival
- Prefer to investigator because of open-label study design (less open to bias)

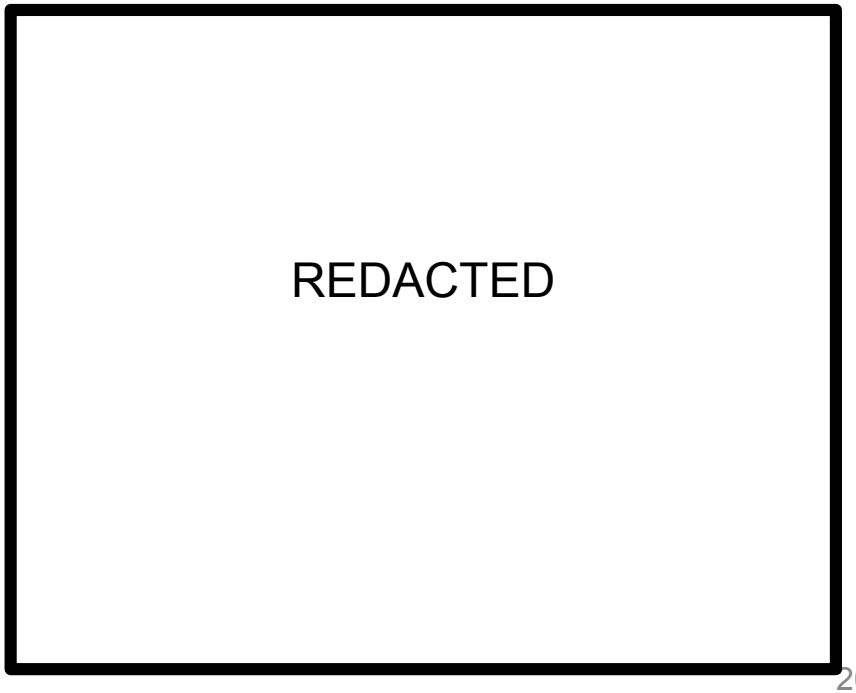
CNS- progression-free survival

- CNS- progression-free survival (CNS-PFS) = survival without any progression events in the CNS
- Option 1 = company base-case
- Option 2 = ERG preferred base-case

Option 1: RECIST or CNS-RECIST



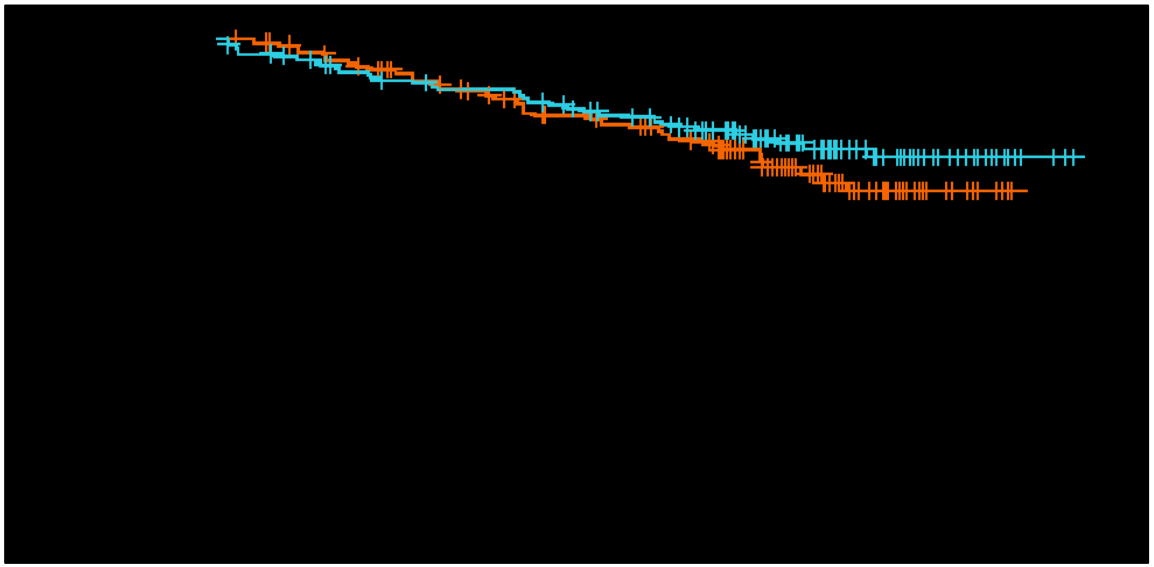
Option 2: RECIST only



ERG comment on CNS- progression-free survival

- Company's preferred approach is that a CNS event recognised by either the RECIST or CNS-RECIST criteria is a CNS progression event
- Patients with non-CNS progression events were not censored in either CNS-PFS analysis (RECIST + CNS-RECIST or RECIST only)
- This means some of the CNS events included in the analysis could be secondary to systemic progression
- ERG could not validate whether CNS events were primary or secondary
- Further uncertainty as company clarification response unclear about whether, after the first progression event, subsequent events were systematically captured (B1 and A10 seemingly contradict)

Secondary outcome results: Overall survival



ITT	Alectinib	Crizotinib
Median duration of follow up (range)	18.6 (0.5 to 29.0)	17.6 (0.3 to 27.0)
Median overall survival (months)	NE	NE
Hazard ratio (95% confidence interval)	0.76 (0.48, 1.20)	
12-month survival rate (%; 95% confidence interval)	84.3% (78.4, 90.2)	82.5% (76.1, 88.9)

Clinical cut-off: 9th February 2017. Sample not powered to detect significant difference in OS.

Secondary outcome results: Response rates (based on RECIST)

	INV assessment		IRC assessment	
Outcome	**Alectinib (n = 152)**	**Crizotinib (n = 151)**	**Alectinib (n = 152)**	**Crizotinib (n = 151)**
Objective response rate, n (%)	126 (82.9)	114 (75.5)	[redacted]	[redacted]
Stratified: OR (95% CI)	1.62 (0.92 to 2.84)		[redacted]	
Unstratified: OR (95% CI)	1.57 (0.90 to 2.76)		[redacted]	
Complete response, n (%)	6 (3.9)	2 (1.3)	[redacted]	[redacted]
Partial response, n (%)	120 (78.9)	112 (74.2)	[redacted]	[redacted]
Stable disease, n (%)	9 (5.9)	24 (15.9)	[redacted]	[redacted]
Progressive disease, n (%)	8 (5.3)	10 (6.6)	[redacted]	[redacted]
Missing or unevaluable, n (%)	9 (5.9)	3 (2.0)	[redacted]	[redacted]

Clinical cut-off: 9th February 2017. Investigator and IRC assessment based on RECIST v1.1. Stratification factors: race and baseline CNS metastasis. Stable Disease = stable at assessment at least 7 weeks from baseline/study entry. Unevaluable = all post-baseline response assessments reported as not evaluable, or last assessment occurred within 7 weeks from baseline/study entry and was CR, PR or SD. Missing = no post-baseline response assessments available.

Treatment beyond CNS progression

- Both IRCs were blinded and so could not assess whether CNS progression events were symptomatic or asymptomatic
- Investigators could assess whether event was asymptomatic
- If CNS progression was isolated and asymptomatic, patient could continue receiving study treatment at investigator's discretion
- However, an isolated asymptomatic CNS progression event was still considered a relevant survival event for the CNS- progression-free survival analysis

Subset of patients with progressed disease who continued to receive study treatment

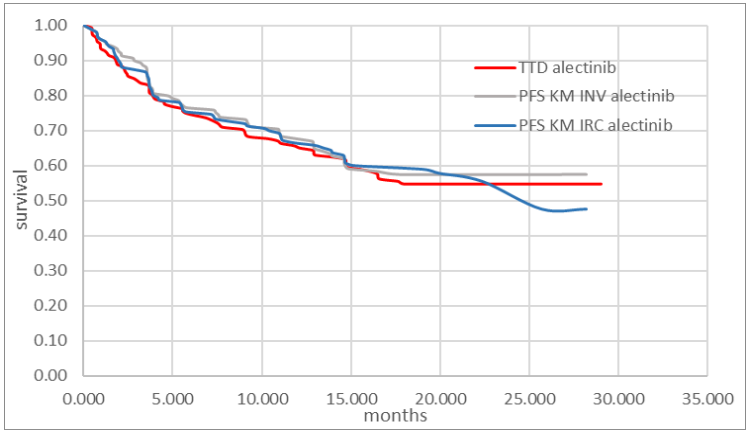
ERG comment:

- Not in marketing authorisation
- But, clinical expert advice and TA500 & TA422 indicate that UK clinical practice may be guided by symptoms rather than radiographic evidence → asymptomatic progression may not be detected in clinical practice

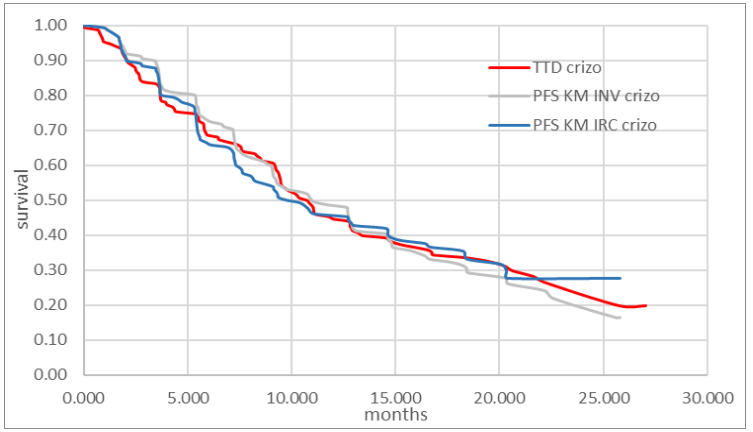
ERG comment on treatment beyond progression

- ERG compared progression-free survival curves to time-to-discontinuation curves
- Time to progression and discontinuation similar in ALEX for both treatments
- (N.B. PFS curves only show systemic progression, not necessarily asymptomatic CNS progression)
- *'continuing treatment beyond detection of an asymptomatic, isolated CNS does not seem problematic at face value (as these patient's CNS progression would not be captured in routine clinical practice'*

Alectinib



Crizotinib



ERG comment on treatment beyond progression

Alectinib:

- Uncertainty about whether clinicians would use alectinib beyond progression
- Discussed in TA406 and TA500; ~75% patients received treatment beyond progression in PROFILE 1014 (crizotinib) and ASCEND-4 (ceritinib)
- Current practice = treating patients with same ALK inhibitor after progression, but not covered in alectinib's marketing authorisation → uncertainty

Crizotinib:

- ASCEND-4 and PROFILE 1014 evidence: crizotinib given beyond progression
- Bias against crizotinib if given for a shorter period in ALEX than in clinical practice (assuming that alectinib will be used according to license)
- May also underestimate cost of treatment for crizotinib

TKI treatment sequence:

- Uncertainty about impact of subsequent TKI treatment after alectinib
- Disagreement from clinical experts about whether a 1st generation TKI (crizotinib) would be used after a 2nd generation TKI (alectinib)

Patient reported outcome results

EORTC QLQ-C30 and LC13

- [redacted]alectinib and [redacted] crizotinib patients completed baseline questionnaire
- [redacted] reported a confirmed deterioration in the composite symptom endpoint of cough, chest pain, dyspnoea
- [redacted]
- [redacted]
- Patient-reported outcome data [redacted] compared with crizotinib
- [redacted] treatments in the time to confirmed patient-reported clinically meaningful deterioration in HRQoL ([redacted])

Patient-reported deterioration in HRQoL: ERG *'does not consider there to be robust evidence for a meaningful difference between groups particularly give the low questionnaire completion rates by the time the curves appear to diverge'*

Subgroup analyses

Pre-planned subgroups:

- PFS for patients with/without baseline CNS metastases
- Objective response rate for patients with measurable CNS lesions at baseline with/ without prior brain radiation
- Time to CNS progression, excluding patients who had pre-treatment radiation therapy for CNS lesions
- Sex
- Age (<65 vs ≥65 years)
- Race (non-Asian vs Asian)

- Alectinib performs better than crizotinib in all groups apart from 'active smokers' (HR: 1.16, 95% CI: 0.35, 3.90) and 'ECOG PS' of 2 (HR: 0.67, 95%: 0.21, 2.13)
- Similar results in investigator assessed subgroups

- During clarification, company also explored overall survival for patients with/without baseline CNS metastases → no statistical difference in either arm

ERG clinical expert: ECOG PS, CNS metastases and subsequent therapies may be important prognostic factors → requested subgroup analyses at clarification

Subgroup analyses

- Overall survival in patients recorded as having subsequent anti-cancer treatment after alectinib vs patients not recorded:

	Subsequent anti-cancer tx	Not recorded
Alectinib	[redacted]	
Crizotinib	[redacted]	

- Overall survival for patients based on subsequent TKI treatment:

	Subsequent TKI	Not recorded
Alectinib	[redacted]	
Crizotinib	[redacted]	

- Company: analysis non-randomised with small sample → risk of bias
- High proportion of the 121 patients captured as 'no subsequent treatment' were still progression free and on alectinib ∴ likely to ↑ OS outcomes

ERG comment on subgroup analyses

CNS metastases:

- Kaplan-Meier curves indicate ↓ overall survival for patients with baseline brain metastases in both treatment arms; however, not significant

Subsequent therapies:

- PROFILE 1014 subgroup analysis showed that subsequent treatment with ALK TKI can have substantial impact on overall survival
- Subsequent therapy data not systematically captured; 54.4% of alectinib arm and 61.9% crizotinib arm missing → uncertainty
- Conclusions about impact of subsequent therapies limited by immaturity of overall survival data, small subgroups and missing data

ECOG performance status:

- Overlapping confidence intervals across ECOG PS scores indicate differences might not be statistically significant

All-cause adverse events

- Safety population = ITT population
- 97% patients in each arm reported at lease one adverse event
- Higher median duration of treatment for alectinib than crizotinib
- 35 (23%) alectinib patients vs 40 (27%) crizotinib patients died during the trial
- 29 (19%) alectinib patients vs 31 (21%) crizotinib patients died due to disease progression

	Alectinib n=152	Crizotinib n=151
Median tx duration, months (range)	17.9 (0 to 29)	10.7 (0 to 27)
Patients with ≥1 AE, n (%)	147 (97)	146 (97)
Serious AEs, n (%)	43 (28)	44 (29)
Grade 3–5 AEs, n (%)	63 (41)	76 (50)
Fatal AEs, n (%)	5 (3)	7 (5)
AEs leading to discontinuation, n (%)	17 (11)	19 (13)
AEs leading to dose reduction, n (%)	24 (16)	31 (21)
AEs leading to dose interruption, n (%)	29 (19)	38 (25)
Mean dose intensity, % (SD)	96 (10.3)	92.4 (14.1)

Treatment-related adverse events

- 77% alectinib arm experienced at least one treatment-related adverse event vs 89% crizotinib arm
- Most common (≥20% of patients in either arm; alectinib vs crizotinib):
  - nausea (7% vs 42%)
  - constipation (26% vs 21%)
  - diarrhoea (6% vs 38%)
  - vomiting (3% vs 29%)
  - increased alanine transaminase (ALT) (13% vs 29%)
  - increased aspartate transaminase (AST) (14% vs 22%)
  - peripheral oedema (9% vs 23%)

ERG comment:

- Safety assessments not blinded → potential attribution bias (particularly in treatment related events)

Innovation & End of life considerations

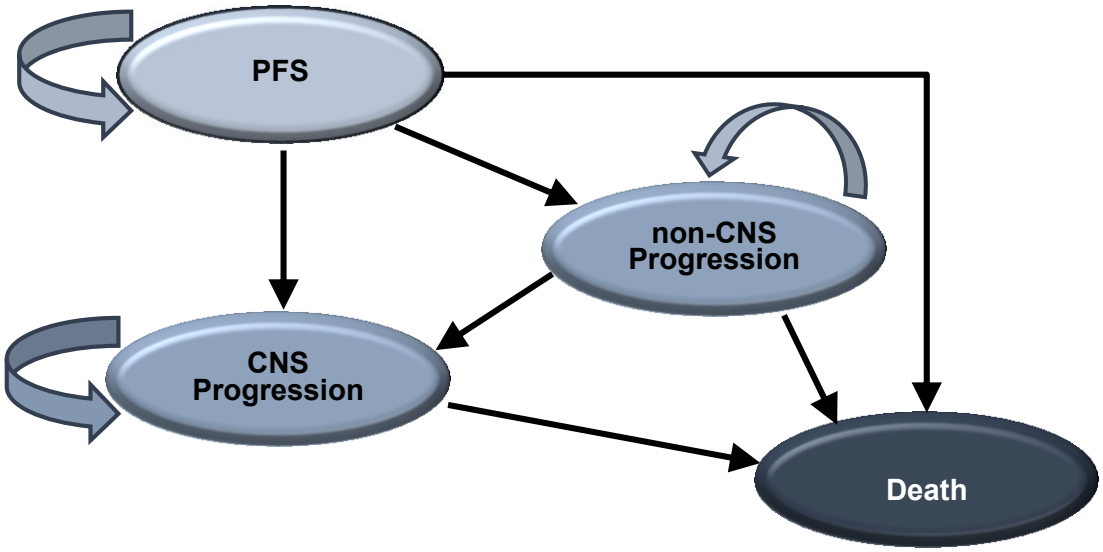
- Company considers alectinib to be innovative:
  - Crizotinib = 69% patients progression within 18 months → unmet clinical need
  - Granted a Promising Innovative Medicine designation by Medicines and Healthcare Products Regulatory Agency (MHRA)
  - Early Access to Medicines Scheme (EAMS) also approved by MHRA → significant advance over other ALK inhibitors
  - Delays CNS progression

- Company does not consider alectinib to meet end of life criteria

ERG comment on clinical evidence

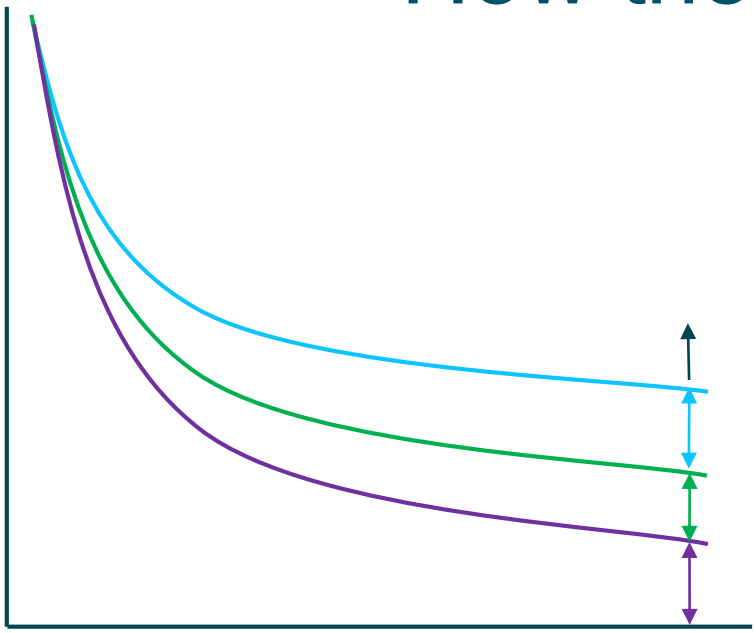
- ERG's preferred PFS analysis (IRC RECIST) shows significant benefit of alectinib over crizotinib → median PFS = 25.7 vs 10.4 months
- Alectinib PFS benefit present across majority of subgroups (except active smokes & ECOG PS 2; small sample sizes)
- ALEX not powered to detect differences in overall survival → median OS in alectinib vs crizotinib = 18.6 vs 17.6 months (HR: 0.76, 95% CI: 0.48, 1.20)
- ALEX doesn't demonstrate that alectinib PFS benefit translates to OS benefit
- Treatment related adverse events higher in crizotinib (89%) than alectinib (77%); however, open label → could be due to attribution bias
- Uncertainty around company's preferred PFS & CNS-PFS analyses (IRC RECIST & CNS-RECIST) → non-CNS progressive events censored in PFS analysis but not censored in CNS-PFS
- CNS-RECIST may not reflect clinical practice → ERG prefers RECIST only
- Challenge of treatment beyond asymptomatic CNS progression
- Subsequent therapies not captured systematically → limits ability to assess role on overall survival

Company's model



- Comparison of alectinib versus crizotinib (using evidence from ALEX)
- Cohort based area-under-the-curve (AUC) or 'partitioned survival' model
- 4 health states: progression-free survival, CNS progressed disease, non-CNS progression and death
- 30 year time horizon (considered a 'lifetime' horizon given typical age at diagnosis and expected survival times)
- 3.5% annual discount rate applied to costs and benefits; weekly cycle with half-cycle correction; NHS and PSS perspective

How the model works



Death	= 1 – P(OS)
CNS progression	= P(OS) – P(CNS-PFS)
Non-CNS progression	= P(CNS-PFS) – P(PFS)
Progression-free	= P(PFS)

- Proportion of patients in each health state derived from proportion of patients taken from PFS, CNS-PFS and OS curves
- Patients start in the progression-free survival health state
- Patients move forward through model to any ‘later’ state:
  - Can move from PFS to non-CNS progressed, CNS progressed or death
  - Can move from non-CNS progressed to CNS progressed or death
  - Can move from CNS progressed to death

Non-CNS progression & censoring

- Non-CNS progression events were not censored in CNS-PFS analysis
- CNS-progressed state could hence include both:
  1. CNS-progressions as the first progression event (primary event)
  2. CNS-progressions after systemic progression event (secondary event)
- Company justify not censoring: *'When such censoring was applied, the CPFS* [CNS-PFS] *curves crossed the OS curves, which produce implausible outcomes (negative population of the CPFS* [CNS-PFS] *health state), given the partitioned survival model structure.'*

- ERG assumed that all first CNS events were also systemic progressions, and therefore captured in the PFS curve
- ERG not concerned that secondary CNS events aren't explicitly modelled because in the model a CNS progression always 'trumps' a systemic disease progression → costs & QALYs appropriately captured
- ERG accepts company's justification for not censoring non-CNS events

Intervention, comparator & population

Technologies in model:

	Alectinib	Crizotinib
Administration	Oral; prescribed at outpatient appointments	
Dose	1200mg once daily	500mg once daily
Wastage	Full pack administered every 4 weeks (lung cancer clinic); death or discontinuation within timeframe → wastage	
Discontinuation	Until progression or unacceptable toxicity (anticipated license)	Until progression or unacceptable toxicity (clinical opinion but not in SmPC)

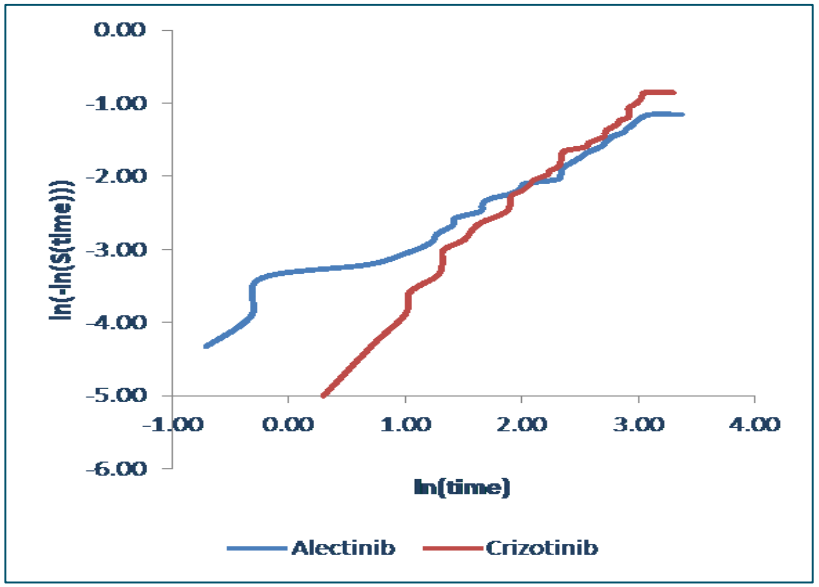
Population parameters:

Variable	Value	Distribution
Age	55.05 years	Fixed
Body weight	66.60 kg	Fixed
Height	164.70 cm	Fixed
Body surface area	1.73 m^2	Fixed

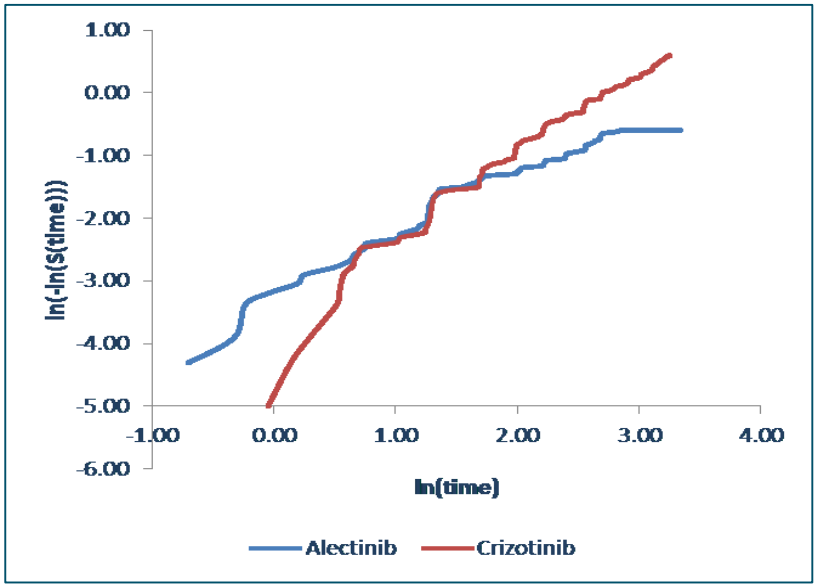
Proportional hazards assumption for survival extrapolation

- Log cumulative hazard plots for overall survival and progression-free survival cross → non-proportional hazards

Overall survival



Progression-free survival (investigator)



- ERG agrees with independent fit approach (although notes that proportional hazards assumption wasn't assessed for 'RECIST only' CNS-PFS data

Clinical data in the model

- Primary data source for clinical outcomes, adverse events and quality of life was ALEX
- Company base-case PFS & CNS-PFS modelled based on IRC RECIST and CNS-RECIST;

ERG's preferred RECIST only analysis explored through sensitivity analysis

- Median OS not met in either arm
- Median investigator-assessed progression-free survival not met in alectinib arm

Extrapolation of progression-free and overall survival curves

Choice of extrapolation distribution:

- Statistical fit assessed using AIC & BIC
- Goodness of fit also assessed visually
- Clinical plausibility assessed through visual inspection and external validation against available longer term data.

Overall survival extrapolation

	Alectinib		Crizotinib	
Distribution	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	**246.59**	**249.61**	**234.24**	**237.26**
Weibull	247.98	254.03	232.71	238.74
Log-normal	247.97	254.02	230.88	236.91
Gamma	249.79	258.86	232.79	241.84
Log-logistic	247.91	253.96	232.10	238.13
Gompertz*	248.59	254.63	234.72	240.76

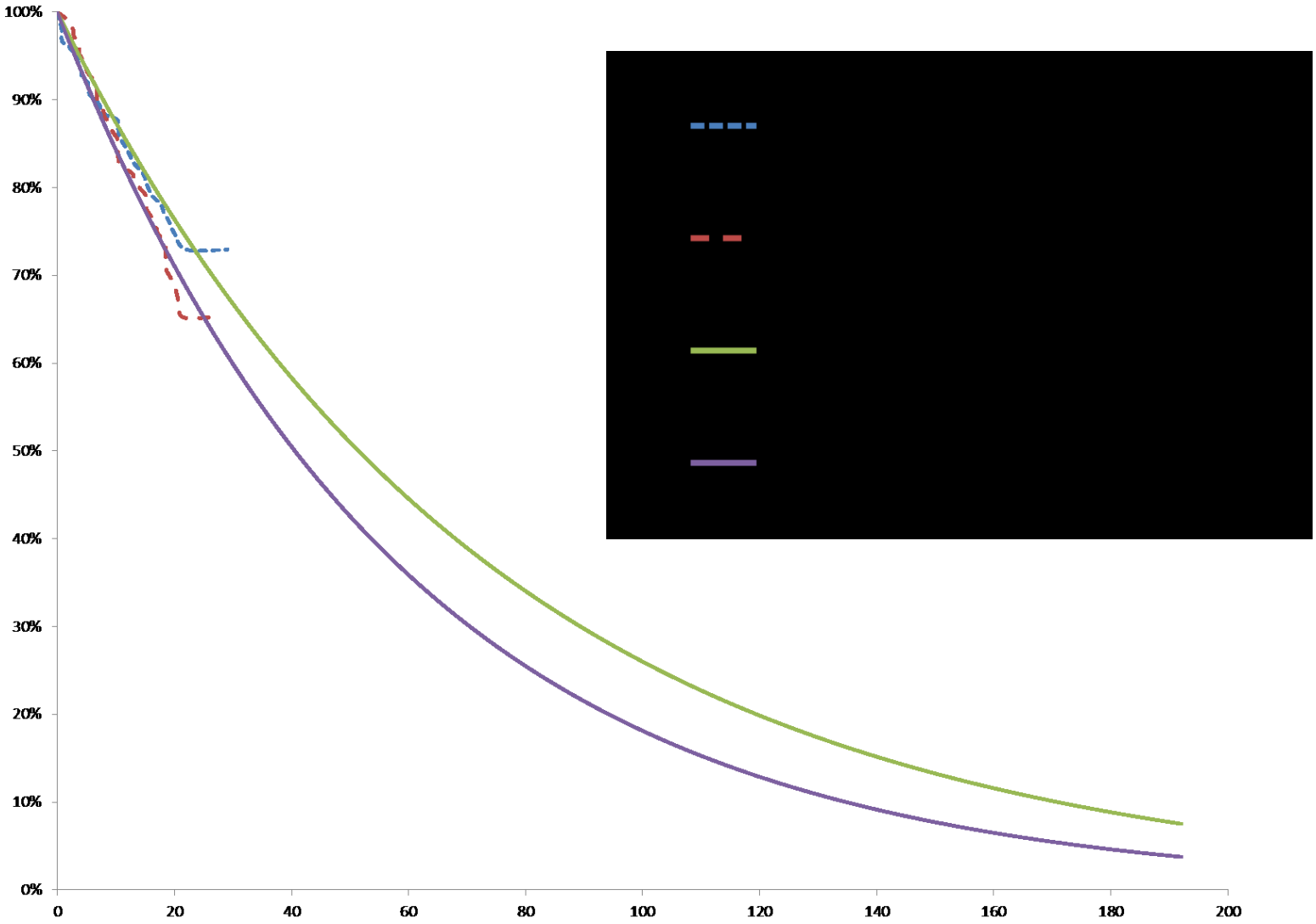
*Gompertz did not converge for alectinib ∴ excluded

- Distributions assessed against visual fit to ALEX Kaplan-Meier data
- None of the extrapolations for crizotinib meet the 4 year overall survival for people treated with crizotinib in the PROFILE 1014 trial (expected as the PROFILE population healthier than ALEX)
- Gamma = best fit to PROFILE data but implausible ↑ hazard after 140 months
- Exponential is second best fit to PROFILE data → plausible but conservative

Exponential extrapolation used as base case for alectinib & crizotinib

Overall survival extrapolation

Exponential extrapolation base case



ERG comment overall survival

- Subsequent treatment has substantial impact on overall survival → uncertainty as only 41% subsequent treatment data available from ALEX
- Previous appraisals have considered that PROFILE 1014 survival estimates were overestimated. In TA406, PROFILE 1014 data were adjusted to better reflect real-world data
- Potential for ALEX data to be adjusted in similar way → more conservative survival estimates
- ERG considers that ALEX does not provide robust evidence of a long term overall survival benefit of alectinib over crizotinib
- Exponential curves conservative
- Exponential curves imply proportional hazards; company have demonstrated assumption not met
- ERG explored Kaplan-Meier with exponential tail
- ERG also explored spline model; able to fit model which was visually similar to exponential but does not imply proportional hazards

Progression-free survival extrapolation
Statistical fit

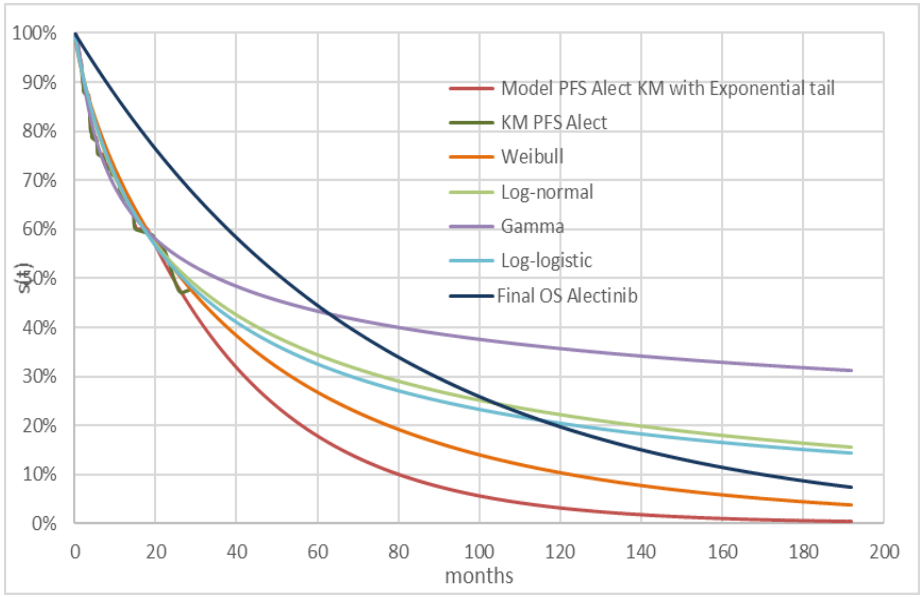
Progression-free survival based on IRC RECIST and CNS-RECIST

	Alectinib		Crizotinib	
Distribution	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	381.93	384.96	384.40	387.42
Weibull	378.95	385.00	384.30	390.34
Log-normal	371.85	377.90	370.73	376.77
Gamma	369.76	378.83	369.26	378.31
Log-logistic	376.07	382.12	375.01	381.04
Gompertz	383.93	389.98	386.40	392.44

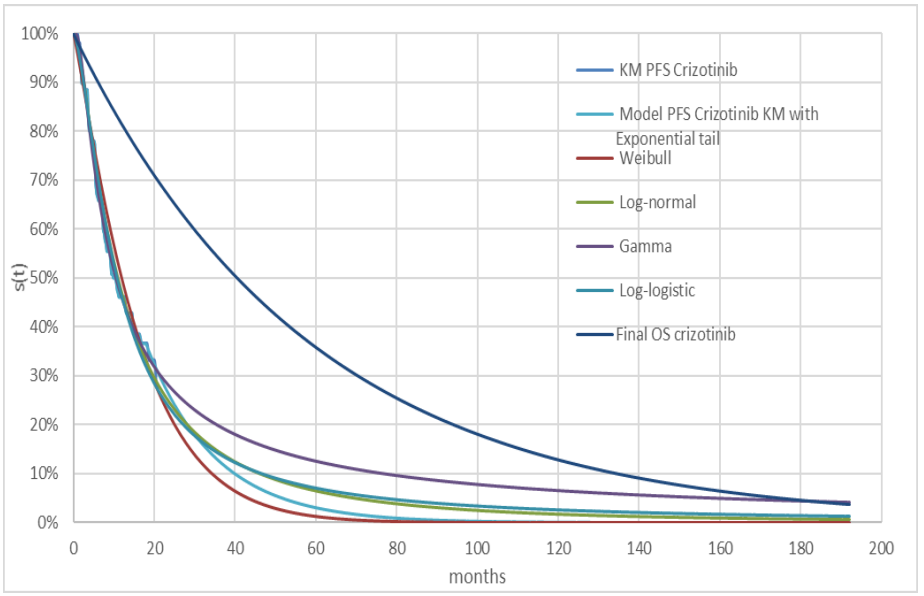
- Company's original base-case was based on investigator-assessed progression-free survival; extrapolated using Kaplan-Meier data with an exponential tail
- Following clarification, company updated model structure with new analysis for CNS-PFS extrapolation based on CNS-RECIST and RECIST
- Company's updated PFS curve was *'projected using [Kaplan-Meier] + exponential for consistence with previous modelling of PFS and as this still provided a good fit to this endpoint'*

Progression-free survival curves

Alectinib



Crizotinib



Kaplan-Meier with exponential tail used as base case extrapolation

Progression-free survival extrapolation

Kaplan-Meier with exponential tail extrapolation

REDACTED

Company's preferred base-case: 'Adapted' PFS (IRC; CNS RECIST & RECIST)

- ALEX survival outcomes likely to be overestimates (committee's consideration of PROFILE 1014 in TA500)
- ERG agrees with using exponential tail as conservative
- Consequence of using exponential tail after 18 months is that hazard ratio between treatments becomes proportional; inconsistent with company's assessment of proportional hazards
- ERG considers 18 month cut-off point for Kaplan-Meier data arbitrary

CNS-PFS extrapolation

Company's base case: IRC RECIST & CNS-RECIST

	Alectinib		Crizotinib	
Distribution	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	298.93	301.95	372.19	375.21
Weibull	299.56	305.61	368.48	374.51
Log-normal	297.25	303.29	353.97	360.01
Gamma	**298.98**	**308.05**	**352.46**	**361.51**
Log-logistic	298.89	304.94	358.53	364.57
Gompertz	300.93	306.98	373.87	379.90

- Company extrapolated CNS-PFS using Gamma distribution
- Justification: "*levelling off of cumulative CNS metastasis incidence in the long term, demonstrated by the poster presented by Betts et al. at the 2016 AMCP Managed Care & Specialty Pharmacy Annual Meeting in San Francisco*".
- Proportion of patients who transitioned out of CNS-PFS into death used to model membership into non-CNS progressed and CNS progressed states
- Assumed to be a fixed proportion: alectinib = 62.07%, crizotinib = 87.50%

Base-case CNS-PFS extrapolation

REDACTED

Kaplan-Meier data for CNS-PFS measured by IRC CNS-RECIST & RECIST and IRC RECIST only

- Gamma distribution was one of the worst fitting curves (based on AIC/BIC) → lognormal or log-logistic appear better, but updating had negligible impact

Subgroup analyses

- Worse OS in patients recorded as having subsequent anti-cancer treatment after alectinib vs patients not recorded…

	Subsequent anti-cancer tx	Not recorded
Alectinib	[redacted]	
Crizotinib	[redacted]	

- Company: high proportion of the 121 patients captured as 'no subsequent treatment' were still progression free and on alectinib ∴ likely to ↑ outcomes
- No difference in OS for those having subsequent TKI treatment after vs patients not having subsequent TKI treatment for either treatment…

	Subsequent TKI	Not recorded
Alectinib	[redacted]	
Crizotinib	[redacted]	

Utilities from ALEX

- EQ-5D-3L questionnaire: every 4 weeks until progression, post-treatment visit (4 weeks after treatment discontinuation), and every follow-up appointment (every 8 weeks for 6 months, then every 12 weeks)
- Random intercept model analysed relationship of sex, age, race (Asian vs non-Asian), CNS lesions at baseline and health state* with EQ-5D
- ERG requested company use stepwise approach and drop covariates with p >0.1

Mixed model for EQ-5D estimates

Covariate	Estimate	St. Error	DF	P value
Intercept	0.8956	0.05270	240	<0.0001
Age	-0.00190	0.000909	241	0.0380
Race (Asian)	0.04857	0.02300	237	0.0357
Disease Progressed	-0.08918	0.009546	4361	<0.0001

Resulting utility estimates based on ALEX

Health state	Utility	Variance
Progression-free Survival	[redacted]	[redacted]
Progressed Disease	[redacted]	[redacted]

CNS progression utilities

- Following clarification and amendments to model, company used mixed model to re-estimate utilities for CNS-PFS and CNS-progressed states

Utility values for CNS analysis:

	IRC CNS-RECIST & RECIST		IRC RECIST only	
Health state	Utility	SE	Utility	SE
Progression-free	[redacted]	[redacted]	[redacted]	[redacted]
CNS-progressed	[redacted]	[redacted]	[redacted]	[redacted]

- CNS-progressed disease utility higher than previously estimated utility for overall progressed disease state → insufficient evidence from ALEX to capture detrimental effect of CNS metastases on patients (perhaps due to small sample and limited follow-up time post-progression)
- Peters et al. (2016) & Roughley et al. (2014) report average utility for patients with brain metastases as 0.52
- Company used estimate of 0.52 and applied to all patients entering CNS-progressed state

Base case utilities

State	Utility value: mean (SE)	Justification
Progression-free state	[redacted]	Derived using mixed-model from EQ-5D data collected during ALEX trial - in-line with reference case
Progressed disease state	[redacted]	As above
CNS-progressed disease state	[redacted]	Peters et al. (2016) & Roughley et al. (2014). SE based on assumption.

- Roughley et al. was conference abstract so ERG could not compare demographics with ALEX population
- Roughley et al. do not report utilities for non-CNS progressed disease → cannot compare with value in ALEX and check consistency
- ERG explored CNS progression utility in scenario analysis

Adverse event disutilities

- Base case analysis includes grade 3 & 4 treatment-related adverse events with incidence of ≥3% in either arm & all grade 5 treatment-related adverse events
- Base case does **not** model disutilities (assumed to be captured through EQ-5D)
- Adverse event disutilities modelled in scenario analyses (neutropenia: -0.09, pneumonitis: -0.2; both applied for 5 days)

Adverse events included in model:

	Alectinib (n=152)		Crizotinib (n=151)	
	Occurrence	%	Occurrence	%
Alanine aminotransferase ↑	7	4%	25	14%
Asparatate aminotransferase ↑	10	5%	17	9%
Cardiac Arrest	0	0%	1	1%
QT interval prolongation	0	0%	6	3%
Neutropenia	0	0%	13	3%
Pneumonitis	0	0%	3	2%

- ERG considers modelling of adverse events to be reasonable

Acquisition and administration costs

- Alectinib and crizotinib both have confidential PAS discounts
- Both-administered as full pack at lung cancer clinic (every 4 weeks)
- Model incorporates 'wastage' if a patient dies/discontinues
- 'No wastage' assumption explored as scenario analysis

Drug	Concentration	Pack volume	Dose p/pack	Cost p/pack	Source	Cost p/ administration
Alectinib	150 mg	224	33,600 mg	£5,032.00	BNF	£9.20 (pharmacist; 12 min every 4 wks)
Crizotinib	250 mg	60	15,000 mg	£4,689.00	BNF	

- Crizotinib pack = 30 day treatment, alectinib pack = 28 day treatment
- Cycle = 28 days ∴ 2 days crizotinib wasted (not accounted for in 'wastage')
- ERG amended model so crizotinib bought every 30 days (instead of 28)

ERG comment on resource use

- Cost estimations generally correct. However, ERG updated crizotinib costing so one pack was purchased every 30 days instead of 28 days
- Clinical experts indicated that frequency of oncologist visits was underestimated → ERG ran additional analysis with visits every 4 weeks
- Company base-case assumes stereotactic radiosurgery (SRS) used for 100% patients with CNS metastases. All patients additionally received steroids.
- However, SRS only available for patients with ≤2 metastatic sites.
- Company scenario analysis: 23% receive SRS, 77% receive whole-brain radiotherapy (WBRT); all patients receive steroids
- ERG clinical expert: 23% receive SRS + steroids, 77% steroids only

Subsequent treatment resource use

- Company base-case: weighted subsequent treatments (ALEX distribution)
- Subsequent treatment utilities explored through scenario analysis
- Scenario analysis of distribution based on UK clinical practice
- Assumes 100% patients receive 2L treatment & treatments mutually exclusive
- Mean time on subsequent treatment taken from trials & literature
- Subsequent therapies assumed same regardless of CNS metastasis

- Only 41% ALEX subsequent treatment data captured
- Clinical experts: subsequent TKI treatment not usually given if CNS metastases has developed
- As alectinib has protective effect on CNS, likely that ↑ proportion of alectinib arm would receive subsequent TKI compared to crizotinib arm
- ERG ran 3 scenario analyses that reflected distribution of subsequent treatments in clinical practice

ERG comment on subsequent treatments scenario analysis

- Company model of patients receiving subsequent TKI therapy: 29% alectinib patients vs 72% crizotinib patients
- Subsequent TKI treatment ↑ outcomes ∴ if higher proportion of crizotinib patients receive a TKI, alectinib incremental QALY gain ↓
- Clinical experts: often patients do not receive subsequent TKI treatment is because the development of CNS metastases leave patients too ill to tolerate
- As alectinib has protective effect on CNS, likely that higher proportion of alectinib patients would receive subsequent TKI compared to crizotinib patients
- Scenario analysis also does not include consequence of CNS metastases on HRQoL → underestimates benefit of alectinib
- Estimates used in company model are poor reflection of clinical practice
- Company did not run a QALY scenario analysis that reflected distribution of subsequent treatments in clinical practice → ERG ran 3 additional scenario analyses

Subsequent treatment distribution

	Alectinib		Crizotinib	
Treatment	**n**	**%**	**n**	**%**
Any subsequent anti-cancer tx	40	59%	44	42%
Any TKI	19	48%	36	82%
Ceritinib	4	10%	14	32%
Alectinib	0	0%	10	23%
Crizotinib	9	23%	2	5%
Other	6	13%	10	23%
Platinum compound	19	48%	6	13%
Antimetabolite	17	43%	6	13%
Taxane (paclitaxel, docetaxel)	3	8%	1	2%
Immunostimulant (nivolumab)	2	5%	0	0%
Angiogenesis inhibitor	2	5%	0	0%
Other	4	10%	1	2%
Patients on TKIs		**29%**		**72%**
Patients on non-TKIs		**71%**		**28%**

- Explored through scenario analysis
- Data from 2nd/3rd line subsequent treatments from ALEX merged and reweighted to account for patients with data not captured

Company results

based on list prices

Based on IRC CNS-RECIST & RECIST (company's base case)

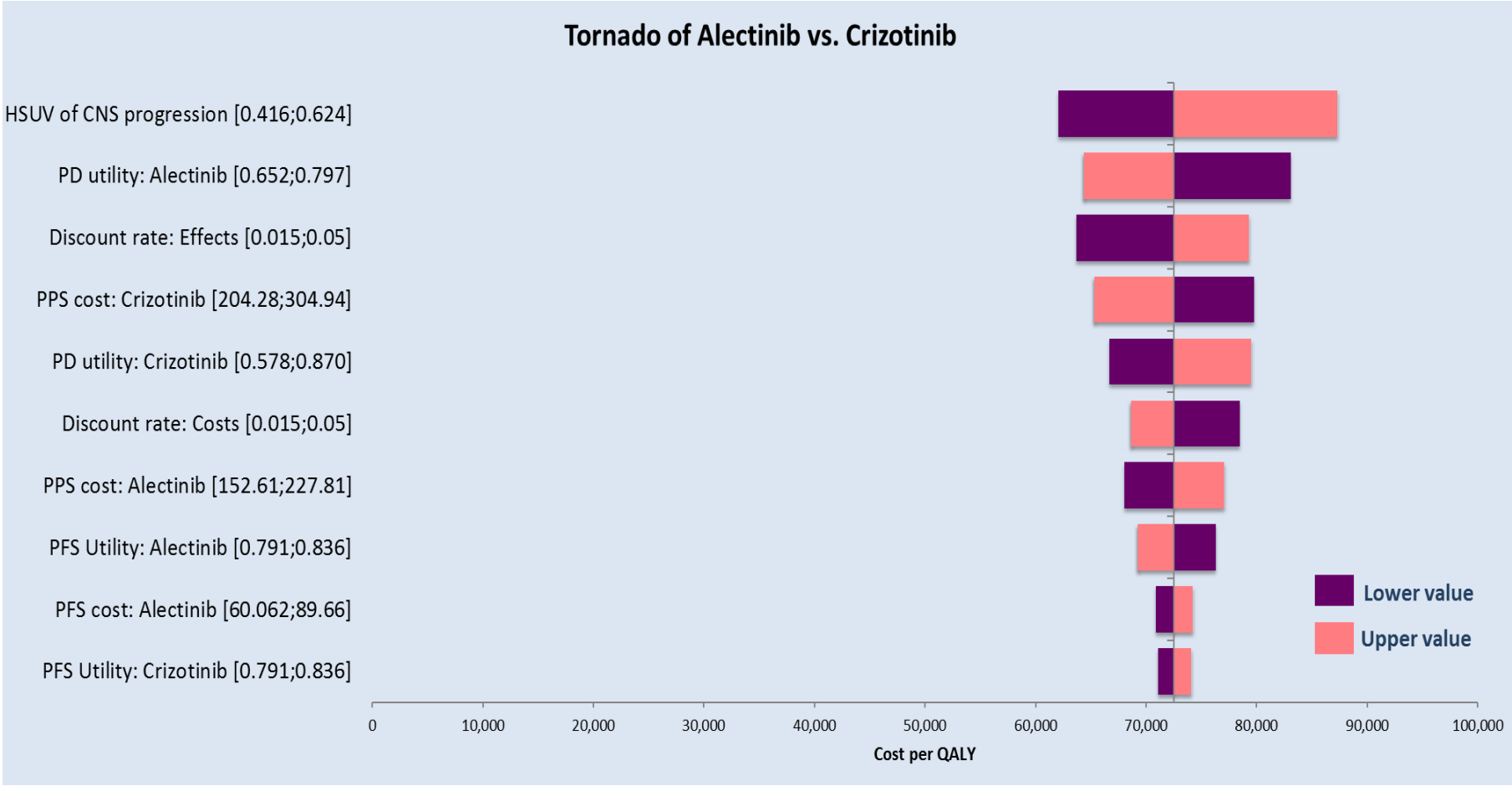
	Total costs	Total LYG	Total QALYs	Inc costs	Inc LYG	Inc QALYs	ICER £/QALY
Crizotinib	£135,955	4.25	2.61				
Alectinib	£219,643	5.17	3.77	£83,688	0.93	1.15	£72,544

Probabilistic sensitivity analysis results (1000 iterations):

	Costs		QALYs		ICERs	
	Base case	PSA	Base case	PSA	Base case	PSA
Crizotinib	£135,955	£132,761	2.61	2.61		
Alectinib	£219,643	£216,573	3.77	3.77	£72,544	£72,651

Deterministic sensitivity analysis

- Majority of parameters varied across a +/- 50% range (excluding utilities)
- Parameter values with most influence on results shown in tornado diagram



ERG preferred range of ICERs

based on list prices

Preferred assumptions:

- PFS and CNS-PFS outcomes measured by RECIST only
- Extrapolating overall survival curves using Kaplan-Meier + exponential tails
- Frequency of oncologist visits = every 4 weeks
- 23% of patients receive stereotactic radiosurgery and 77% patients receive whole-brain radiotherapy; all patients receive additional steroids (company's scenario analysis)
- Proportion of patients receiving subsequent TKI (alectinib vs crizotinib): a) 71% vs 31.4%; b) 31.4% vs 31.4%; c) 19.1% vs 31.4%

		Alectinib		Crizotinib		ICER (inc. all other changes)
	Scenario	Total QALYs	Total costs	Total QALYs	Total costs	
a	71% vs 31.4%	3.83	£241,685	3.01	£139,839	**£142,060**
b	31.4% vs 31.4%	3.78	£228,927	3.01	£139,839	**£132,635**
c	19.1% vs 31.4%	3.76	£224,113	3.01	£139,839	**£129,324**

Company scenario analyses

based on list prices

1. Progression-free survival extrapolations
2. Post-progression utilities
3. Subsequent treatment distributions
4. CNS-PFS extrapolations
5. Overall survival extrapolations
6. Capping of OS and PFS treatment effect duration
7. Adverse event disutilities
8. Wastage assumption
9. % of patients receiving SRS vs corticosteroids at CNS progression
10. PFS/CNS-PFS measurement and modelling

Company scenario analysis results (1)

		Alectinib		Crizotinib		
	Scenario	Total QALYs	Total costs	Total QALYs	Total costs	ICER
	Base-case	3.77	£219,643	2.61	£135,955	£72,544
1	Exponential	3.77	£223,070	2.61	£134,675	£76,155
	Weibull	3.83	£268,958	2.61	£130,927	£112,485
	KM+Weibull	3.83	£266,779	2.61	£131,972	£110,302
2	1 PPS utility (ALEX)	3.77	£219,643	2.61	£135,955	£72,544
	2/3rd line PPS utilities	3.24	£219,643	2.36	£135,955	£95,820
3	ALEX trial (base case)	3.77	£219,643	2.61	£135,955	£72,544
	Clinical practice	3.77	£234,346	2.61	£149,575	£73,483
4	Exponential	3.59	£220,376	2.53	£136,027	£79,142
	Weibull	3.73	£219,773	2.50	£134,534	£69,122
	Log-normal	3.77	£219,641	2.54	£136,334	£67,876
	Log-logistic	3.77	£219,643	2.56	£136,272	£68,932
	KM with Gamma tail	3.75	£219,712	2.61	£135,960	£73,673

Company scenario analysis results (2)

		Alectinib		Crizotinib		
	Scenario	Total QALYs	Total costs	Total QALYs	Total costs	ICER
5	Weibull	4.32	£223,668	2.02	£130,952	£40,238
	Log-normal	6.12	£237,942	3.05	£139,093	£32,194
	Gamma	5.47	£232,250	3.36	£142,426	£42,607
	Log-logistic	5.43	£231,842	2.76	£135,902	£35,917
6	3 years	3.39	£187,198	2.61	£135,955	£66,065
	5 years	3.53	£204,416	2.61	£135,955	£75,095
	7 years	3.61	£212,495	2.61	£135,955	£76,668
	10 years	3.69	£217,286	2.61	£135,955	£75,792
7	AE disutility	3.77	£219,643	2.61	£135,955	£72,533
8	No wastage	3.74	£218,238	2.66	£130,944	£80,450
9	76.74% steroid use	3.77	£213,432	2.61	£126,173	£75,640
10	Original modelling	3.74	£219,941	2.71	£149,539	£68,508
	RECIST only	3.82	£225,992	2.80	£154,013	£70,514

ERG scenario analyses

based on list prices

1. Company's corrected base case using RECIST outcomes
2. KM + exponential tail used for OS extrapolation
3. Visits to oncologist every 4 weeks

4/5. Proportion of patients receiving subsequent TKI (QALYs/costs):

   a) 71% alectinib vs 31.4% crizotinib
   b) 31.4% alectinib vs 31.4% crizotinib
   c) 19.1% alectinib vs 31.4% crizotinib

6. 77% patients receive only steroids rather than WBRT to manage CNS metastasis
7. Varying CNS metastasis utilities over range

ERG scenario analysis results
Based on list prices

		Alectinib		Crizotinib		
	Scenario	Total QALYs	Total costs	Total QALYs	Total costs	ICER
1	Company RECIST base-case	3.82	£225,992	2.80	£149,354	**£75,079**
2	KM + exponential OS	3.79	£225,841	2.84	£149,912	**£80,146**
3	Oncology visits p/4 week	3.82	£227,309	2.80	£150,048	**£75,689**
4a	71% alect. & 31.4% criz.	3.83	£225,992	3.01	£149,354	**£93,856**
4b	31.4% alect. & 31.4% criz.	3.78	£225,992	3.01	£149,354	**£100,220**
4c	19.1% alect. & 31.4% criz.	3.76	£225,992	3.01	£149,354	**£102,851**
5a	71% alect. & 31.4% criz.	3.82	£241,685	2.80	£139,839	**£99,774**
5b	31.4% alect. & 31.4% criz.	3.82	£228,927	2.80	£139,839	**£87,275**
5c	19.1% alect. & 31.4% criz.	3.82	£224,113	2.80	£139,839	**£82,560**
7	Steroids vs WBRT	3.82	£218,134	2.80	£137,108	**£79,378**

EUnetHTA evaluation of alectinib

- EUnetHTA recently published HTA of alectinib
- Considered clinical effectiveness of alectinib vs crizotinib (& vs ceritinib)

Considerations:

- ALEX population generalizable to ALK-positive NSCLC population
- Most important limitation = immature overall survival data
- ALEX provides high quality evidence of progression-free survival outcomes
- Alectinib has significant improvement in progression-free survival and time-to-CNS progression compared to crizotinib (based on ALEX)
- Quality of life evidence from ALEX has high risk of bias due to open-label design and low completeness of baseline questionnaires
- Alectinib and crizotinib have similar safety profiles for serious adverse events; alectinib has more favourable profile in non-serious adverse events that affect quality of life (e.g. nausea, diarrhoea, vomiting)

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Alectinib for untreated anaplastic lymphoma kinase-positive advanced non-small cell lung cancer [ID925]

Document B

Company evidence submission

October 2017

File name	Version	Contains confidential information	Date
ID925_alectinib_ALK+ NSCLC_Document B	1	Yes	24/10/17
ID925_alectinib_ALK+ NSCLC_Document B_1.1	1.1	Yes	25/10/17

Contents

Acronyms

Acronym	Definition
1L	First-line
2L	Second-line
3L	Third-line
ADR	Adverse drug reaction
AE	Adverse event
AIC	Akaike Information Criterion
ALK	Anaplastic lymphoma kinase
ALT	Alanine transaminase
ANC	Absolute neutrophil count
AST	Aspartate transaminase
ATP	Adenosine triphosphate
AUC	Area-Under-the-Curve
BIC	Bayesian Information Criterion
BID	Twice-daily
BL	Baseline
BNF	British national formulary
BSC	Best supportive care
CAD	Canadian dollars
CC	Critical care
CDF	Cancer Drugs Fund
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CLL	Chronic lymphocytic leukemia
CNS	Central nervous system
CPK	Creatine phosphokinase
CR	Complete response
CT	Computerised tomography
CYP	Cytochrome P450
DF	Degrees of freedom
DMD	Dictionary of Medicines and Devices
DOR	Duration of response
DSU	Decision Support Unit
EAMS	Early access to medicine scheme
EC	European Commission
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group performance status
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
eMIT	Electronic market information tool
EORTC	European Organisation for Research and Treatment of Cancer
EPAR	European public assessment report
ePRO	Electronic patient-reported outcome
ERG	Evidence review group
EU	European Union

Acronym	Definition
FISH	Fluorescence in situ hybridization
GI	Gastrointestinal
GP	General practitioner
HR	Hazard ratio
HS	Health state
HSUV	Health state utility value
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IHC	Immunohistochemistry
INV	Investigator
IRC	Independent Review Committee
ITT	Intention-to-treat
KM	Kaplan-Meier
LYG	Life years gained
MHRA	Medicine and Healthcare products Regulatory Agency
MOA	Mechanism of action
MRI	Magnetic resonance imaging
NA	Not applicable
NE	Not evaluable
NHS	National Health Service
NR	Not recorded
NSCLC	Non-small cell lung cancer
OR	Objective response
ORR	Objective response rate
OS	Overall survival
PAS	Patient access scheme
PASLU	Patient Access Schemes Liaison Unit
PCR	Polymerase chain reaction
PD	Progressive disease
PF	Progression-free
PFS	Progression-free survival
P-gp	Permeability glycoprotein
PH	Proportional hazards
PIM	Promising Innovative Medicine
PO	Oral
PPS	Post-progression survival
PR	Partial response
PSA	probabilistic sensitivity analysis
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life years
QTc	Corrected QT interval
R	Randomise
RCT	Randomised clinical trials
RECIST	Response Evaluation Criteria in Solid Tumours
RU	Resource use
SAE	Serious adverse event
SAP	Safety Analysis Population
SCLC	Small cell lung cancer

Acronym	Definition
SD	Stable disease
SD	Standard deviation
SDF	Survival distribution function
SE	Standard error
SLR	Systematic literature review
SMC	Scottish Medical Consortium
SmPC	Summary of Product Characteristics
TK	Tyrosine kinase
TKI	Tyrosine-kinase inhibitor
TTOT	Time to off-treatment
UK	United Kingdom
ULN	Upper limit of normal
US	United States
vs	Versus
WBRT	Whole brain radiotherapy

Tables

Figures

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.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with untreated anaplastic lymphoma kinase positive (ALK-positive) advanced non-small cell lung cancer (NSCLC)	Adults with untreated anaplastic lymphoma kinase positive (ALK-positive) advanced non-small cell lung cancer (NSCLC)	NA
Intervention	Alectinib	Alectinib	NA
Comparator(s)	Crizotinib	Crizotinib	NA
Outcomes	• overall survival • progression-free survival • response rates • adverse effects of treatment • Health-related quality of life.	• overall survival • progression-free survival • response rates • adverse effects of treatment • Health-related quality of life.	NA

[NICE: National Institute for Health and Care Excellence; ALK: anaplastic lymphoma kinase, NSCLC: non-small cell lung cancer, NA: not applicable]

B.1.2 Description of the technology being appraised

The technology being appraised is described in Table 2. See Appendix C for details of the summary of product characteristics (SmPC) and European Public Assessment Report (EPAR).

Table 2: Description of the technology

UK approved name and brand name	UK approved name: alectinib Brand name: Alecensa®
Mechanism of action	Alectinib is a small molecule, CNS active, highly selective, and potent oral next generation inhibitor of ALK and RET tyrosine kinase receptors. While binding to the tyrosine kinase domain of ALK, alectinib prevents the binding of ATP and thus autophosphorylation of the ALK receptor, restoring apoptosis and inhibiting tumour cell growth and proliferation. In nonclinical studies, inhibition of ALK tyrosine kinase activity led to blockage of downstream signalling pathways including "signal transducer and activator of transcription 3" (STAT3) and phosphoinositide 3-kinase/AKT and therefore induction of apoptosis.(Sakamoto et al., 2011) Alectinib induced tumour regression in nonclinical mouse xenograft models, including anti-tumour activity in the brain, and prolonged survival in intracranial tumour animal models.(Kodama et al., 2014)
Marketing authorisation/CE mark status	The EC granted a marketing authorisation for alectinib as a monotherapy *"for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib."* on 16/02/2017. A further full submission has been made to the EMA for the indication considered in this appraisal, with a positive CHMP opinion adopted on 12/10/2017. Marketing authorisation anticipated [redacted].
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Current marketing authorisation: "*Alecensa as monotherapy is indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib.*" Anticipated marketing authorisation relevant to this appraisal: "*Alectinib as a monotherapy is indicated for the first line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).*"
Method of administration and dosage	Oral, 600 mg BID (four 150 mg capsules)

Additional tests or investigations	None. Testing for ALK rearrangement and hence sensitivity to ALK inhibitors is a standard part of the diagnostic work up of lung-cancer specimens
List price and average cost of a course of treatment	List price per pack: £5,032.00 Based on the economic model, the median treatment duration is 22.5 months, mean is 30.8 months
Patient access scheme (if applicable)	A simple discount has been submitted to the Department of Health, but has not yet been approved.

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

B.1.3.1 Disease overview

Lung cancer is the third most common cancer in the UK, accounting for 13% of all new cancer cases (n=46,403) in 2014. It is responsible for 22% of all cancer deaths in the UK, making it the most common cause of cancer death. Around 35,900 people died of lung cancer in the UK in 2014. One in 13 men and 1 in 17 women will be diagnosed with lung cancer during their lifetime (Cancer Research UK, 2017a).

Lung cancer is classified based upon its histology and can be broadly divided between small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLC represented 88% of all lung cancer cases in the UK (31,700 cases in England) in 2015 (Royal College of Physicians, 2017) and includes several subtypes, including adenocarcinoma and squamous cell carcinoma. Molecular analysis of NSCLC tumours allows further subdivision of adenocarcinomas. A number of genetic events have been identified as oncogenic drivers in NSCLC, including ALK rearrangements, EGFR mutations, BRAF mutations and ROS1 rearrangements. The identification of these drivers has led to new therapeutic options which are now approved or in early- to late-stage development (Dolly et al., 2017).

Early diagnosis of NSCLC is difficult, as early-stage disease is often asymptomatic, and symptoms of late-stage or advanced disease are non-specific (Hicks et al., 2007). As a result, most lung cancers are diagnosed at an advanced stage, when the cancer has spread to lymph nodes and other organs in the chest (locally advanced disease; stage III) or to other parts of the body (metastatic disease; stage IV). In 2015, approximately 31,700 people were diagnosed with NSCLC in England, of whom 74% had stage III or stage IV disease (Royal College of Physicians, 2017).

Approximately 3-5% of people with advanced NSCLC have ALK fusion genes (Dearden et al., 2013; Dolly et al., 2017; Hallberg and Palmer, 2013), equating to approximately 365 people in England. As ALK-fusion proteins represent an actionable target for therapy lung cancer biopsies are routinely tested for ALK rearrangements during diagnostic work-up. The detection of ALK gene rearrangements is based on FISH and/or IHC assays (Iacono et al., 2015).

The one year survival rate for patients with stage IV NSCLC in the UK was 17% in 2014 (Cancer Research UK, 2017b). The emergence of therapies directly targeting ALK mutations

has improved outcomes in patientes with ALK-positive NSCLC relative to the overall NSCLC population. Real world studies of unselected ALK-positive patients and updated results from the PROFILE 1014 trial have demonstrated median overall survivals ranging from 30.9–51.1 months from time of diagnosis for patients treated with crizotinib, with improved survival for patients treated with a second generation ALK inhibitor such as alectinib or ceritinib (Gainor et al., 2015; Duruisseaux et al., 2017; Watanabe et al., 2016; Mok et al., 2017).

Approximately 40% to 50% of patients with NSCLC develop central nervous system (CNS) metastases during the course of their disease which are associated with poor median survival (4 to 9 months with chemotherapy, 2 months if untreated) (Peters et al., 2016). Brain metastases are common in patients with ALK-positive metastatic NSCLC, with 20-30% of patients presenting with brain metastases at baseline, although higher incidence rates have been reported (Johung et al., 2016; Rangachari et al., 2015; Shaw et al., 2017). The incidence of brain metastases in patients with ALK-positive NSCLC increases to a post-diagnosis cumulative incidence of 58% after 3 years, indicating a higher prevalence of brain metastases compared to the overall NSCLC population (Rangachari et al., 2015).

The symptoms of lung cancer include cough, dyspnea, hemoptysis, and systemic symptoms such as weight loss and anorexia (Latimer KM and Mott TF, 2015). Additionally patients with brain metastases may suffer from headaches, cognitive impairment, ataxia, seizures, and visual and speech problems. In comparison with other metastatic sites patients with brain metastases have been shown to face a significant reduction in health-related quality of life (HRQoL) (Roughley et al., 2014; Peters et al., 2016). Healthcare costs and resource utilisation have also been shown to increase following diagnosis of brain metastases (Peters et al., 2016). The high symptom burden in patients with advanced NSCLC has a highly negative impact on HRQoL, well-being and on family functioning (Nafees et al., 2008; Sarna et al., 2002).

The direct costs associated with the treatment of lung cancer places a considerable burden on healthcare budgets, especially since the diagnosis, treatment and follow-up of lung cancer predominantly occurs within secondary care (Kennedy et al., 2016). Lung cancer is also associated with a significant burden on caregivers, which can include social isolation, psychological impairment and poorer quality of life. A study investigating the consequences of caring for patients with lung cancer in five European countries (including the UK) concluded that caregivers had significantly higher odds of being diagnosed with depression, headache, insomnia and gastrointestinal symptoms, and worse HRQoL, compared with non-caregivers. Moreover, caregivers also shoulder an economic burden with higher annual

indirect costs with presenteeism-related impairment (impairment while working) and overall work impairment (Jassem et al., 2015). A modelling study estimated the mean cost of providing informal care to lung cancer patients at the end of life in England and Wales to be £73m, approximately one third of the total cost of care for this patient group (Round et al., 2015).

Therefore there remains a high unmet need for effective treatments that offer improved efficacy, tolerability and quality of life to patients with ALK-positive NSCLC, which could also potentially ease the considerable burden placed on caregivers.

B.1.3.2 Clinical pathway of care

The information presented below is based on the current NICE guidelines for the diagnosis and management of lung cancer [CG121] (NICE, 2011).

First-line chemotherapy for advanced or metastatic ALK-positive NSCLC

For several years non-specific cytotoxic chemotherapy was the only treatment available for lung cancer that has spread such that local treatment (surgery or radiotherapy) was inappropriate. However, as the biology of lung cancer became understood targeted treatments have emerged enabling the oncogenic products of certain genetic abnormalities to be specifically targeted resulting in highly effective treatments with relatively little off-target toxicity. Actionable mutations include EGFR (in around 15% of caucasian patients), ALK (3–5%), BRAF (around 2%) and ROS 1 (1–2%) (Dolly et al., 2017).

Crizotinib is the current standard of care for first-line treatment of ALK-positive NSCLC. It was recommended for routine use in this indication in NICE TA406.(NICE, 2016c) However, patients treated with crizotinib often develop resistance, with systemic progression generally occurring within one year from start of treatment, with CNS metastases often being the first site of progression (Solomon et al., 2016). Crizotinib is also associated with adverse effects including ocular and GI disturbances, cardiac and endocrine abnormalities, and peripheral oedema.(Dikopf et al., 2015). These events often lead to dose interruptions or require additional management. Therefore, although crizotinib was a step forward compared to the non-specific chemotherapy that went before it, there is a high unmet medical need for treatments that offer improved efficacy, stronger CNS activity, and improved tolerability for patients with ALK-positive NSCLC, as also highlighted in the Early Access to Medicines Public Assessment Report for alectinib (MHRA, 2017).

The proposed positioning of alectinib in the NICE clinical guidance for lung cancer pathway is represented in

Figure 1; based on the anticipated indication, alectinib will provide an alternative and superior treatment option for all patients with previously untreated ALK-positive NSCLC (indicated by dotted box). Clinical experts[1] have informed Roche that, if approved in the first-line setting, alectinib would be the preferred treatment option for ALK-positive NSCLC patients (Roche Products Ltd, 2017).

Second-line chemotherapy for advanced or metastatic ALK-positive NSCLC

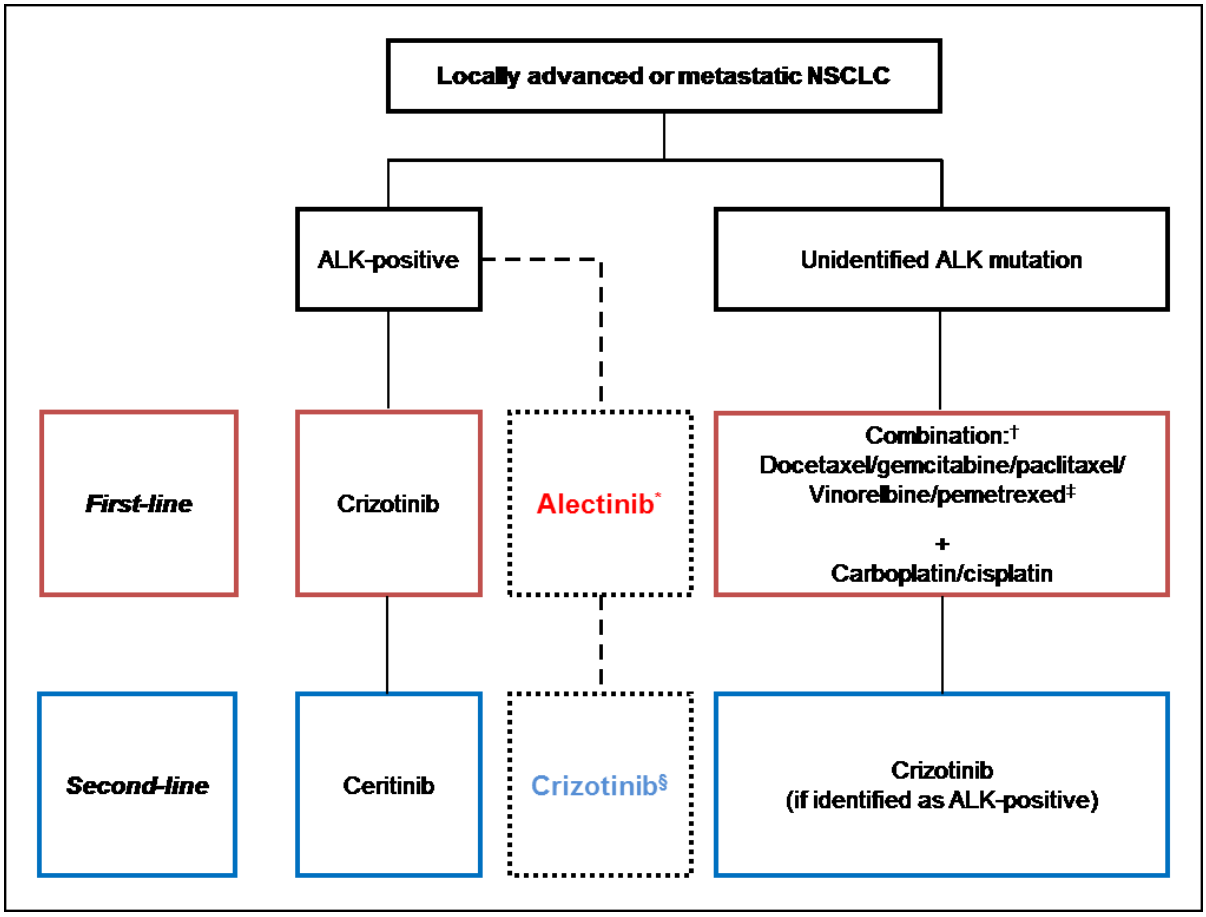
The following treatment options are recommended for use as second-line treatments for patients with ALK-positive NSCLC:

- Crizotinib is recommended by NICE for previously treated adults with ALK-positive NSCLC [TA422] (NICE, 2016b)
- Ceritinib is also recommended as an option for treating advanced ALK-positive non-small cell lung cancer in adults who have previously had crizotinib [TA395] (NICE, 2016a)

Clinical experts have advised Roche that in cases where ceritinib was not suitable, chemotherapy would be considered in clinical practice in the second-line setting (Roche Products Ltd, 2017). A majority of clinicians experienced with ceritinib reported greater toxicity issues (particularly nausea) resulting in dose modifications with ceritinib, in comparison to crizotinib.

[1] [1]An expert advisory board was consulted at a one-day meeting in July 2017. The panel consisted of consultant oncologists specialising in the management of patients with NSCLC. The panel was selected based on their significant clinical and research experience

Figure 1: Advanced or metastatic NSCLC treatment pathway based on NICE guidance CG121



*Dotted box indicates proposed position of alectinib based on anticipated indication, i.e. first-line ALK-positive patients and patients identified as ALK-positive during first-line chemotherapy †If patients cannot tolerate a platinum combination, offer single-agent chemotherapy with a third-generation drug; ‡ Pemetrexed in combination with cisplatin is recommended as an option for the first-line treatment of patients with locally advanced or metastatic NSCLC only if the histology of the tumour has been confirmed as adenocarcinoma or large-cell carcinoma; § Dotted box indicates potential treatment pathway subsequent to alectinib.

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 appraised.

B.2.2 List of relevant clinical effectiveness evidence

Table 3: Clinical effectiveness evidence

Study	NCT02075840 (ALEX), BO28984 (Peters et al., 2017)				
Study design	Randomised, open-label, Phase III study				
Population	• Age ≥18 years old • ECOG PS 0 or 1 • Measurable disease by (RECIST v1.1) • No prior systemic treatment for advanced or recurrent NSCLC or metastatic NSCLC • Adequate haematological and end-organ function • Patients with asymptomatic brain or leptomeningeal metastases were eligible				
Intervention(s)	Alectinib, 600 mg, twice daily				
Comparator(s)	Crizotinib, 250 mg, twice daily				
Indicate if trial supports application for marketing authorisation	Yes	✓	Indicate if trial used in the economic model	Yes	✓
	No			No	
Rationale for use/non-use in the model	ALEX was a registration Phase III trial comparing against crizotinib, the current standard or care, and comparator highlighted in the decision problem				
Reported outcomes specified in the decision problem	• **Overall survival** • **Progression-free survival** • Response rates • **Adverse effects of treatment** • **Health-related quality of life.**				
All other reported outcomes	• Duration of response • Time to CNS progression				

ECOG PS, Eastern Cooperative Oncology Group performance status; NSCLC, non-small cell lung cancer; RECIST, Response Evaluation Criteria in Solid Tumours.

An additional study, J-ALEX (JapicCTI-132316) has also been conducted for alectinib in Japanese patients with crizotinib-naïve NSCLC. This has not been used to populate the economic model due to differences in the patient population and dosing, but has been included in sections 2.2 to 2.6 as supportive evidence of the clinical benefit of alectinib over crizotinib in terms of efficacy and tolerability in the ALK-positive NSCLC patient population (Hida et al., 2017; Takiguchi et al., 2017).

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

Unless otherwise stated, information on the ALEX study was sourced from the primary manuscript and clinical study report (Peters et al., 2017; F. Hoffmann-La Roche Ltd, 2017).

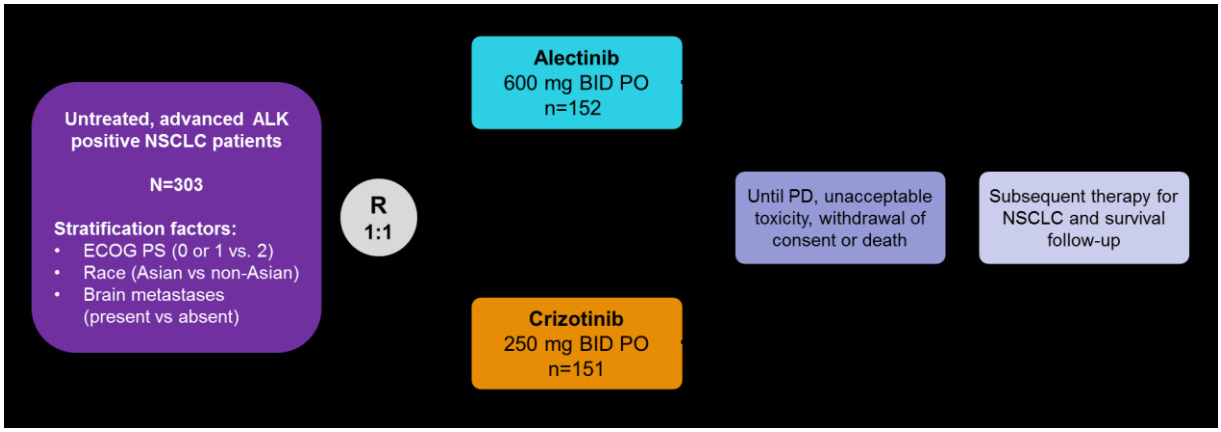
B.2.3.1 Study design

ALEX is a Phase III, open-label, multicentre, randomised study to investigate the efficacy and safety of alectinib compared with crizotinib in patients with previously untreated, advanced ALK-positive NSCLC. The primary data analysis (clinical cut-off 9th February 2017) has taken place (Peters et al., 2017; F. Hoffmann-La Roche Ltd, 2017).

Eligible patients (N=303), were randomly assigned in a 1:1 ratio to receive either alectinib (n=152) or crizotinib (n=151). Assignment was by means of a block-stratified randomisation procedure with the use of an interactive voice or Web-based response system. Patients were stratified by ECOG PS (0 or 1 vs 2), race (Asian vs non-Asian), and CNS metastases at baseline (present vs absent).

The study scheme for ALEX is summarised in Figure 2 below.

Figure 2: ALEX study design scheme schematic



B.2.3.2 Summary of study methodology

Table 4: Summary of study methodology

	ALEX (BO28984, NCT02075840)
Settings and locations of data collection	A total of 303 patients were randomised at 98 study sites in 29 countries. **Countries, number of patients (centres)** • South Korea, 48 (6) • United States, 24 (10) • Italy, 23 (9) • Hong Kong, 19 (5) • Thailand, 19 (5) • Canada, 18 (4) • Russian Federation, 17 (4) • Australia, 16 (5) • Singapore, 14 (2) • Taiwan, 14 (4) • Portugal, 7 (3) • Turkey, 7 (4) • New Zealand, 4 (1) • Israel, 4 (2) • Ukraine, 4 (2) • Costa Rica, 3 (1) • Mexico, 3 (1) • Serbia, 3 (3) • United Kingdom, 3 (3)

	• Poland, 13 (4) • China, 10 (2) • Switzerland, 9 (4) • France, 8 (4) • Spain, 8 (5) • Bosnia and Herzegovina, 1 (1) • Brazil, 1 (1) • Chile,1 (1) • Egypt, 1 (1) • Guatemala, 1 (1)
Trial design	ALEX is a Phase III, open-label, multicentre, randomised study to investigate the efficacy and safety of alectinib compared with crizotinib in patients with previously untreated, advanced *ALK-positive* NSCLC
Eligibility criteria	**Inclusion criteria** • Age ≥18 years old • Histologically or cytologically confirmed diagnosis of advanced or recurrent (Stage IIIB not amenable for multimodality treatment) or metastatic (Stage IV) NSCLC that is ALK-positive as assessed by the Ventana IHC test o Sufficient tumour tissue to perform ALK IHC and ALK FISH required • No prior systemic treatment for advanced or recurrent NSCLC or metastatic NSCLC • Measurable disease as defined by (RECIST v1.1) • ECOG PS 0 or 1 • Life expectancy ≥12 weeks • Prior brain or leptomeningeal metastases allowed if asymptomatic (e.g., diagnosed incidentally at study baseline) o Patients with neurological symptoms must complete whole brain radiation or gamma knife irradiation treatment o Radiation treatment must be completed ≤14 days before enrolment and patients must be clinically stable • Adequate haematologic and end-organ function, defined by the following laboratory results o Platelet count ≥100×10^9/L o ANC ≥1500 cells/μL o Haemoglobin ≥9.0 g/dL o An estimated glomerular filtration rate calculated using the Modification of Diet in Renal Disease equation of ≥45 mL/min/1.73 m^2 • Patients must have recovered from effects of any major surgery or significant traumatic injury ≤28 days before first dose of study medication • For both female patients and male patients, agreement to remain abstinent or use highly effective form(s) of contraception and to continue its use for 3 months after the last dose of study medication o For females of childbearing potential, a negative pregnancy test must be obtained within 3 days before starting study treatment • Able and willing to provide written informed consent and to comply with the study protocol **Key exclusion criteria**

	• Patients with a previous malignancy within the past 3 years (other than curatively treated basal cell carcinoma of the skin, early GI by endoscopic resection, in situ carcinoma of the cervix, or any cured cancer that is considered to have no impact in PFS and OS for the current NSCLC)
	• Any GI disorder that may affect absorption of oral medicines
	• Liver disease characterised by either
	  o ALT or AST >3×ULN (≥5 ULN for patients with confirmed concurrent liver metastasis)
	  o Impaired excretory function, synthetic function or other conditions of decompensated liver disease
	  o Acute hepatitis
	• Patients with baseline QTc >470 ms or symptomatic bradycardia
	• Administration of agents with potential QT interval prolonging effects within 14 days prior to first dose of study medication for all patients and while on treatment through to the end of the study for crizotinib-treated patients only
	• Administration of strong/potent cytochrome P450 (CYP)3A inhibitors or inducers within 14 days prior to first dose of study medication and while on treatment

Trial drugs and concomitant medications	**Trial drugs** Patients were randomised 1:1 to the two treatment arms: Crossover between the treatment arms was not allowed, although patients assigned to crizotinib may have received alectinib or other ALK inhibitors after disease progression in countries where these medications were already approved or available. **Alectinib** • Alectinib (600 mg) was administered orally BID • Selection of the alectinib dose was based on clinical safety, efficacy and pharmacokinetic data observed in the Phase I/II studies and supportive nonclinical data **Crizotinib** • Crizotinib (250 mg) was administered orally BID, consistent with the approved label for ALK-positive NSCLC(Pfizer, 2016) **Concomitant medications** **Permitted concomitant medications** • Anticoagulants and antithrombotic agents (such as coumarin-derived anticoagulants, unfractionated heparin or low-molecular heparins, aspirin [≤325 mg/day], and clopidogrel) • Paracetamol up to 2 g/day • Gastric pH elevating medications (such as proton pump inhibitors, H2 blockers, or antacids) • Local therapy (e.g., stereotactic radiotherapy or surgery) may be given to patients with isolated asymptomatic CNS progression (e.g., new CNS oligometastases)

	Caution was exercised when the following were co-administered with alectinib:
	• Substrates of P-gp transporter or breast cancer resistance protein transporter
	  o Substrates with a narrow therapeutic indices (e.g., methotrexate, digoxin)
	
	Caution was exercised when the following were co-administered with crizotinib:
	• Medications which are predominately metabolised by CYP3A
	  o Dose reductions may be required
	  o CYP3A substrates with narrow therapeutic indices
	• Medications which are predominately metabolised by CYP2B6 (e.g., bupropion, efavirenz)
	• Substrates which are predominately metabolised by pregame X receptor and constitutive androstane receptor-regulated enzymes (e.g., CYP3A4, CYP2B6, CYP2C8, CYP2C9, UGT1A1)
	• Agents known to cause bradycardia (e.g., beta-blockers, non-dihydropyridine calcium channel blockers, clonidine, and digoxin)
	• Substrates of P-gp (e.g., digoxin, dabigatran, colchicine, pravastatin)
	
	• **Prohibited concomitant medications** Potent inducers of CYP3A (e.g., rifampin, rifabutin, phenobarbital, phenytoin, carbamazepine, and St. John's wort) within 2 weeks or 5 half-lives (whichever is longer) before the first dose of study drug treatment and while on treatment with study drugs
	• Potent inhibitors of CYP3A (e.g., ketoconazole) within 2 weeks or 5 half-lives (whichever is longer) before the first dose of study drug treatment and while on treatment with study drug
	• Any concomitant medications known to affect QT interval duration, including but not limited to the following drugs: amiodarone, cisapride, clarithromycin, methadone, and quinidine, within 2 weeks before the first dose of study drug treatment for **all patients** and while on treatment through the end of the study for **crizotinib-treated patients** only
	• Systemic immunosuppressive drugs, cytotoxic or chemotherapeutic agents (other than study drug treatment), ergot derivatives, probenecid, and bile acid-binding resins while on study treatment.
	• Systemic chemotherapy
	• Radiotherapy/radionuclide therapy except for palliative radiotherapy to bone lesions or for pain control
	• Additional investigational drug (except for during the follow-up period)

Primary outcome	**Primary endpoint** • PFS – interval between date of randomisation and date of first documented PD as determined by investigator using RECIST v1.1 or death from any cause

Other outcomes used in the economic model/specified in the scope	**Secondary endpoints**
	• ORR – percentage of patients who attain CR or PR as determined by investigator using RECIST v1.1
	• DOR – interval between first documented response (CR or PR) and first documented PD or death
	• Time to CNS progression – interval between date of randomisation and date of first document PD in the CNS as determined by IRC using RECIST v1.1
	  o C-PR – CNS progression rates at 6, 12, 18 and 24 months on the basis of cumulative incidence
	  o C-ORR – ORR in patients with CNS metastases who have measurable disease in the CNS at baseline
	  o C-DOR – DOR in patients who have a CNS OR
	• PFS – interval between date of randomisation and date of first documented PD as determined by IRC using RECIST v1.1 or death from any cause
	• OS – time from the date of randomisation to the date of death due to any cause
	
	Safety endpoints Safety and tolerability of alectinib compared to crizotinib
	
	Patient-reported outcomes
	Time-to-deterioration of lung cancer symptoms, patient functioning, and HRQoL between treatment arms as measured by the EORTC Quality-of-Life Questionnaire Core 30 (QLQ-C30) and its Lung Cancer Module (LC13)
	
	Key exploratory outcome
	To evaluate and compare patient's health status as assessed by the EuroQoL 5 Dimension (EQ-5D-3L) questionnaire to generate utility scores for use in economic models for reimbursement

Pre-planned subgroups	**Pre-planned subgroup analyses** • PFS for patients with/without baseline CNS metastases • ORR for patients with measurable CNS lesions at baseline with/without prior brain radiation • Time to CNS progression, excluding patients who had pre-treatment radiation therapy for CNS lesions • Sex • Age (<65 vs ≥65 years) • Race (non-Asian vs Asian)

ALK, anaplastic lymphoma kinase; ALT, alanine transaminase; ANC, absolute neutrophil count; AST, aspartate transaminase; C-DOR, CNS duration of response; CNS, central nervous system; C-ORR, CNS objective response rate; C-PR, CNS progression rate; CR, complete response; CYP, cytochrome P450, DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EORTC, European Organisation for Research and Treatment of Cancer; FISH, fluorescence in situ hybridization; GI, gastrointestinal; HRQoL; health-related quality of life IHC, immunohistochemistry; IRC, Independent Review Committee; NSCLC, non-small cell lung cancer; OR, objective response; ORR, objective response rate, OS, overall survival; PD, progressive disease; P-gp, Permeability glycoprotein; PFS, progression-free survival; PR, partial response; QTc,

corrected QT interval; RECIST, Response Evaluation Criteria in Solid Tumours; ULN, upper limit of normal, vs, versus.

B.2.3.3 Patient demographics and baseline characteristics

The crizotinib and the alectinib arms were well balanced in terms of baseline demographic and disease characteristics. The demographic characteristics in both arms were generally consistent with that of an ALK-positive NSCLC population, with a higher proportion of women (58% crizotinib; 55% alectinib) and generally no smoking history (65% crizotinib; 61% alectinib). The majority of patients had baseline ECOG PS 0 or 1, Stage IV disease, and adenocarcinoma histology. There were more non-Asian patients (54% crizotinib; 55% alectinib) compared with Asian patients in both arms. Overall, 38% of patients in the crizotinib arm and 42% of patients in the alectinib arm had CNS metastases at baseline as assessed by the IRC.

Table 5: Patent demographics and baseline characteristics in ALEX (ITT population)

	Alectinib n=152	**Crizotinib n=151**
Mean age, years (SD) Median age, (range)	56.3 (12.0) 58.0 (25–88)	53.8 (13.5) 54.0 (18–91)
Male, n (%)	68 (45)	64 (42)
Race, n (%) Asian Non-Asian	 69 (45) 83 (55)	 69 (46) 82 (54)
ECOG PS, n (%) 0 or 1 2	 142 (93) 10 (7)	 141 (93) 10 (7)
Smoking status, n (%) Active smoker Former smoker Nonsmoker	 12 (8) 48 (32) 92 (61)	 5 (3) 48 (32) 98 (65)
Current stage of disease, n (%) IIIB IV	 4 (3) 148 (97)	 6 (4) 145 (96)
Histologic type, n (%) Adenocarcinoma Undifferentiated or other*	 137 (90) 15 (10)	 142 (94) 9 (6)
Presence of CNS metastases as assessed by IRC, n (%)	64 (42)	58 (38)
Prior brain radiation, n (%)	26 (17)	21 (14)
Treatment for CNS metastases, n (%) Brain surgery Radiosurgery Whole-brain radiotherapy Other†	n=27 1 (4) 5 (19) 17 (63) 4 (15)	n=22 1 (5) 4 (18) 16 (73) 1 (5)

Percentages have been rounded and may not total 100%

*Other includes squamous-cell carcinoma, large-cell carcinoma and mixed with a predominately adenocarcinoma component, † One patient in the crizotinib group and three patients in the alectinib group underwent brain surgery combined with radiotherapy. An additional patient in the alectinib group underwent both radiosurgery and whole-brain radiotherapy.
CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; IRC, independent review committee, SD, standard deviation; eCRF,electronic Case Report Form; EDC, electronic data capture; ePRO, electronic patient-reported outcome, ITT, intention-to-treat; SDF, survival distribution function

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

Unless otherwise stated, information for ALEX is sourced from the protocol and primary manuscript (F. Hoffmann-La Roche Ltd, 2016; Peters et al., 2017). The participant flow for ALEX is presented in Appendix D.

Determination of sample size

The primary endpoint of PFS was used to determine the sample size of the ALEX study, with 286 patients planned to be enrolled in the intention-to-treat (ITT) population. The final enrolment was 303 patients.

Analysis plan

No interim analysis for efficacy or futility was planned.

Secondary endpoints were planned to be tested after statistical significance of the primary endpoint of PFS was demonstrated. Secondary endpoints were analysed with a hierarchical testing strategy in the following sequence

- PFS by IRC
- Time to CNS progression
- ORR
- OS

Analysis populations

Randomised population (ITT)

The primary population for efficacy analyses was the ITT population, defined as all randomised patients

Safety population

The primary population for safety analyses was the Safety Analysis Population (SAP), defined as all patients who received at least one dose of study medication.

Subgroup analysis

- Pre-specified subgroup analyses were PFS in patients with/without baseline CNS metastases, and time to CNS progression, excluding patients who had pre-treatment radiation therapy for CNS lesions
- Pre-specified subgroup analyses in the safety population were sex, age (<65 vs ≥65 years), and race (non-Asian vs Asian)

Primary hypothesis

The primary endpoint of ALEX was duration of PFS. The null and alternative hypotheses for PFS analysis were phrased in terms of the survival distribution functions SDF (alectinib) and SDF (crizotinib):

H_0: SDF (alectinib) = SDF (crizotinib) versus H_1: SDF (alectinib) $\neq$ SDF (crizotinib)

The treatment comparison of PFS was based on a stratified log-rank test at the 5% level of significance (two-sided). The stratification factors were the randomisation stratification factors: ECOG PS (0/1 vs 2), race (Asian vs non-Asian), and CNS metastases at baseline (yes vs no),

The Kaplan-Meier method was used to estimate the median PFS for each treatment arm with 95% confidence limits, and a Kaplan-Meier curve was constructed to provide a visual description of the difference between the treatment arms. A stratified Cox proportional regression model was used including treatment in order to provide an estimate of the treatment effect expressed as an hazard ratio (HR; alectinib vs crizotinib), as well as a 95% confidence interval (CI).

Assumptions

The primary analysis of PFS was planned after 170 events and was carried out after 164 events. The number of PFS events needed to achieve 80% power at a two-sided alpha level of 5% was calculated based on the following assumptions:

- Median PFS in the crizotinib arm is 10.9 months;
- Patients are enrolled over 24 months on the basis of non-linear recruitment;
- Targeted HR of 0.65 for alectinib versus crizotinib.

Handling of missing data and censoring methods

An overview of the analysis (and censoring, if applicable) methods used for the efficacy parameters in ALEX is summarised below.

Table 6: Summary of analysis methods for efficacy parameters

Endpoint	Definition	Censoring	Methodology
PFS per RECIST v1.1*	Interval between date of randomisation and date of first documented PD per RECIST v1.1 or death	Last tumour assessment for those w/o PD and alive or at date of randomisation for those w/o post-BL assessments	Kaplan-Meier methodology, stratified log-rank test, and stratified Cox regression
Time to CNS progression per RECIST v1.1	Interval between date of randomisation and date of first documented CNS progression	Last tumour assessment for those w/o PD and alive or at date of randomisation for those w/o post-BL assessments	Log-rank test, cumulative incidence functions, and Gray's test to compare risk of progression between arms
ORR per RECIST v1.1	Proportion of patients achieving best response of CR or PR per RECIST v1.1	Patients without any post baseline tumour assessments and patients with a best response of SD, PD or NE were considered non responders	Clopper-Pearson methods for 95% CI of response rates and stratified Mantel-Haenszel test for difference in rates
DOR	Interval between first documented objective response (CR or PR) and first documented PD or death	Date of last tumour measurement	Kaplan-Meier methodology and Cox proportional regression model
OS	Time from the date of randomisation to the date of death due to any cause	Date patient last known to be alive or at date of randomisation for those w/o post-BL information	Kaplan-Meier methodology, stratified log-rank test, and stratified Cox regression

*Methodology for secondary endpoint of PFS by IRC is the same as specified for the primary endpoint of investigator assessed PFS
BL, baseline; CNS, central nervous system; CR, complete response; DOR, duration of response; NE, not evaluable; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; ORR, objective response rate; OS, overall survival; SD, stable disease

Summary of statistical analyses

Data management

Data entered manually were collected via electronic data capture (EDC) using electronic case report forms (eCRFs). eCRFs were completed by designated, trained site staff. Study monitors performed source data verification of data entered into eCRFs to ensure data were accurate, complete and verifiable from source documents.

Patients used ePRO devices provided by an ePRO vendor to capture patient-reported outcome (PRO) data. Data were transmitted automatically after entry to a centralised database at the ePRO vendor.

Patient withdrawals

Within the ITT population a total of 68 patients (45%) in the alectinib arm and 105 patients (70%) in the crizotinib arm discontinued treatment. Further information on reasons for discontinuation is detailed in Appendix D.

Table 7: Summary of statistical analyses

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
NCT02075840 BO28984 (ALEX)	For SDF of the parameter PFS: H0: SDF (alectinib) = SDF (crizotinib) versus H1: SDF (alectinib) ≠ SDF (crizotinib)	Stratified log-rank test, Kaplan-Meier method and stratified Cox proportional representation model in the ITT population	Sample size = 286 Targeted HR for PFS = 0.65 170 PFS events required to achieve 80% power at a two-sided alpha level of 5%	Data management: EDC via eCRFs and ePRO devices Treatment discontinuations: Alectinib – 68 (45%) Crizotinib – 105 (70%)

ALK, anaplastic lymphoma kinase; BID, twice-daily; ECOG PS, Eastern Cooperative Oncology Group performance status; NSCLC, non-small cell lung cancer PD, progressive disease; PO, oral; PFS, progression-free survival; R, randomise; vs, versus.

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

Critical appraisal of the included randomised clinical trials (RCTs) 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.

Study question	ALEX (NCT02075840)
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	N/A (open label study)
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	N/A (open label study)
Were there any unexpected imbalances in drop-outs between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes

B.2.6 Clinical effectiveness results of the relevant trials

The data discussed in this section has been taken from the primary analysis (clinical cut-off 9th February 2017), in which a total of 303 patients were randomised; 152 in the alectinib arm and 151 in the crizotinib arm (Peters et al., 2017; Shaw et al., 2017; Gadgeel et al., 2017; F. Hoffmann-La Roche Ltd, 2017).

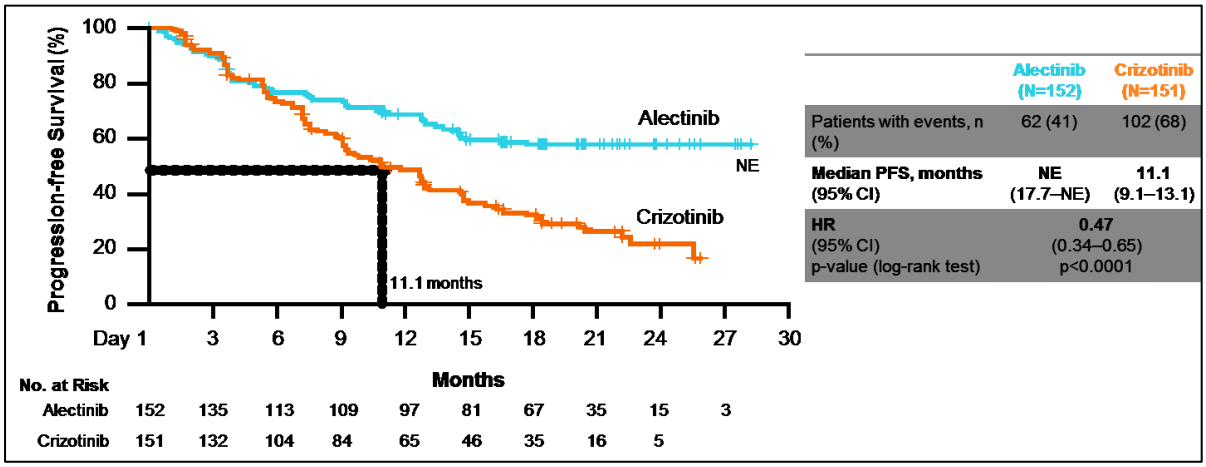
Primary endpoint

Investigator-assessed PFS per RECIST v1.1

The ALEX study met its primary endpoint; treatment with alectinib was associated with a statistically significant and clinically meaningful improvement in investigator-assessed PFS, compared with crizotinib in the ITT population (HR 0.47, 95% CI: 0.34, 0.65; p<0.0001). The median duration of follow-up was 17.6 months in the crizotinib group and 18.6 months in the alectinib group. Median PFS with alectinib was not reached (95% CI: 17.7 months, NE) compared with 11.1 months (95% CI: 9.1, 13.1) with crizotinib (

Figure 3). The initial overlap of the Kaplan-Meier treatment curves reflects the similar response rates of alectinib and crizotinib, before separation after approximately 6 months of follow-up as patients treated with crizotinib begin to relapse. The rate of investigator-assessed 12-month event-free survival was 68.4% (95% CI: 61.0, 75.9) for alectinib compared with 48.7% (95% CI: 40.4, 56.9) for crizotinib.

Figure 3: Kaplan-Meier plot of investigator-assessed PFS, stratified analysis (ITT)



	Alectinib (N=152)	Crizotinib (N=151)
Patients with events, n (%)	62 (41)	102 (68)
Median PFS, months (95% CI)	**NE (17.7–NE)**	**11.1 (9.1–13.1)**
HR (95% CI) p-value (log-rank test)	**0.47 (0.34–0.65) p<0.0001**	

The results of the J-ALEX trial, which studied alectinib in the first-line setting in a Japanese patient population, are supportive of the results for investigator-assessed PFS. After a median follow-up of 12.0 months in the alectinib group and 12.2 months in the crizotinib group PFS was significantly improved with alectinib compared with crizotinib (HR 0·34, 95% CI 0·21, 0·54).

Secondary endpoints

IRC-assessed PFS per RECIST v1.1

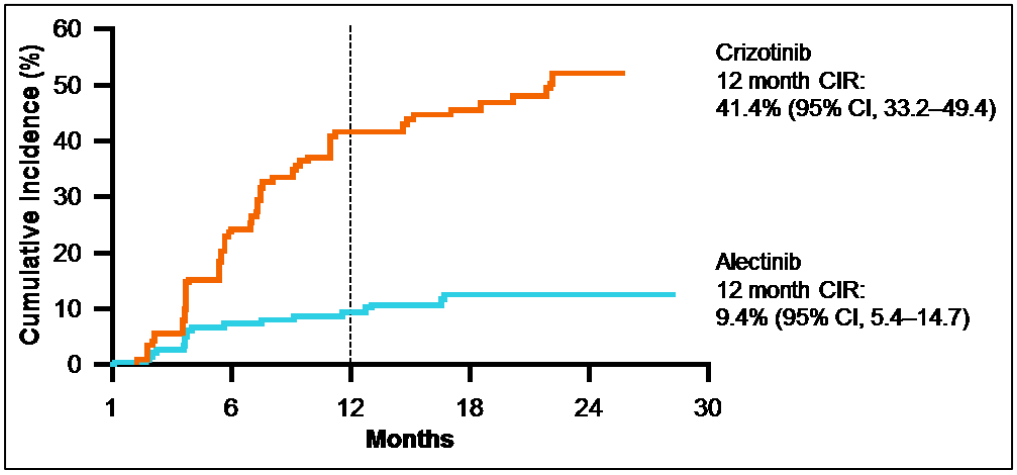
IRC-assessed PFS was also significantly longer with alectinib than with crizotinib; HR 0.50 (95% CI: 0.36, 0.70, p<0.001). Median PFS was 25.7 months with alectinib (95% CI: 19.9, NE) vs 10.4 months with crizotinib (95% CI: 7.7, 14.6). The observation of significant improvement in IRC-assessed PFS with treatment with alectinib compared with crizotinib was consistent with the results of the J-ALEX trial. After a median follow-up duration of 20.5 months in the alectinib arm and 20.4 months in the crizotinib arm the HR for IRC-assessed PFS was 0.38 (95% CI: 0.26, 0.55; p<0.0001). Median PFS with alectinib was 25.9 months (95% CI: 20.3, NE) compared with 10.2 months (95% CI: 8.3, 12.0) with crizotinib (Takiguchi et al., 2017).

IRC-assessed CNS progression per RECIST v1.1

The time to CNS progression was significantly decreased with alectinib compared with crizotinib in the ITT population; (cause specific HR 0.16 [95% CI: 0.10, 0.28, p<0.0001]). Eighteen patients (12%) in the alectinib group and 68 patients (45%) in the crizotinib group had events of CNS progression. The cumulative incidence rate of CNS progression (with adjustment for competing risks of non-CNS progression and death) was consistently lower

with alectinib than with crizotinib, with 12-month cumulative incidence rates of 9.4% (95% CI: 5.4, 14.7) and 41.4% (95% CI: 33.2, 49.4) respectively.

Figure 4: Cumulative incidence of CNS progression (ITT)



ORR per RECIST v1.1

The proportion of patients with a confirmed response per RECIST v1.1 in the ITT population was high and similar in both arms; 82.9% (95% CI: 76.0, 88.5) in the alectinib arm and 75.5% (95% CI: 67.8, 82.1) in the crizotinib arm (Table 8).

Table 8: Summary of ORR

	Alectinib n=152	Crizotinib n=151
Responders, n (%) (95% CI)	126 (82.9) (76.0, 88.5)	114 (75.5) (67.8, 82.1)
Complete response, n (%) (95% CI)	6 (3.9) (1.5, 8.4)	2 (1.3) (0.2, 4.7)
Partial response, n (%) (95% CI)	120 (78.9) (71.6, 85.1)	112 (74.2) (66.4, 80.9)
Stable disease, n (%) (95% CI)	9 (5.9) (2.7, 10.9)	24 (15.9) (10.5, 22.7)
Progressive disease, n (%) (95% CI)	8 (5.3) (2.3, 10.1)	10 (6.6) (3.2, 11.8)

CI, confidence interval

CNS response rates were higher in the alectinib group than in the crizotinib group in the subgroup of patients with CNS lesions at baseline, with more patients in the alectinib arm achieving a CNS complete response (CR) compared with crizotinib (see Appendix E for further details). The improved response rate applied to both patients with and without prior brain radiation.

Duration of response

The median duration of response (DOR) among responders was longer with alectinib than crizotinib (HR 0.36 95% CI: 0.24, 0.53). Median DOR was 11.1 months (95% CI: 7.9, 13.0) in the crizotinib group and not estimable in the alectinib group. Median DOR was also extended with alectinib compared to the crizotinib group in patients with brain metastases at baseline (Table 9).

Table 9: Summary of DOR

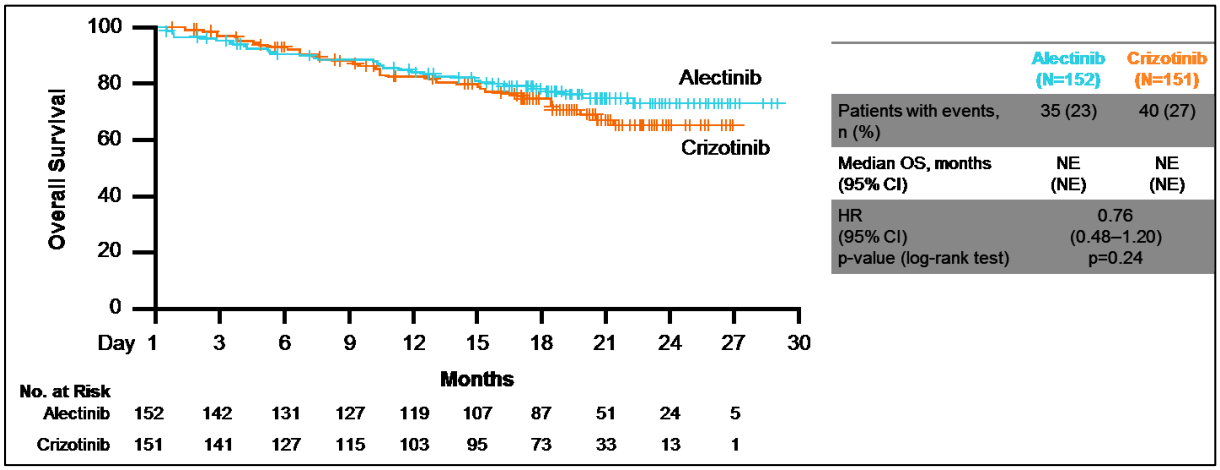
	Alectinib n=152	**Crizotinib n=151**
All responders		
Median DOR, (months) (95% CI)	NE (NE)	11.1 (7.9, 13.0)
Responders with measurable CNS lesions at baseline		
Number of patients	21	22
Median DOR, (months) (95% CI)	17.3 (14.8, NE)	5.5 (2.1, 17.3)
Responders with measurable or nonmeasurable CNS lesions at baseline		
Number of patients	64	58
Median DOR, (months) (95% CI)	NE (17.3, NE)	3.7 (3.2, 6.8)

CI, confidence interval; CNS, central nervous system; DOR, duration of response; NE, not estimable.

Overall survival

On the basis of sample size the trial the ALEX trial was not powered to detect a significant difference in OS. At the time of primary analysis (median duration of follow-up: 18.6 months [range, 0.5–29.0] in the alectinib group and 17.6 months [range, 0.3–27.0] in the crizotinib group) the median overall survival was not estimable in either treatment group, with a trend towards improved survival with alectinib (HR=0.76, 95% CI: 0.48, 1.20). The 12-month survival rates were similar in both treatment arms; 84.3% (95% CI, 78.4, 90.2) with alectinib and 82.5% (95% CI: 76.1, 88.9) with crizotinib, though with clear signs of a separation in the survival curves starting to emerge and favouring alectinib.

Figure 5: Kaplan-Meier plot of OS, stratified analysis (ITT)



	Alectinib (N=152)	Crizotinib (N=151)
Patients with events, n (%)	35 (23)	40 (27)
Median OS, months (95% CI)	NE (NE)	NE (NE)
HR (95% CI) p-value (log-rank test)	0.76 (0.48–1.20) p=0.24	

Patient-reported outcomes: EORTC QLQ-C30, EORTC QLQ-LC13 and EQ-5D-3L

Questionnaire compliance rates

Baseline compliance for both treatment arms was [redacted] in the ITT Population with [redacted] alectinib-treated patients and [redacted] crizotinib-treated patients completing their baseline assessment. Among patients who had patient-reported outcome (PRO) baseline data, [redacted] were observed in the alectinib-treated arm. Compliance rates in the crizotinib arm [redacted] in the alectinib arm, [redacted]. The last PRO assessment completed, where there was [redacted] of the PRO-evaluable Population remaining in each arm, was [redacted] of PFS in the alectinib arm.

Disease burden/morbidity

Patients' perspectives regarding the severity of disease symptoms commonly associated with lung cancer including cough, dyspnea, chest pain, arm/shoulder pain, pain in other parts, hemoptysis and fatigue were captured through data collected in the EORTC questionnaires.

[redacted] treatment arms was observed in the time to confirmed patient-reported clinically meaningful deterioration in the composite symptom endpoint of cough, chest pain, dyspnoea (LC13 multi-item scale), with [redacted] reporting a confirmed deterioration in the composite endpoint.

[redacted]

Treatment burden/tolerability

Patient-reported outcome data, collected via the EORTC questionnaire, [redacted] as compared with crizotinib. Clinically meaningful improvement in [redacted] was observed for both treatment arms.

HRQoL

Time to confirmed patient-reported clinically meaningful deterioration in Global Health Status/HRQoL, was [redacted]. On average, patients in the [redacted].

In the pre-specified subgroup of patients with CNS metastases at baseline, a lower proportion [redacted] Furthermore, fewer [redacted]. Within the PRO-evaluable population, [redacted]

EQ-5D-3L

Results from the EuroQoL 5 Dimension (EQ-5D-3L) patient reported outcome questionnaire are discussed in Section B.3.

B.2.7 Subgroup analysis

Pre-planned subgroup analyses were carried out by age (<65 vs ≥65 years old), sex, race (Asian vs non-Asian), smoking status, ECOG PS (0 or 1 vs 2), presence of CNS metastases at baseline and patients with pre-treatment radiation therapy for CNS lesions. Efficacy results from the subgroup analyses of patients with CNS metastases have been published (Gadgeel et al., 2017).

The improvement in investigator assessed PFS with alectinib compared with crizotinib was generally consistent across pre-planned subgroups. There was no significant difference between the treatment arms in the subgroups of active smokers and patients with an ECOG PS of 2, although numbers of patients in these subgroups was small. For more detail please see Appendix E.

In patients with CNS metastases at baseline (N=122) investigator-assessed PFS was significantly improved with alectinib compared with crizotinib; HR 0.40 (95% CI: 0.25, 0.64, p <0.0001). A significant improvement in PFS was also observed with alectinib over crizotinib in patients without CNS metastases at baseline (N=181); HR 0.51 (95% CI: 0.33, 0.80, p=0.0024). See Appendix E for further details.

B.2.8 Meta-analysis

The evidence source for alectinib in untreated metastatic ALK-positive NSCLC is made up of one clinical trial: the phase III study, ALEX, which compared alectinib to the current standard of care, crizotinib. Therefore a meta-analysis was not considered necessary.

B.2.9 Indirect and mixed treatment comparisons

The evidence source for alectinib in untreated metastatic ALK-positive NSCLC is a single, randomised, open-label, phase 3 trial (BO28984 (ALEX)), which compared alectinib (600 mg twice daily) to crizotinib (250 mg twice daily). Crizotinib is currently the only treatment recommended by NICE for untreated ALK-positive advanced non-small cell lung cancer (TA 406). The recommendation from NICE in September 2016 has resulted in ALK testing becoming ingrained in clinical practice, and upon confirmation of positive ALK mutation in a patient, the only treatment actively used is crizotinib. This is consistent with the final scope issued for this appraisal. Given ALEX provides direct clinical evidence of alectinib versus the current standard of care for patients with a confirmed positive ALK mutation, an indirect or mixed treatment comparison was not considered necessary.

B.2.10 Adverse reactions

The safety population in the ALEX study included all randomised patients who received at least one dose of study drug. This population comprised all patients in the ITT population (n=152 in the alectinib arm and n=151 in the crizotinib arm). An overview of the safety profile of alectinib compared with crizotinib in ALEX is presented in Table 10. The median duration of treatment was longer with alectinib, as compared to crizotinib (17.9 months vs 10.7 months). This substantial difference made it considerably more likely that adverse events would be reported by patients on alectinib. The mean dose intensity was similar in both treatment arms; 95.8% with alectinib and 92.4% with crizotinib (Peters et al., 2017; F. Hoffmann-La Roche Ltd, 2017).

Table 10: Overview of the safety profile of alectinib compared with crizotinib

	Alectinib n=152	**Crizotinib n=151**
Median treatment duration, months (range)	17.9 (0–29)	10.7 (0–27)
Patients with ≥1 AE, n (%)	147 (97)	146 (97)
Serious AEs, n (%)	43 (28)	44 (29)
Grade 3–5 AEs, n (%)	63 (41)	76 (50)
Fatal AEs, n (%)	5 (3)	7 (5)
AEs leading to treatment discontinuation, n (%)	17 (11)	19 (13)
AEs leading to dose reduction, n (%)	24 (16)	31 (21)
AEs leading to dose interruption, n (%)	29 (19)	38 (25)
Mean dose intensity, % (SD)	96 (10.3)	92.4 (14.1)

AE, adverse event; SD, standard deviation.

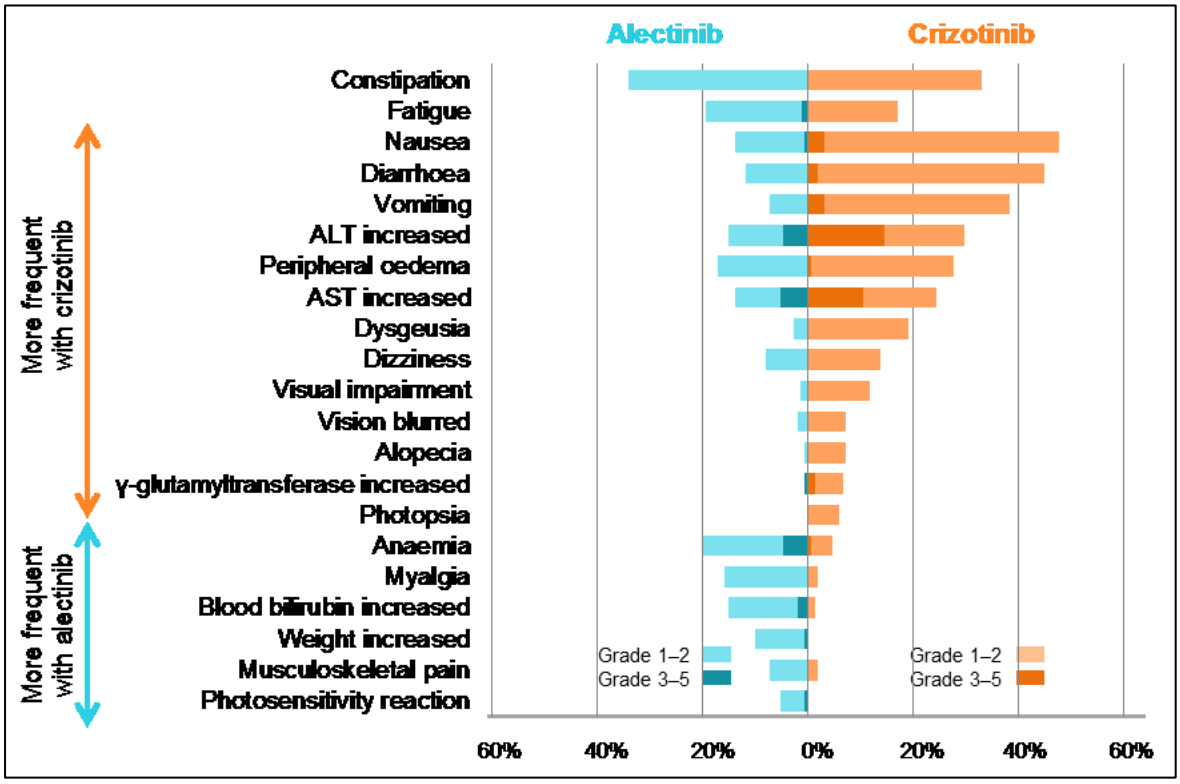
All grade adverse events

The majority of patients (97%) in each arm reported at least one AE (any grade). AEs reported by at least 10% of patients in either treatment arm or with a difference of at least 5% between treatment arms are shown below (Figure 6).

Adverse events that occurred at a higher incidence with alectinib than with crizotinib by 5 percentage points or more were anaemia (20% vs 5% with alectinib), myalgia (16% vs 2%), increased blood bilirubin (15% vs 1%), increased weight (10% vs 0%), musculoskeletal pain (7% vs 2%) and photosensitivity reaction (5% vs 0%). Increased weight was identified as a new adverse drug reaction (ADR) for alectinib, a further assessment of all 15 patients with increased weight identified no evidence of an association between weight increase and oedema. Adverse events that were more common with crizotinib included nausea (48% vs 14% with alectinib), diarrhoea (45% vs 12%), vomiting (38% vs 7%), peripheral oedema

(28% vs 17%), dysgeusia (19% vs 3%), dizziness (14% vs 8%), alopecia (7% vs 1%) elevated liver enzymes, and eye disorder AEs.

Figure 6: All cause adverse events, any grade (reported in ≥10% of patients or ≥5% difference between arms)



ALT, alanine transaminase; AST, aspartate transaminase.

Treatment-related adverse events

Overall, 77% in the alectinib arm, and 89% of patients in the crizotinib arm experienced at least one AE considered related to treatment, despite the considerably longer time on treatment for alectinib patients.

The most common (≥20% of patients in either arm) treatment-related AEs were nausea (7% alectinib vs 42% crizotinib), constipation (26% vs 21%), diarrhoea (6% vs 38%), vomiting (3% vs 29%), increased ALT (13% vs 29%), increased AST (14% vs 22%) and peripheral oedema (9% vs 23%).

Grade 3-5 treatment-related AEs occurring in ≥3% (rounding to one decimal place) of patients in either arm included increased ALT (4% alectinib vs 14% crizotinib), increased AST (5% vs 9%), neutropenia (0% vs 3%) and QT interval prolongation (0% vs 3%).

Serious adverse events

A similar proportion of patients in both treatment arms reported serious adverse events (SAEs); 28% alectinib and 29% crizotinib. SAEs occurring in ≥2% in either treatment arm are reported in Table 11.

Table 11: Serious adverse events reported in ≥2% of patients in either arm

n, (%)	Alectinib n=152	Crizotinib n=151
Patients with an SAE	43 (28)	44 (29)
Pneumonia	5 (3)	4 (3)
Lung infection	3 (2)	0 (0)
Pneumonitis	2 (1)	4 (3)
Pulmonary embolism	2 (1)	3 (2)
Pyrexia	1 (1)	3 (2)
ALT increased	1 (1)	4 (3)
Acute kidney injury	4 (3)	0 (0)
Nausea	0 (0)	3 (2)

ALT, alanine transaminase; SAE, serious adverse event.

SAEs reported in a higher proportion of patients in the alectinib arm than in the crizotinib arm (≥2% difference between treatment arms) were lung infection (2% vs 0%) and acute kidney injury (3% vs 0%). All cases of lung infection were considered to be unrelated to the study treatment. 3/4 of the cases of acute kidney injury were judged to be related to treatment with alectinib. All three of these cases were resolved; alectinib treatment was discontinued in two cases and interrupted in one case, with no further event related to kidney injury reported after resumption of alectinib. SAEs occurring in a higher proportion of patients in the crizotinib arm were pneumonitis (3% vs 1% with alectinib), increased ALT (3% vs 1%) and nausea (2% vs 0%).

Adverse events of special interest

Selected adverse events

Selected adverse events of special interest are summarised in Table 12.

Table 12: Selected adverse events of special interest

n, (%)	Alectinib n=152				Crizotinib n=151			
	All grade	Grade 3–5	Serious	Leading to treatment discontinuation	All grade	Grade 3–5	Serious	Leading to treatment discontinuation
Patients with at least one AE	127 (83.6)	35 (23.0)	15 (9.9)	13 (8.6)	142 (94.0)	53 (35.1)	15 (9.9)	15 (9.9)
Gastrointestinal tract AEs	84 (55.3)	2 (1.3)	0	0	120 (79.5)	10 (6.6)	5 (3.3)	0
Muscular AEs, CPK elevations	58 (38.2)	5 (3.3)	1 (0.7)	0	46 (30.5)	3 (2.0)	0	0
Hepatocellular or cholestatic damage AEs and abnormal liver function tests	48 (31.6)	17 (11.2)	3 (2.0)	7 (4.6)	50 (33.1)	26 (17.2)	4 (2.6)	9 (6.0)
Skin disorders	41 (27.0)	2 (1.3)	1 (0.7)	0	38 (25.2)	0	0	0
Vision disorders	12 (7.9)	0	0	0	50 (33.1)	0	1 (0.7)	0
Hematologic abnormalities	36 (23.7)	8 (5.3)	2 (1.3)	1 (0.7)	25 (16.6)	9 (6.0)	0	0
Abnormal kidney function AEs	28 (18.4)	7 (4.6)	7 (4.6)	4 (2.6)	13 (8.6)	2 (1.3)	1 (0.7)	0
Interstitial lung disease	3 (2.0)	0	2 (1.3)	1 (0.7)	9 (6.0)	3 (2.0)	5 (3.3)	5 (3.3)
QT interval prolongation	0	0	0	0	7 (4.6)	5 (3.3)	0	1 (0.7)

AE, adverse event; CPK, creatine phosphokinase.

Hy's law cases

One patient in the alectinib arm experienced Grade 4 hepatoxicity; this was considered treatment-related and led to treatment discontinuation.

Two patients in the crizotinib arm experienced Grade 4 drug-induced liver injury, both events were considered treatment-related. Treatment was permanently discontinued in one patient, due to the event, the other patient had discontinued treatment due to Grade 4 elevated ALT prior to the diagnosis of drug-induced liver injury

Fatal adverse events

A total of 35 (23%) patients in the alectinib arm and 40 (27%) patients in the crizotinib arm died; the majority (29 [19%] and 31 [21%] of patients, respectively) died due to disease progression.

The incidence of Grade 5 AEs was 3% (5 patients) in the alectinib arm, and 5% (7 patients) in the crizotinib arm. No individual AE was reported as Grade 5 in more than one patient.

Two Grade 5 AEs, pneumonitis and cardiac arrest, which both occurred in patients in the crizotinib arm, were considered related to treatment by the investigator, vs none in the alectinib arm.

Overview of the safety profile

The safety data from ALEX are consistent with the known safety profile of alectinib, (Ou et al., 2016; Shaw et al., 2016; Hida et al., 2017). No additional ADRs reported in other studies but not in ALEX were identified (see Appendix F). Alectinib was well tolerated, with a favourable safety profile compared with crizotinib. Specifically, alectinib treated patients had fewer Grade 3–5 AEs than crizotinib treated patients (41% vs 50% with crizotinib). In addition lower rates of AEs leading to dose reduction and interruption (30% vs 37%), or discontinuation (11% vs 13%) were observed in the alectinib arm despite the longer duration of treatment compared with the crizotinib arm (17.9 months vs 10.7 months).

B.2.11 Ongoing studies

The ALEX study is currently ongoing. [redacted]

A Phase Ib study of alectinib in combination with the PD-L1 inhibitor atezolizumab in patients with treatment-naïve ALK-positive NSCLC is currently ongoing (ClinicalTrials.gov NCT02013219, 2017). Alectinib is also being investigated in combination with bevacizumab in a Phase I/II study of patients with ALK-positive NSCLC with untreated or progressive CNS metastases (ClinicalTrials.gov NCT02521051, 2017) and in combination with cobimetinib in patients who have undergone disease progression on alectinib (ClinicalTrials.gov NCT03202940, 2017).

B.2.12 Innovation

There is an unmet medical need for the development of new therapies for NSCLC. Crizotinib is the current standard of care for first-line ALK-positive NSCLC. Although substantial benefit has been observed with crizotinib therapy, relapse remains the norm with 69% of patients progressing within 18 months (Solomon et al., 2014). Ceritinib, a second-generation oral ALK inhibitor previously approved for patients who had failed crizotinib treatment, has recently had received marketing authorisation in the EU for the first-line treatment of adult patients with ALK-positive NSCLC. Ceritinib has not yet been assessed by NICE in the first-line setting. Crizotinib and ceritinib are also associated with toxicities such as GI disturbances and liver enzyme elevations (Solomon et al., 2014; Soria et al.).

The CNS is a common site of initial progression in ALK-positive NSCLC patients treated with crizotinib (Solomon et al., 2016; Weickhardt et al., 2012); therefore, CNS-active treatments for ALK-positive NSCLC are important targets for development.

Alectinib has lipophilic properties contributing to a good penetration through the blood-brain barrier. This high level of CNS diffusion is reinforced by the fact that based on non-clinical data, alectinib is not a P-gp nor breast cancer resistance protein substrate, in contradistinction to crizotinib or ceritinib (Avrillon and Perol, 2017; Kodama et al., 2014). Alectinib induced tumour regression in nonclinical mouse xenograft models, including anti-tumour activity in the brain, and prolonged survival in intracranial tumour animal models (Kodama et al., 2014).

Clinical data from the ALEX study indicate that alectinib is superior to the standard of care (crizotinib) in substantially delaying disease progression, with a marked delay in the spread of disease to the CNS. Alectinib was also shown to be well tolerated, with a favourable safety profile compared with crizotinib.

Alectinib has been granted a Promising Innovative Medicine (PIM) designation by the Medicines and Healthcare Products Regulatory Agency (MHRA), indicating that alectinib has the potential to address unmet clinical need for patients with a life-threatening condition. An Early Access to Medicines Scheme (EAMS) was approved by the MHRA in September 2017. This indicates that the MHRA believe that alectinib represents a significant advance over other approved ALK inhibitors and fills a significant clinical need for treatments that offer improved protection from relapse, greater central nervous system (CNS) activity and improved tolerability for patients (MHRA, 2017).

Roche also believes that alectinib addresses the significant unmet need for this patient population and represents a clinically significant innovative therapeutic option for the treatment of patients, particularly in the prevention of CNS progression, which will provide significant positive impact on patients' and carers' lives.

B.2.13 Interpretation of clinical effectiveness and safety evidence

Analysis of the primary and key secondary endpoints of the ALEX study showed that alectinib was significantly superior to the current standard of care, crizotinib, in the treatment of treatment naïve patients with advanced, recurrent or metastatic ALK-positive NSCLC

Summary of clinical efficacy

These results of the ALEX study confirm that alectinib substantially slows disease progression compared with crizotinib. The study met its primary endpoint of investigator-assessed PFS; alectinib was associated with a 53% lower risk of disease progression or death compared with crizotinib, HR 0.47 (95% CI: 0.34, 0.65; p<0.0001). The key secondary endpoints of IRC-assessed PFS and time to CNS progression were significantly superior in patients in the alectinib arm compared with the crizotinib arm. Overall, ORR was high (>75%) in both treatment arms; although DOR was considerably longer in the alectinib arm, and median DOR had not been reached at data cut-off.

The time to CNS progression was significantly decreased with alectinib compared with crizotinib in the ITT population with an 84% lower risk of disease progression based upon CNS-RECIST criteria compared with crizotinib. The 1-year risk of CNS progression and cumulative CNS progression over time were also significantly lower in the alectinib arm than in the crizotinib arm. Taken together this demonstrates that alectinib reduces the number of patients with new or progressive CNS metastases compared with crizotinib.

The efficacy of alectinib in patients with CNS metastases at baseline was also superior to crizotinib. In patients with CNS metastases at baseline, there was a significant improvement in CNS ORR, and CNS DOR was also significantly longer in patients in the alectinib arm. In the context of a treatment that substantially improves time without progression of disease and worsening of symptoms with a more favourable tolerability profile for all patients, CNS activity and protection is particularly valued as the presence of CNS metastases has a significant impact on patients' quality of life.

Median OS was not estimable at the time of data cut-off for this primary analysis: 35 patients in the alectinib arm and 40 patients in the crizotinib arm had died at the time of analysis (HR 0.76) Long-term OS follow-up including the nature and duration of subsequent therapies is ongoing. However, it is a testament to the remarkable efficacy of ALK-directed therapies in general that patients with what was once considered a particularly aggressive form of lung cancer can now typically look forward to several years of living with their disease well-controlled. This has already been achieved with the first-generation drug crizotinib and it remains to be seen the exact extent to which alectinib is even more effective in this regard.

Patients in both treatment arms reported clinically meaningful improvements in several lung cancer symptoms over the course of treatment, with patients in the alectinib arm typically reporting clinically meaningful improvements for a longer period of time. Time to deterioration of symptoms was generally similar in both treatment arms, which is expected as both crizotinib and alectinib produce high levels of tumour shrinkage that is associated with arrest of symptomatic deterioration. However, a trend towards greater benefit was seen with alectinib that is expected to increase as crizotinib patients become treatment-resistant. Furthermore, quality of life improvements with alectinib treatment are likely to be under estimated as patients with debilitating conditions, such as brain metastases, are less likely to be represented due to being unable to respond to questionnaires (Leung et al., 2011). This is reflected by lower compliance rates in the crizotinib arm compared with the alectinib arm. Patient-reported outcome data suggest greater tolerability with alectinib for commonly reported treatment-related symptoms as compared with crizotinib, and are consistent with its safety profile.

Summary of safety

Safety assessment showed that alectinib was generally better tolerated than crizotinib despite a longer duration of treatment received by patients in the alectinib arm (median duration 17.9 months alectinib vs 10.7 months crizotinib). The majority of patients in both

arms experienced at least one AE. A smaller proportion of patients in the alectinib arm experienced treatment-related AEs (77% vs 89%), Grade 3–5 AEs (41% vs 50%), and AEs that led to treatment discontinuation (11% vs 13%), dose interruption (19% vs 25%) or dose reduction (16% vs 21%) compared with the crizotinib arm.

Strengths and limitations of clinical evidence

Alectinib was compared against the current standard of care for patients with ALK-positive NSCLC: crizotinib. The median PFS achieved with crizotinib in ALEX (11.1 months) was consistent with that observed in previous trials (10.9 months in PROFILE 1014, and 11.1 months in PROFILE 1029). Furthermore, the PFS results for both arms were aligned with those from the J-ALEX clinical trial in Japanese patients with ALK-positive NSCLC (Hida et al., 2017; Takiguchi et al., 2017).

An additional strength of the trial is that the method of analysis of CNS endpoints takes into account the competing risks inherent in evaluating CNS progression and was based on assessment by the IRC that was conducted solely for the purpose of assessing CNS disease. It should be noted that the rate of CNS metastases at baseline in ALEX appears higher (38–42%) than in other trials such as PROFILE 1014 (26–27%) and ASCEND-4 (31–33%) (Solomon et al., 2014; Soria et al.), thus arguably, the patient population could be considered of a poorer prognosis than has been captured in other trials.

One limitation of the evidence is that OS data were immature at the time of the primary analysis. Long-term OS follow-up including the nature and duration of subsequent therapies is ongoing. Although crossover from the alectinib arm to crizotinib was not allowed subsequent treatment of patients in either arm may potentially confound OS data.

Overall, the study demonstrated the superiority of alectinib over crizotinib and confirmed a favourable benefit-risk profile for alectinib in patients with treatment-naïve advanced, recurrent or metastatic ALK-positive NSCLC, and showed improved CNS activity in particular preventing or delaying CNS progression.

End-of-life criteria

Alectinib does not meet the end-of-life criteria.

Table 13 End-of-life criteria

Criterion	Data available	Reference in submission (section and page number)
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Real world studies of unselected ALK-positive patients have demonstrated median overall survivals ranging from 30.9–51.1 months from time of diagnosis. Clinical experts have advised Roche that they expect a four year overall survival may be obtainable with the current standard of care.	Section B.1.3.1, page 10
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	OS data is not mature and is likely confounded by subsequent treatment, based on OS extrapolation it is anticipated that alectinib will have >3 months overall survival benefit.	Section B.3.3.2, page 59

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

A SLR was conducted to identify cost effectiveness evidence in the first-line treatment of patients with ALK-positive NSCLC. An overview of the identified studies is available below (Table 14). Alternatively, detailed descriptions of the search strategy and extraction methods are provided in Appendix G.

Summary of identified studies and results

A total of six studies considered previously untreated NSCLC patients in their analyses. With the exception of Djalalov et al. 2014, which included patients with ALK-negative or unknown statuses, all other evaluations included only patients who were ALK-positive.

Table 14: Summary list of published cost-effectiveness studies

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Gay-Molina (Gay-Molina et al., 2012)	2012	State transition model (Markov)	Advanced or metastatic ALK+ NSCLC	NA		ICER/LYG vs GEM + cisplatin: • Pemetrexed + cisplatin: $56,775.9 • Docetaxel + cisplatin: dominated • Crizotinib: $42,105.6
Djalalov (Djalalov et al., 2014)	2014	Decision tree with state transition model (Markov)	Advanced non-squamous NSCLC	• Crizotinib: 0.5668 (0.453 - 0.680) • Platinum doublet (cisplatin and gemcitabine) during treatment: 0.5353 (0.428 - 0.642) • Platinum doublet (cisplatin and gemcitabine) after treatment: 0.6166 (0.493 - 0.740) • Pemetrexed during treatment: 0.4537 (0.363 - 0.544) • Pemetrexed after treatment: 0.5704 (0.456 - 0.684) • Erlotinib: 0.4798 (0.384 - 0.576)	CAD • IHC test: $40 ($28 - $52) • FISH test: $388 ($272 - $504) • Rebiopsy: $712 ($498 - $926) • Crizotinib: $7,000 ($4,900 - $9,100) • Platinum doublet (cisplatin and GEM): $1,527 ($1,069 - $1,985) • Pemetrexed: $5,900 ($4,130 - $7,670) • Erlotinib: $2,229 ($1,560 - $2,898) • BSC: $582 ($407 - $757)	Advanced NSCLC patients, EML4-ALK fusion testing vs standard care: • ICER/QALY: $255,970 • ICER/LYG: $160,583 EML4-ALK+ patients, first-line crizotinib vs standard care: • ICER/QALY: $250,632 • ICER/LYG: $148,011

pCODR crizotinib submission 2012/ resubmission 2015 (pCODR, 2012; pCODR, 2015)	2012/2015	State transition model (assumed based on information available)	Locally advanced or metastatic ALK+ NSCLC	NR	CAD Drug costs/day: • Crizotinib: $293.33 • Pemetrexed: $173.64 • Cisplatin: $35.57 • Carboplatin: $2.38	ICER/QALY, crizotinib vs standard therapy: $153,597 ICER/LYG, crizotinib vs standard therapy: $224,872

Lu (Lu et al., 2016)	2016	State transition model (Markov)	Advanced (stage IIIB or IV) ALK+ NSCLC	• PFS: 0.65 (0.26-0.87) • Progressed survival: 0.47 (0.19-0.58)	USD Drug costs: • Pemetrexed per 500 mg: $2,083.97 • Traditional chemotherapy per cycle other than pemetrexed: $518.40 • Crizotinib per day: $238.10 Other costs: • Follow-up per unit: $55.60 • Salvage chemotherapy per cycle: $2,352.70 • Palliative care in end-of-life: $2,042.91 • Supportive care per cycle: $337.50 • Serious AEs in initial chemotherapy per cycle: $507.40 • Ventana IHC ALK rearrangement testing: $31.75 • IHC ALK rearrangement testing: $15.87 • qRT-PCR ALK rearrangement testing: $396.83 • FISH ALK rearrangement testing: $476.19	ICER/QALY, with patient assistance program: • Crizotinib/Ventana IHC vs control: $16,820 • Crizotinib/IHC plus FISH confirmation vs control: $16,850 • Crizotinib/qRT-PCR vs control: $24,424 ICER/QALY, without patient assistance program: • Crizotinib/Ventana IHC vs control: $223,242 • Crizotinib/IHC plus FISH confirmation vs control: $223,271 • Crizotinib/qRT-PCR vs control: $254,668

NICE TA406 (NICE, 2016c)	2016	State transition model (semi-Markov)	Locally advanced or metastatic ALK+ NSCLC	Utilities: • PF, crizotinib: redacted • PF, pemetrexed + platinum: redacted • Treatment beyond progression with crizotinib: redacted • PD, docetaxel: 0.66 • PD, BSC: 0.47 Disutilities associated with AEs: • Elevated transaminases: 0.00 • Neutropenia: 0.09 • Anaemia: 0.07 • Leukopenia: 0.09 • Thrombocytopenia: 0.09	GBP Drug costs/cycle: • Crizotinib: £4,689.00 • Pemetrexed: £1,440.00 (with wastage) • Cisplatin: £47.00 (with wastage) • Carboplatin: £34.18 (with wastage) Other costs: • AEs (one-off cost, chemotherapy arm only): £163.20 • FISH test: £120 per test	ICER/QALY, pemetrexed plus platinum chemotherapy vs crizotinib: £47,291 with PAS
SMC 1152/16 (SMC, 2016)	2016	State transition model (Markov)	Advanced ALK+ NSCLC	• PF, crizotinib: 0.81 • PF, pemetrexed + platinum: 0.72 • PD, docetaxel: 0.66 • PD, BSC: 0.47	NR	ICER/QALY, crizotinib vs pemetrexed plus cisplatin/ carboplatin: £48,355

AE, adverse event; ALK+, anaplastic lymphoma kinase positive; BSC, best supportive care; FISH, fluorescence in situ hybridization; ICER, incremental cost-effectiveness ratio; IHC; immunohistochemistry; LYG, life years gained; NR, not recorded; PAS, patient access scheme; PCR, polymerase chain reaction; PD, progressive disease; PF, progression-free; QALYs, quality-adjusted life years.

B.3.2 Economic analysis

The cost-effectiveness studies identified in section B.3.1 were utilized to inform the model structure of the economic analysis. However, as none of the identified literature appraised alectinib for the first-line treatment of adult patients with ALK-positive NSCLC, a de novo economic model was built to inform decision making.

B.3.2.1 Patient population

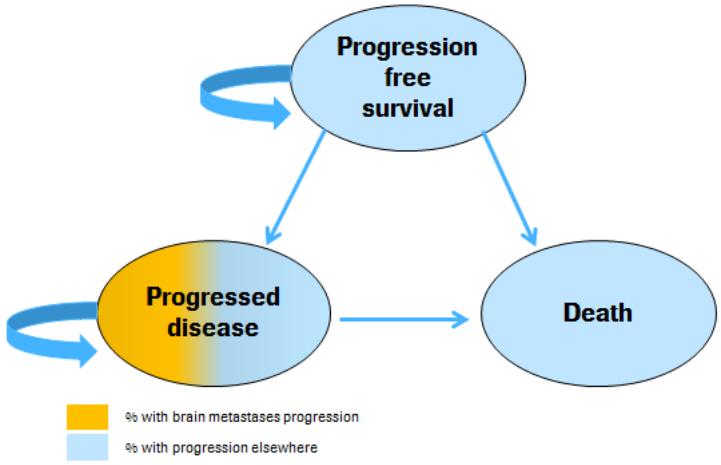
The de novo analysis assesses alectinib for the first-line treatment of adult patients with ALK-positive NSCLC. This population is consistent with both the appraisal scope, decision problem, Marketing Authorisation, and the study population of BO28984 (ALEX).

B.3.2.2 Model structure

The economic evaluation was developed in Microsoft Excel and is an Area-Under-the-Curve (AUC; or 'partitioned survival') model. The AUC model was selected in order to reduce the number of assumptions required when assessing and extrapolating immature OS, and to allow for full use of the ALEX data as opposed to alternative data sources where populations may not be equivalent.

The model is composed of 3-mutually exclusive health states, consistent with previous appraisals accepted by NICE for this, and other metastatic oncology indications (NICE, 2016a; NICE, 2016c; NICE, 2016b): "progression-free survival (PFS)", "progressed disease (PD)" and "death". Whereas most previous appraisals have not distinguished between progression locations, the model structure utilised in this submission does, driven by the significant quality of life impact and economic burden experienced through progression in the CNS: a common site of progression for patients with ALK-positive NSCLC (see sections B.2.6, B.3.4.1 and B.3.5.2). The resulting structure can be found in Figure 7.

Figure 7: Area under the curve model structure



The health economic model was developed to compare the cost-effectiveness of alectinib versus crizotinib, the only NICE recommended treatment, and standard of care for first-line treatment of adult patients with ALK-positive advanced NSCLC. Crizotinib is the only comparator included within the base case cost-effectiveness analysis and is the treatment most likely to be displaced from UK clinical practice if alectinib is reimbursed.

The model inputs (efficacy, safety and tolerability) were based on the results of the phase III ALEX trial. Results are reported in terms of cost per life years gained (LYG) and costs per quality adjusted life years (QALY) gained. This appropriately reflects the decision problem.

Within the AUC model, health states are based on the partitioning of the proportion of patients alive into “PFS” and “PD” at discrete time points, based on the PFS and OS curves from ALEX, with the proportion of patients in the “PD” health state assumed to be the difference between the two. The health states in the model represent the stages of disease in ALK-positive advanced NSCLC.

All patients start in the PFS health state and remain in this health state until they progress. At progression, defined as per the Response Evaluation Criteria in Solid Tumours (RECIST) criteria, patients transition into PD health state or enter the absorbing health state of Death. Patients in the PD health state stay in that health state until death. Patients cannot transition to an improved health state (back to PFS); a restriction that is consistent with previous economic modelling in oncology.

Due to the structural form of the model, patient transitions between the health states are not explicitly modelled. The partitioned survival approach allows for modelling of OS and PFS based on study-observed events, which is expected to accurately reflect disease

progression and the long-term expected survival profile of patients treated with alectinib. However, the primary limitation of this approach is that as transitions are not explicitly modelled, the model structure is rigid and does not allow exploratory or sensitivity analysis to be explored by changing the transition probability between different health states.

Costs and health-related utilities are allocated to each health state and multiplied by state occupancy to calculate the weighted costs and QALYs per cycle. PD health state costs and utilities are a weighted average, based on the proportion of patients progressing in the CNS as opposed to other locations, as derived from the ALEX trial.

The economic model uses a time horizon of 30 years, which was considered to be appropriate as the lifetime horizon for patients with ALK-positive advanced NSCLC, taking into account typical age at diagnosis and expected survival times following the treatment pathway. Whilst this time horizon is greater than previously used in the crizotinib appraisal of untreated ALK-positive NSCLC (NICE TA406), a greater time horizon becomes necessary when accounting for the change in the treatment pathway, resulting from the NICE recommendation of ceritinib for use after crizotinib, and accounting for the expected increased benefit of alectinib.

The model has been designed to use a weekly cycle, with the proportion of patients in each health state calculated each week. Transition between health states can occur at any time within the cycle. To account for the over or under estimation of transitions occurring at the beginning or end of the cycle, half-cycle correction was applied to each time interval in the Markov trace sheets of the model. This is also consistent with previous NICE STAs in this disease area.

Table 15: Features of the economic analysis

Factor	TA406	This appraisal	Justification
Time horizon	15 years	30 years	In-line with guidance in NICE reference case
Treatment waning?	No	Explored as a sensitivity analysis	Not incorporated as the base case, in-line with previous HTAs in this disease area. However, explored as a sensitivity analysis to acknowledge the uncertainty regarding long term benefit
Source of utilities	PROFILE 1014 using EQ-5D PROFILE 1007 Nafees *et al.* 2008	EQ-5D-3L data from ALEX Peters et al., 2016 Roughley et al., 2014	EQ-5D from trial In-line with guidance in NICE reference case, however did not accurately capture quality of life in patients with brain metastases, therefore literature utilised.
Source of costs	NHS reference costs Literature Expert opinion	NHS reference costs PSSRU BNF Published literature Expert opinion	Widely used and accepted sources of cost and RU data in UK HTAs

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

B.3.2.3 Intervention technology and comparators

The final scope of this appraisal includes crizotinib as the only relevant comparator to alectinib in ALK-positive advanced NSCLC. Hence, the comparator assessed in the economic model is crizotinib, driven from direct evidence obtained in the ALEX trial.

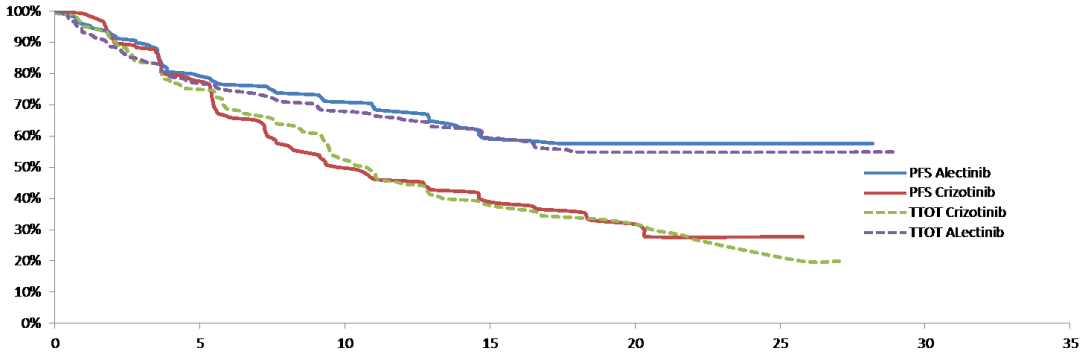
Alectinib and crizotinib are both oral medications prescribed and dispensed at outpatient appointments. In the base case, both treatments are dosed per protocol (alectinib: 1200 mg administered orally once-daily from day 1; crizotinib: 500 mg administered orally once-daily from day 1).

In clinical practice, both alectinib and crizotinib would be administered as a full pack at a specified lung cancer clinic. This is incorporated in to the economic model by applying the full pack cost up front. If a patient dies or discontinues within the specified administration timeframe, the remaining pack is considered wastage. Upon consultation with a number of clinical experts, it was determined lung cancer clinics are held every 4 weeks (equivalent of 4 cycles).

As per the anticipated license, alectinib is administered until disease progression or unacceptable toxicity. Whilst the discontinuation rule for crizotinib is not specified in the

SmPC, clinical experts have confirmed the same rule for treatment is implemented. This is further supported by outcomes of the ALEX trial, where the observed median time on treatment is equivalent to median PFS. As such, treatment duration and therefore drug acquisition costs are implemented using PFS data from ALEX. Such an approach is appropriate when assessing the PFS and time to off-treatment (TTOT) data from ALEX (Figure 8).

Figure 8: PFS and TTOT - ALEX



B.3.3 Clinical parameters and variables

B.3.3.1 Incorporation of clinical data into the economic model

The primary data source for the economic model is the phase III pivotal clinical trial, ALEX, comparing alectinib to crizotinib. This study is the data source for the clinical outcomes (OS, PFS), adverse events and quality of life for both the comparator and intervention.

Extrapolation of OS and PFS from ALEX was required, as a significant proportion of patients had not progressed, or died, within the follow-up period of ALEX.

NICE Decision Support Unit (DSU) guidance (Latimer, 2013) was followed to identify base case parametric survival models for OS and PFS. As head to head evidence is available versus the only comparator specified in the decision problem, crizotinib, patient-level data are available. In such a circumstance, NICE TSD 14 specifies it is “unnecessary to rely upon the proportional hazards assumption and apply a proportional hazards modelling approach”. As such, separate parameterisations were fit to each treatment arm.

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 against any longer term data available to help identify the most plausible survival model.

B.3.3.2 OS extrapolation

To determine which extrapolation was the most appropriate fit to the observed data, alternative distributions were mapped to the observed KM data from the trial through paramaterisation. The following candidate distributions were assessed for goodness of fit using AIC, BIC and visual assessment: Exponential, Weibull, Log-normal, Gamma, Log-logistic, and Gompertz (note: Gompertz did not converge).

When assessing the best statistical fit a difference of five or more is generally considered important, thus when extrapolations have a narrow statistical margin between, visual inspection, and clinical plausibility becomes paramount.

As demonstrated in Table 16 below, dependent on the treatment arm, significantly different distributions are considered the best statistical fit to the data. In addition, a number of the distributions are similarly plausible. As statistical fit only assesses the available trial data, visual assessment is required to rule out any implausible distributions.

Table 16: Summary of goodness of fit for OS: alectinib and crizotinib

	Alectinib		Crizotinib	
Parametric distribution	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	246.59	249.61	234.24	237.26
Weibull	247.98	254.03	232.71	238.74
Log-normal	247.97	254.02	230.88	236.91
Gamma	249.79	258.86	232.79	241.84
Log-logistic	247.91	253.96	232.10	238.13
Gompertz	248.59	254.63	234.72	240.76

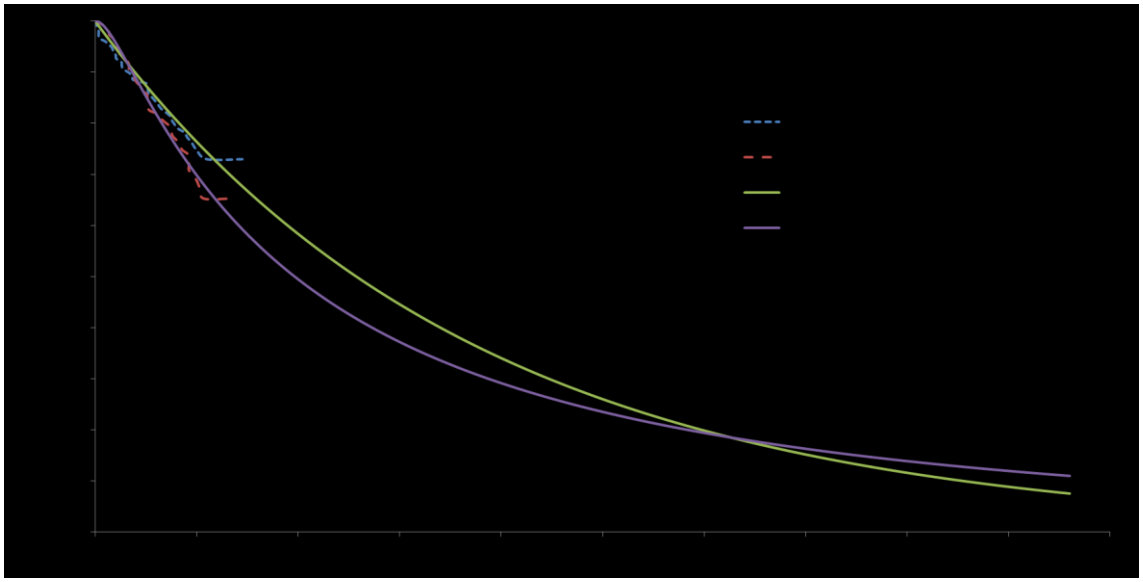
AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

NICE DSU guidance specifies that where the proportional hazards assumption has not been met, or does not need to be assumed, fitting separate types of parametric models to individual treatment arms requires substantial justification, and rather it is most sensible to fit separate parametric models of the same type, allowing a two-dimensional treatment effect on both the shape and scale parameters of the parametric distribution (Latimer, 2013).

This is further supported considering:

- The mechanism of action of both products: as both crizotinib and alectinib are targeted ALK inhibitors, it is sensible to assume they would follow the same distribution of treatment effect
- Consistency with the committee preferred approach for OS extrapolation in the appraisal of crizotinib for untreated ALK+ NSCLC (TA409) (NICE, 2016c), where the same distribution was used for both treatment arms to minimize the differences in assumptions between treatments
- Finally, when assessing the resulting extrapolated curves utilizing the separate types of parametric models, that provide the best for fit each arm individually ,the longer term overall survival curves of both products cross, inconsistent with:
    - Clinical expert opinion on the anticipated survival benefit of alectinib
    - The clear benefit alectinib has demonstrated in CNS progression, arguably reducing the rapid deterioration of patients
    - Assumptions on PFS improvements equating in to OS improvements, previously utilised and recognised in the NICE appraisal of crizotinib (TA409)(NICE, 2016c)
    - The moderate evidence that PFS is a good surrogate for OS, particularly where the PFS benefit is considerable (Mauguen et al., 2013), (Laporte et al., 2013).

Figure 9: OS extrapolated curves by statistical best fit



Thus, all curves utilizing the same type of distribution were assessed for visual fit to the KM data, and clinical plausibility of the entire curve to identify the optimal distribution.

Figure 10 shows the visual fit of all OS distributions, with the exception of Gompertz (which did not converge for alectinib) to the ALEX KM data. As demonstrated, the exponential is not a very good fit to the data, but is kept in for plausibility assessment.

Next, the resulting tails of the distributions were assessed for clinical plausibility in terms of: the proportion of patients alive at set time points; the relative difference between the extrapolated curves; and cross-checking against background mortality.

When assessing the curves against background mortality, it was identified a number of the distributions for both alectinib and crizotinib result in the hazard functions crossing background mortality. Therefore an adjustment was required.

There are two ways to conduct such an analysis:

1. Adding the general population survival hazard to that of alectinib and crizotinib, or
2. Assigning patients to the general population background mortality hazard when the hazards cross.

Both were explored as plausible approaches. However, when assessing the resulting parametric curves of the former approach, many distributions crossed zero earlier than anticipated (in some circumstances, earlier than 10 years for crizotinib, inconsistent with their previous NICE appraisal (NICE, 2016c) demonstrating this approach could be considered too conservative. Therefore, the alternative method was used within the model, with the resulting curves being deemed more clinically plausible, and appropriate as the base case analysis.

As demonstrated in Figure 11, there is considerable separation between the crizotinib and alectinib OS curves irrespective of distribution chosen. This trend is plausible, given the OS benefit and diverging KMs observed within the trial (despite not being powered to demonstrate statistical improvement); the benefit derived from alectinib PFS and importantly, the protective CNS effect alectinib has demonstrated (see section B.2.12).

Figure 10: Visual fit of OS distributions to KM data

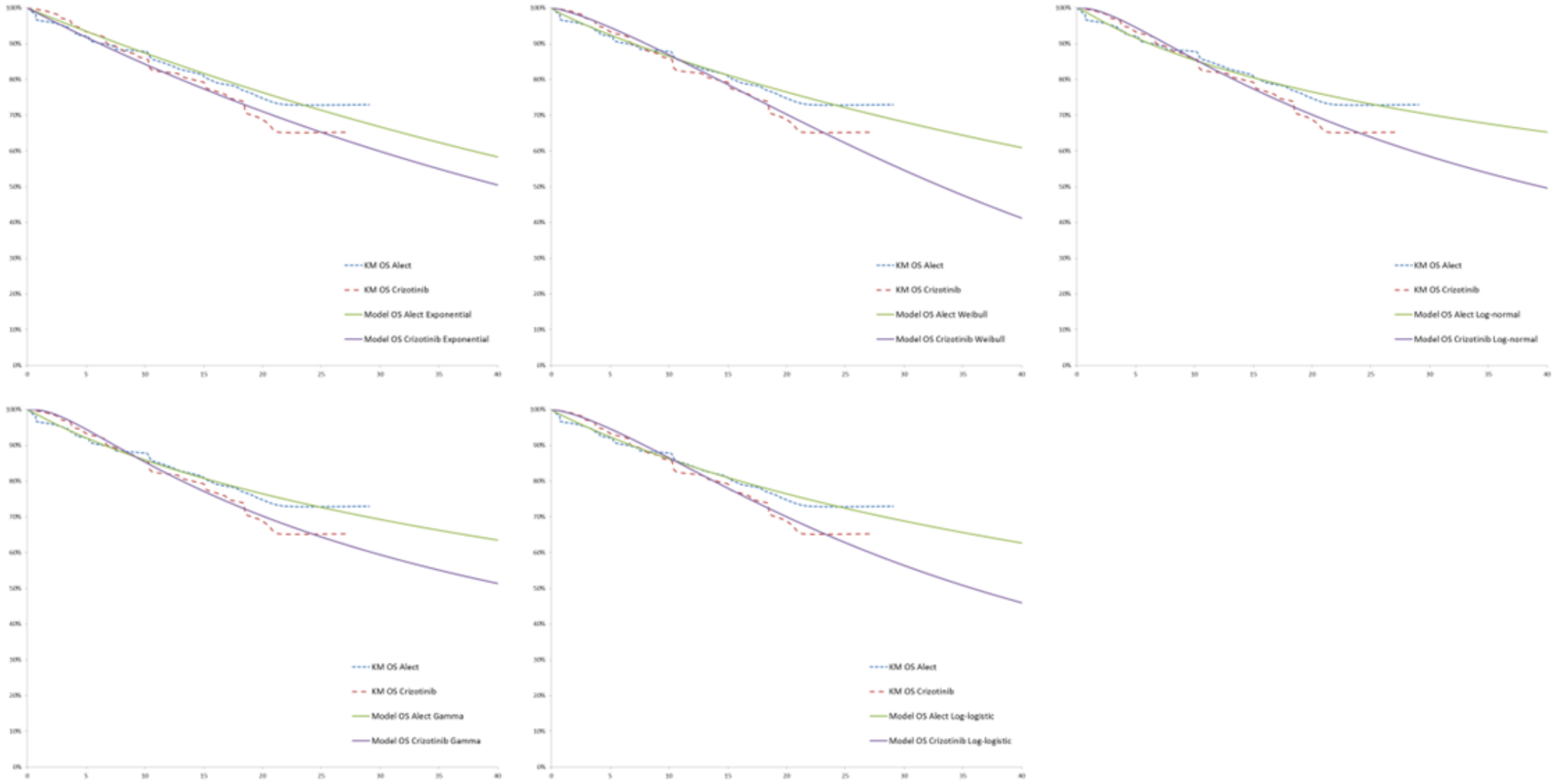
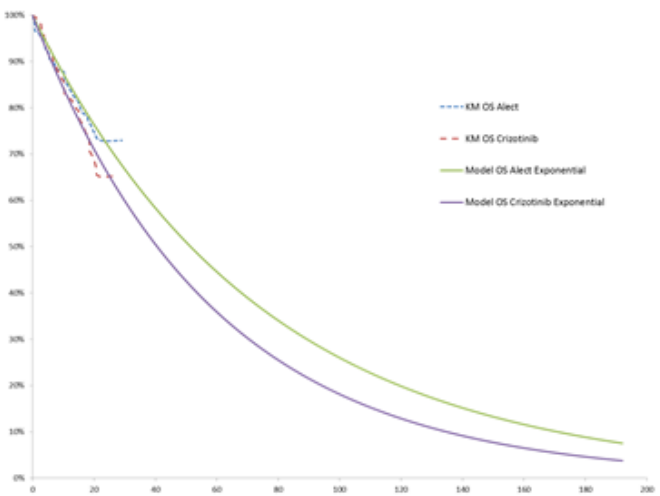
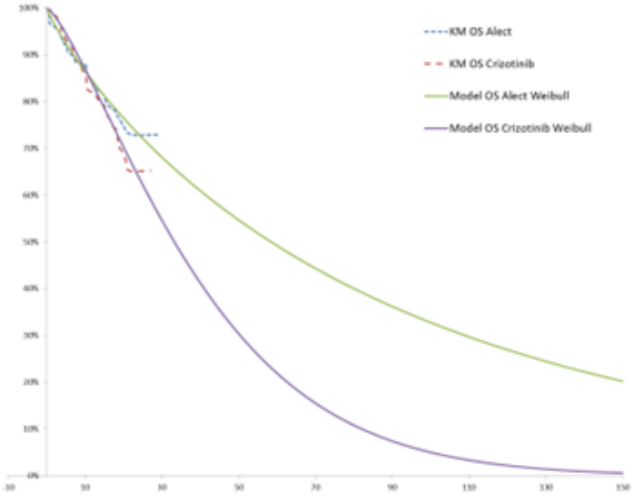
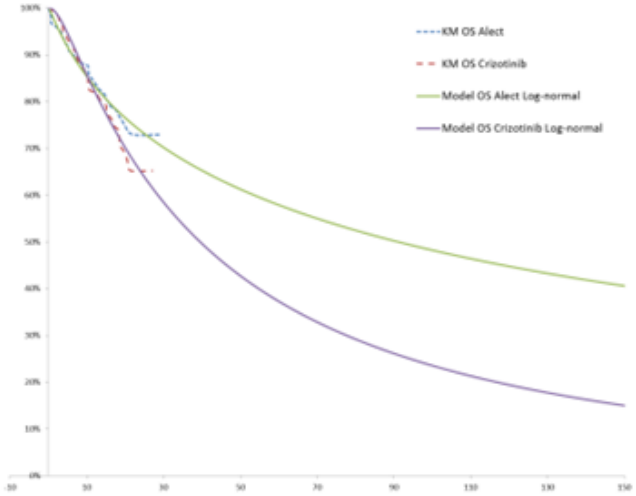
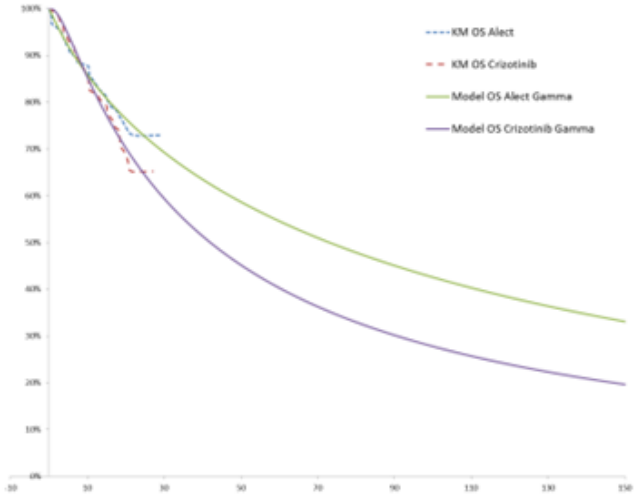


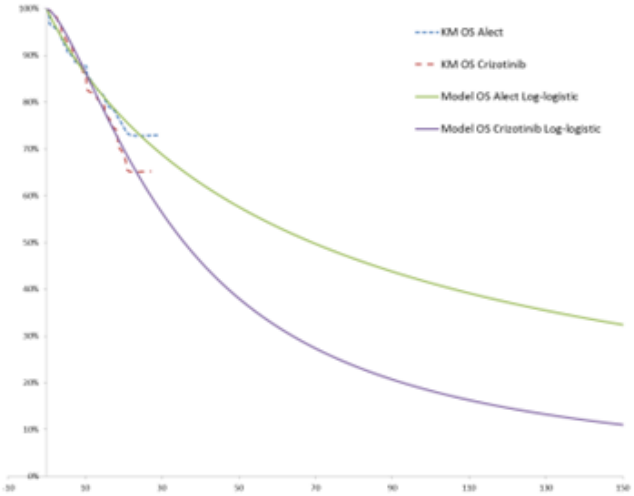
Figure 11: Visual assessment of OS clinical plausibility











Given the immature OS data of ALEX data, more mature OS data for crizotinib was sought to validate the most appropriate distribution.

In September 2017, updated results from the PROFILE 1014 study assessing first-line crizotinib versus chemotherapy in ALK-positive NSCLC were presented at ESMO, providing median follow up of ~46 months (Mok et al., 2017).

The patient characteristics of the PROFILE 1014 and ALEX trials are not equivalent. Of note, patients in the PROFILE 1014 were generally younger, with a lower proportion of brain metastases at baseline, and a higher proportion of patients had received prior treatment for brain metastases at baseline (see Appendix M for details). Thus, in total, patients were generally healthier in the PROFILE 1014 study, and therefore could be expected to perform better. This is further supported when reviewing the NICE appraisal of crizotinib (TA409) where results were adjusted to a real world population, acknowledging the favourable patient population in the trial (NICE, 2016c).

Nevertheless, given this is the most mature, long term data available, the KM curve was digitized, and assessed against the overall survival predictions of crizotinib for each parametric distribution to inform curve selection.

Table 17: Crizotinib OS model comparisons with PROFILE 1014

		12 months	24 months	30 months	36 months	48 months
PROFILE 1014 data *		83%	65%	62%	58%	55%
# at risk *		138	101	89	77	40
Parametric distributions	Exponential	82%	67%	60%	54%	44%
	Weibull	84%	64%	55%	46%	33%
	Log-normal	82%	65%	59%	53%	44%
	Gamma	82%	66%	60%	54%	46%
	Log logistic	83%	64%	57%	50%	40%

* Subject to some uncertainty due to digitizing of the KM

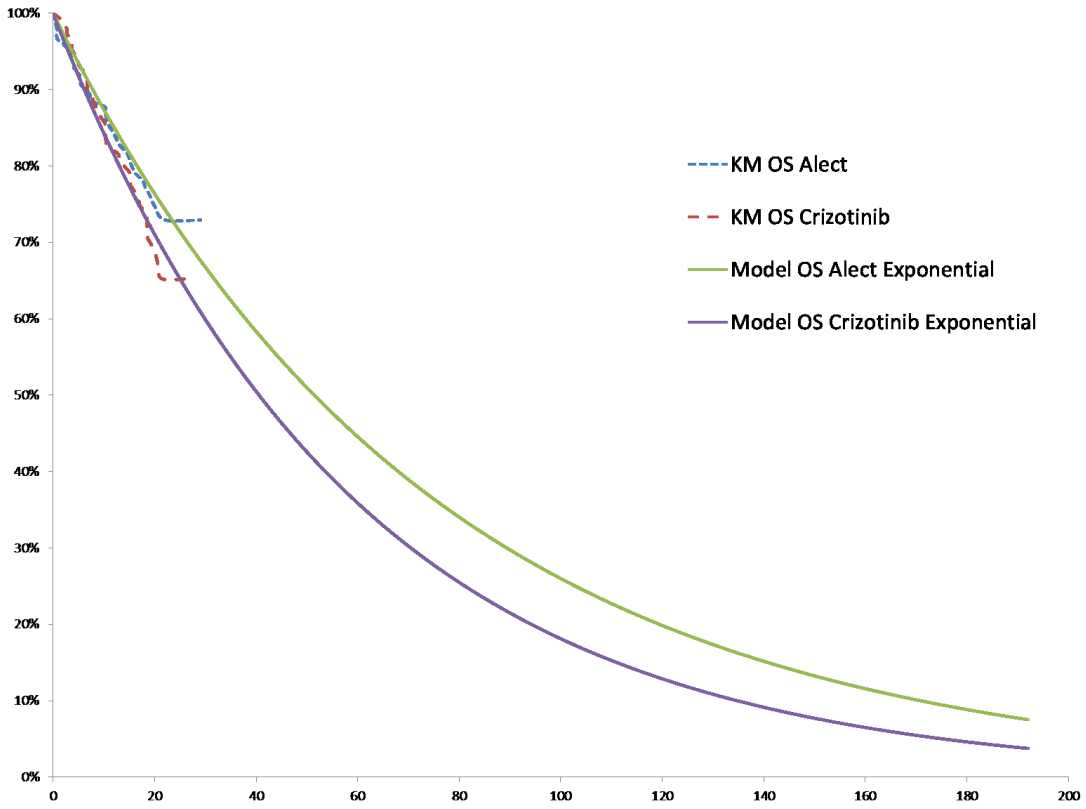
As demonstrated in Table 17, and as expected given the differences in the trial populations, none of the parametric distributions meet the four-year OS data from the recent PROFILE1014 data cut.

Initially, the distribution that provides the closest estimate to the crizotinib 4-year OS data was considered: the Gamma. However, the resulting extrapolation meant 7.2% of alectinib patients were still alive at 35 years, which was queried on whether this could be considered clinical plausibility.

The curve was discussed with a clinical expert, who deemed it could be an appropriate prediction of the anticipated survival of patients on alectinib, accounting for subsequent lines of treatment. However the clinical expert also specified that for both alectinib and crizotinib the hazard was likely to increase at a greater rate from approximately 140 months. However, with a lack of evidence to support splicing of the data, alternative distributions were assessed.

The second best fit to the PROFILE1014 data is the exponential distribution which provides significantly lower anticipated survival gain for both crizotinib and alectinib. Nevertheless, with 3.9% of alectinib patients alive at 20 years, it could be considered a more plausible, but conservative assumption. Therefore this is the distribution used in the base case. The resulting extrapolation can be found in Figure 12.

Figure 12: OS extrapolations: Exponential



To validate the alectinib OS extrapolation the survival estimates were cross checked against all other data sources available for alectinib, and clinical expert opinion was sought.

The longest available follow up for alectinib is from AF-001JP: the Japanese Phase I/II study of alectinib for ALK-inhibitor naïve patients (Tamura et al., 2017). Unsurprisingly, AF-001JP has been conducted in a healthier population than ALEX: in particular no patients with ECOG 2 were included, fewer patients had brain metastases at baseline, and the majority of patients had received prior chemotherapy, inconsistent with ALEX. Nevertheless, it provides valuable information on anticipated survival of alectinib in a similar treatment setting (ALK-naïve).

Table 18 compares the model predictions to ALEX and AF-001JP.

Table 18: Alectinib OS model comparisons with available data

	12 months	24 months	30 months	36 months
Model	85%	73%	67%	62%
ALEX	84%	73%	-	-
# at risk	119	38		
AF-001JP (Tamura et al., 2017)	90%	80%	80%	78%
# at risk	43	39	36	29

As shown in Table 18 the model provides a good fit to the ALEX data at 12 and 24 months. In addition, importantly, the model consistently predicts lower overall survival compare to AF-001JP across the time horizon, and at increasing rates as compared to AF-001JP. Whilst this population is generally in a more favourable cohort of patients, when consulted on with a clinical expert, it was deemed an appropriate source to support overall survival estimates. The clinical expert highlighted that in clinical practice, there are approximately 10–20% of patients who are considered ‘rapid progressors’. These patients are difficult to identify, and would have been captured in the ALEX trial, but likely would not have met the inclusion criteria for AF-001JP. This is reflected in the higher rate of OS in the AF-001JP study from early on. In summary, AF-001JP was considered compelling, and clearly demonstrates the overall survival benefit of alectinib. The growing divergence in the survival estimates demonstrate that the chosen distribution could underestimate the expected long term benefit of alectinib.

Table 19 presents the resulting ranking of OS distributions based on the combined AIC/BIC, visual fit and clinical plausibility, as explored above.

Table 19: Ranking of OS distributions based on combined AIC/BIC, visual fit and clinical plausibility

Parametric distribution	Alec/criz combined AIC	Alec/criz combined BIC	Visual fit to KM	Clinical plausibility	Ranking
Exponential	246.59	249.61	~	✓	1
Weibull	247.98	254.03	✓	~	3
Log-normal	247.97	254.02	✓	~	3
Gamma	249.79	258.86	✓	✓~	2
Log-logistic	247.91	253.96	✓	~	3
Gompertz	248.59	254.63	×	-	4

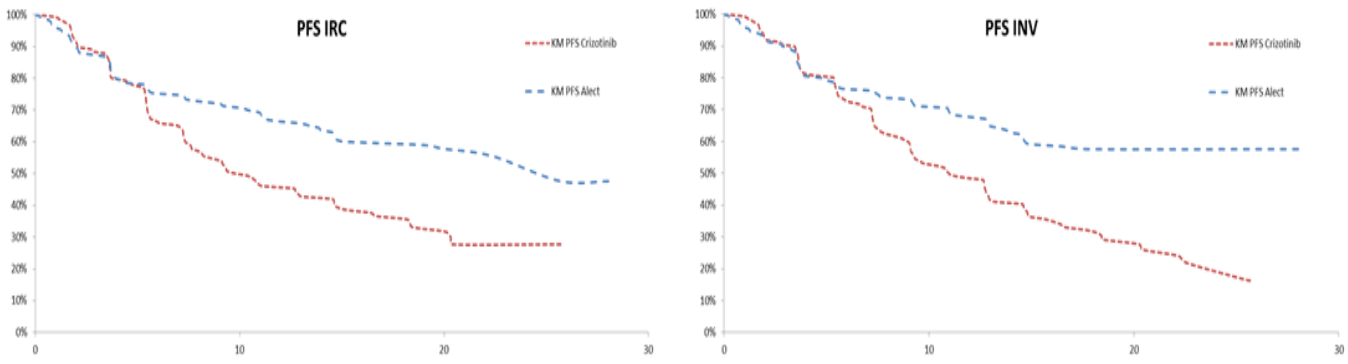
AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion, KM, Kaplan-Meier.

It is acknowledged there is uncertainty regarding the long term treatment effect; therefore scenarios have been conducted capping the hazard function of alectinib at different time intervals beyond the trial data. In addition, recognizing the uncertainty in all overall survival estimates given the immaturity of the data, additional sensitivity analyses have been conducted on all other plausible extrapolations from the ALEX trial.

B.3.3.3 PFS extrapolation

Two PFS endpoints are incorporated into the model, driven by ALEX endpoints: PFS as assessed by investigators (INV) on the trial, and PFS as assessed by an independent review committee (IRC). As PFS by INV is the primary endpoint of the ALEX study, and most likely to represent real world clinical practice, this is the endpoint utilized in the base case. However, it is acknowledged this could be prone to bias, and therefore a sensitivity analysis is provided utilizing the IRC endpoint.

Figure 13: KM comparison: PFS IRC and PFS INV



Similar to the approach taken to incorporate OS in to the economic model, as proportional hazards (PH) does not need to be assumed, alternative distributions were mapped to the observed KM INV PFS data from the trial. Paramaterisation was used to define the most appropriate functional form for fit to the observed data, with candidate curves checked for visual fit to the KM data, and the resulting extrapolation inspected for clinical plausibility.

The AIC and BIC goodness of fit can be found in Table 20.

Table 20: Summary of goodness of fit for PFS: alectinib and crizotinib

	Alectinib		Crizotinib	
Parametric distribution	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	372.50	375.52	381.97	384.99
Weibull	370.83	376.88	375.26	381.30
Log-normal	363.61	369.66	368.66	374.70
Gamma	362.42	371.50	370.66	379.72
Log-logistic	367.43	373.48	370.66	376.69
Gompertz	374.50	380.55	381.20	387.23

AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Similarly to OS, based on NICE DSU guidance, separate parametric models of the same type have been fitted. As both crizotinib and alectinib are targeted ALK inhibitors, it is sensible to assume they would follow the same distribution of treatment effect.

All curves were assessed for visual fit to the KM data, and clinical plausibility of the long term survival to identify the optimal distribution.

Figure 14 shows the visual fit of all PFS distributions to the ALEX KM data, with the exception of Gompertz, as it again did not converge for alectinib. Visual assessment of PFS clinical plausibility is assessed for the remaining curves by mapping against the chosen OS distribution (Figure 15).

To note, similarly to the OS KM curves, PFS of alectinib and crizotinib are aligned and overlapping for the first approximately 6 months, and then start to diverge. Given the similar response rates between the treatment arms the time of separation most likely reflects the time point where patients begin to relapse on crizotinib treatment (see section B.2.12).

Figure 14: Visual fit of PFS distributions to KM data

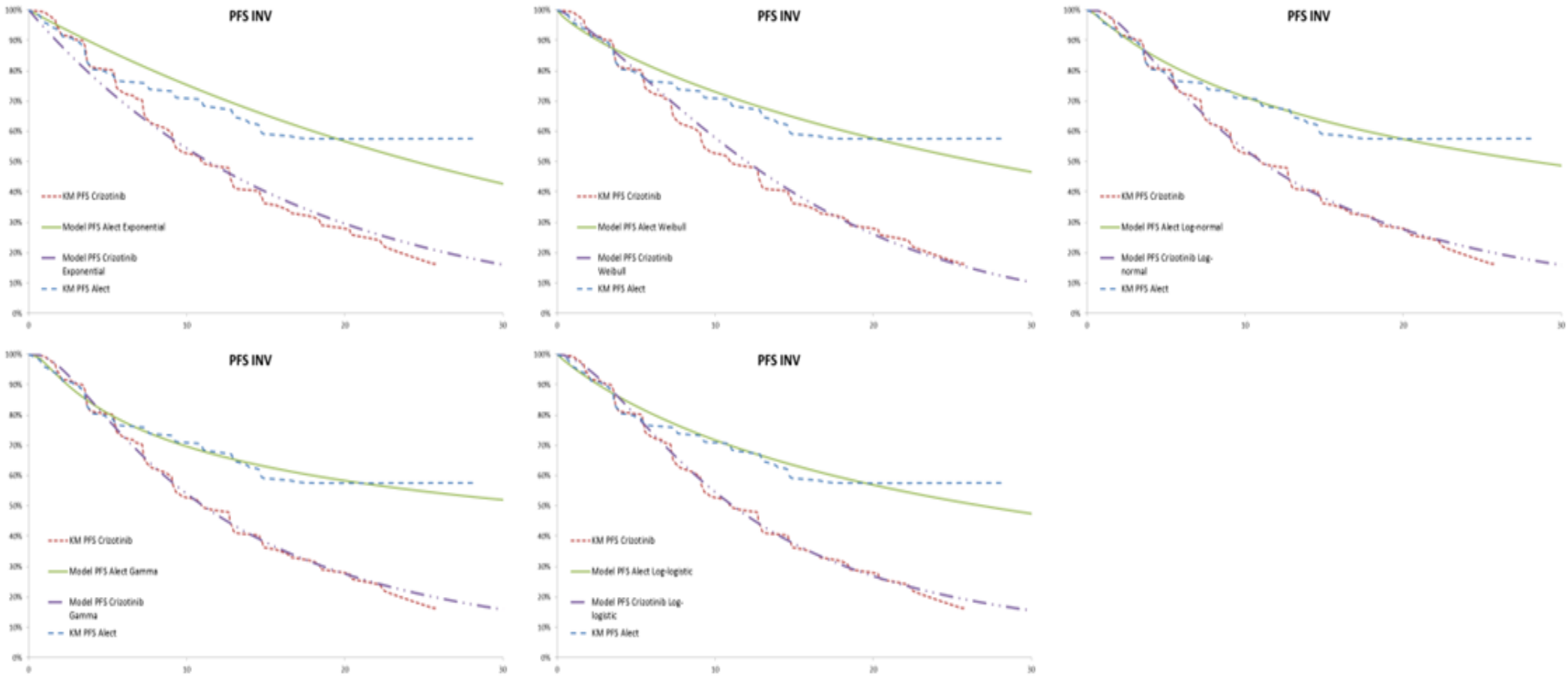
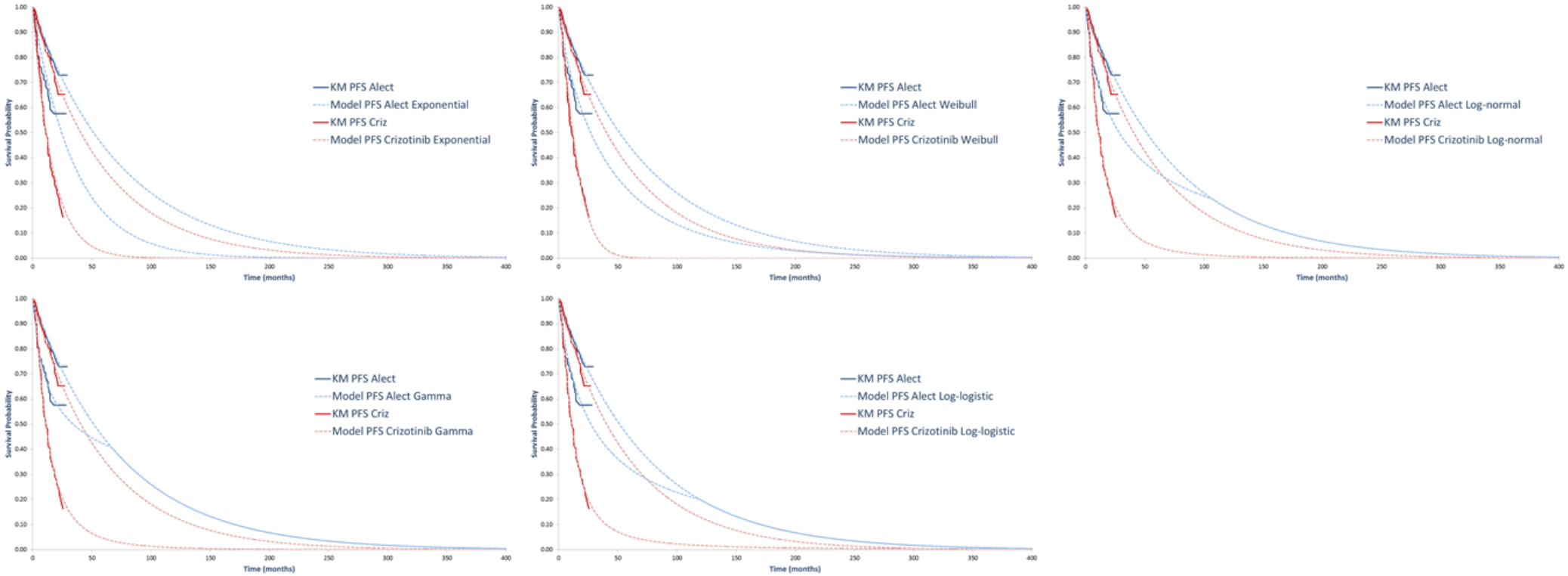


Figure 15: Visual assessment of PFS clinical plausibility against OS



The committee preferred approach for PFS extrapolation in the appraisal of crizotinib for untreated ALK-positve NSCLC (TA409) (NICE, 2016c) was to utilise the parametric distribution with the lowest AIC/BIC statistic.

However, as demonstrated above, the top 3 distributions by the combined best statistical fit (Log-normal, Gamma and Log-logistic) are clinically implausible, as the PFS curves meet the OS curves, and are subsequently capped (i.e. if the cap was not implemented, PFS would cross OS). Weibull also appears to come close to crossing, however was still included as an option for consultation with a clinical experts.

Upon consultation, it was confirmed the Weibull distribution creates clinically implausible PFS estimates for alectinib (10 years = 10% patients still in PFS). Therefore, it was deemed the exponential is the most appropriate distribution to utilize.

However, visual fit to the curves is poor, driven by the delay in the separation of the curves. Therefore, it was deemed more appropriate to utilize the KM data up to 18 months (where censoring increases), with the exponential tail added afterward.

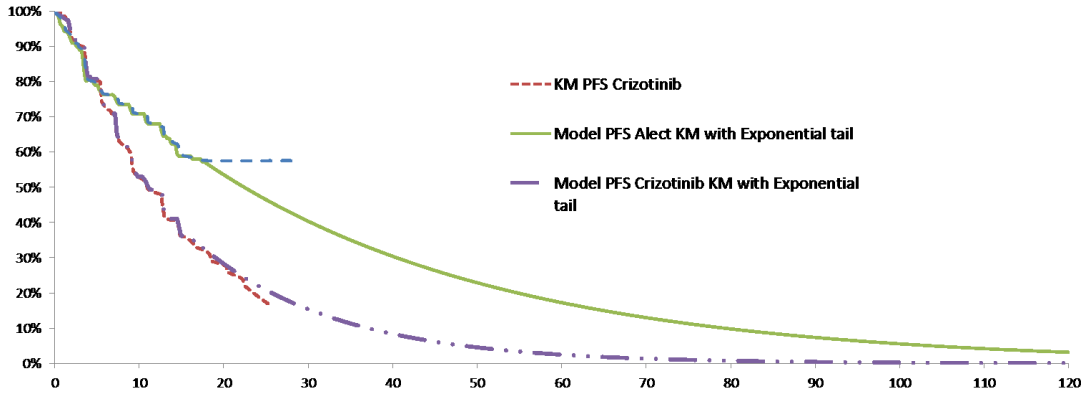
Table 21 presents the resulting ranking of PFS distributions based on the combined AIC/BIC, visual fit and clinical plausibility, as explored above. Figure 16 presents the final extrapolation chosen as the base case for PFS.

Table 21: Ranking of PFS distributions based on combined AIC/BIC, visual fit and clinical plausibility

Parametric distribution	Alec/criz combined AIC	Alec/criz combined BIC	Visual fit to KM	Clinical plausibility	Ranking
Exponential	754.47	760.51	×	✓	1
Weibull	746.09	758.18	~	~	2
Log-normal	732.27	744.36	✓	××	3
Gamma	733.09	751.21	✓	××	3
Log-logistic	738.09	750.17	✓	××	3
Gompertz	755.70	767.78	×	-	4

AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion, KM, Kaplan-Meier.

Figure 16: PFS (INV) extrapolation: KM+Exponential



To explore the sensitivity around this choice, scenario analyses have been run with the incorporation of a treatment effect cap (aligned with OS caps), and on the other plausible distribution (Weibull, and KM+Weibull).

Please see Appendix L for details of how this and other distributions impact PFS as measured by IRC.

B.3.4 Measurement and valuation of health effects

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

Health-related quality of life was evaluated in the ALEX trial using the EuroQoL EQ-5D-3L, EORTC QLQ-C30 and EORTC QLQ-LC13. All HRQoL utilities incorporated in the cost-effectiveness model and described in the following section were derived from this trial. Evaluation of HRQoL using EQ-5D directly from patients is consistent with the NICE reference case, hence is used as the base case analysis. All further details presented in this section refer only to this method.

The EQ-5D-3L questionnaire was administered and completed on Cycle 1, Day 1 (week 0) and thereafter every 4 weeks (in line with treatment administration) until disease progression. Upon disease progression, the EQ-5D was administered at the post-treatment visit (4 weeks after permanent treatment discontinuation), and then every follow up visit: every 8 weeks for the first 6 months, thereafter every 12 weeks.

To date, the EQ-5D has been collected from cycle 1 (week 0) through to Cycle 125 (week 124). Therefore, quality of life estimates on progression-free and post-progression states have been collected. See section B.2.6 for details on completion rates.

Utility values were derived from the EQ-5D using the UK tariff. The data were analysed primarily with a random intercept model, including the following variables: treatment (alectinib vs crizotinib), sex, age, race (Asian vs non-Asian), CNS lesions at baseline, health state (progressed vs non-progressed)[2].

Treatment was not a significant factor in the prediction of utility (P-value = 0.3912), therefore a treatment specific utility was not deemed necessary on either the progression-free, or post progression health states.

As a second step, the random intercept model was re-run, using the same variables, but without a distinction in treatment arms. Table 22 summarizes the linear mixed effects model estimates on utility prediction for each variable included. Progressed vs non-progressed state was the only strongly statistically significant factor in the prediction of utility (p<0.0001).

Table 22: Mixed model for EQ-5D estimates

Covariate	Estimate	St. Error	DF	P value
Intercept	0.9208	0.05541	239	<.0001
Sex (Female)	-0.02641	0.02322	237	0.2566
Age	-0.00189	0.000910	239	0.0385
Race (Asian)	0.04726	0.02303	236	0.0412
CNS metastasis at baseline (yes)	-0.02446	0.02352	239	0.2995
Disease Progressed (Yes)	-0.08911	0.009547	4357	<0.0001

CNS, Central nervous system; DF, degrees of freedom.

Table 23: Resulting utility estimates based on ALEX

Health state	Utility	Variance	Source
Progression-free Survival	[redacted]	[redacted]	ALEX
Progressed Disease	[redacted]	[redacted]	ALEX

As described in section B.2.6, presence of brain metastasis is known to have a significant impact on the quality of life of patients. This has been validated across the literature (Peters et al., 2016; Guerin et al., 2015), clinical expert opinion and other quality of life measures captured in the ALEX trial. However, this is not reflected when analysing the EQ-5D data from the trial.

[2] There was a high proportion of missing data for utility at baseline (>30% in both arms). Therefore this variable was not included in the analysis. As data were missing for both arms, it is not anticipated this will have a significant impact.

This could be due to a number of reasons: firstly due to the time horizon of the analyses. The EQ-5D analysis has not accounted for changes in quality of life across treatment arms over time, whereas alternative measures have captured clinically meaningful worsening of symptoms over time (see section B.2.6). Secondly, the generic measurement of the EQ-5D may not be capturing the differences sufficiently. This could be further emphasised as the analysis has been conducted in the pre-specified subgroup of patients with brain metastases at baseline, who arguably, do not provide a representative valuation of quality of life in this patient group, as their prognosis has allowed for inclusion in to the clinical trial. Rather, quality of life in patients who progress with CNS metastases is a more appropriate analysis, which would provide a better representation of this patient group. Finally, there could be a consideration of sampling bias, whereby response rates between the populations are inconsistent, thus there is an inability to capture the full decrements.

Therefore, it is important to note that there are clear benefits of alectinib treatment that are insufficiently captured by the quality of life derived from the EQ-5D in the ALEX study.

As a result, literature was utilised to incorporate an EQ-5D quality of life estimate for patients with brain metastases in to the analyses.

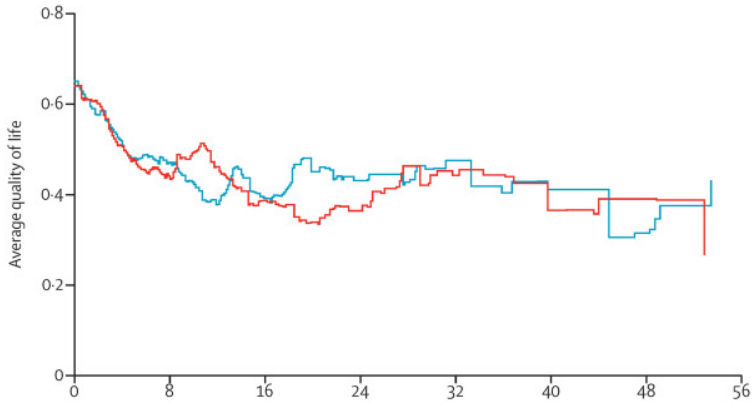
In the ALEX trial, CNS progression was only measured by IRC. At data cut off, as per the IRC endpoint (to ensure consistency) 92 patients had progressed in the crizotinib arm, and 63 patients had progressed on alectinib. Of those, 68 (74%) and 18 (29%) progressions had been in the CNS, respectively. Whilst there is uncertainty in this estimate due to the different endpoints utilised, it is assumed the split of progression in the CNS versus progression in the non-CNS would be consistent across the measures used (INV vs IRC).

Based on this, the progressed disease utility values for each treatment arm were segmented and applied as a function of the proportion of patients progressing in the CNS versus elsewhere.

Peters et al (Peters et al., 2016) reports the quality of life impact of brain metastases through EQ-5D estimations in patients with NSCLC, sourced from an additional study by Roughley et al (Roughley et al., 2014). In these papers, the average utility of a patient with brain metastases is 0.52. An additional study by Mulvenna et al (Mulvenna et al., 2016) explores this further in patients with NSCLC in the QUARTZ study. Whilst an average utility is not reported, the graphic presented (see Figure 17) indicates that the EQ-5D utility derived in Roughley (0.52) could similarly underestimate the quality of life decrements associated CNS metastases. Nevertheless, without further evidence to utilise, patients who progress in the

CNS are allocated a utility value of 0.52, with the remaining patients being allocated the progressed disease utility captured from the ALEX data (0.725).

Figure 17: Average quality of life over study period of NSCLC patients with brain metastases (Mulvenna et al., 2016)



The resulting utilities by health state and treatment arm are reported in Table 24. These are the values utilized in the base case analysis.

Table 24: Utility estimates in the Cost-Effectiveness Model (base case)

Health state	Utility	Variance	Source	Assumption
Progression-free Survival (alectinib & crizotinib)	[redacted]	[redacted]	ALEX	-
Progressed Disease (alectinib)	[redacted]	0.050*	ALEX and Roughley et al.	29% experience utility of 0.52; 71% experience utility of [redacted]
Progressed Disease (crizotinib)	[redacted]	0.050*		74% experience utility of 0.52; 26% experience utility of [redacted]

* The sensitivity analysis is conducted around ±10% of these values.

A scenario is incorporated only using ALEX data for PD.

B.3.4.2 Mapping

As HRQoL was collected using the EQ-5D in the ALEX study, consistent with the NICE reference case, no mapping techniques were required.

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

A SLR was conducted to identify HRQoL evidence in the first-line treatment of patients with ALK-positive NSCLC. An overview of the identified studies is available below (see Table 25).

Alternatively, detailed descriptions of the search strategy and extraction methods are provided in Appendix H.

Summary of identified studies and results

Overall, a total of 11 publications covering five unique studies were identified for inclusion. Only two of these studies were specifically in the first-line population, and therefore relevant for this appraisal.

Both publications focused on the first-line treatment of advanced ALK-positive NSCLC patients in the PROFILE 1014 trial. During the trial, the EQ-5D instrument was used to quantify HRQoL and derive utilities from patients. Both studies evaluated treatment with crizotinib versus chemotherapy. Additionally, Solomon et al. also reported utility estimates in patients treated with docetaxel and pemetrexed.

Consistency with values derived from ALEX

On treatment PFS utility estimates for crizotinib are consistent with those derived from ALEX, and utilized in the base case analysis of the economic model.

Post-progression utilities were not reported in either of the publications; however it is possible to cross reference these publications to the Health Technology Assessments undertaken for crizotinib for the first-line treatment of advanced ALK-positive NSCLC (as identified in Section B.3.1). Unsurprisingly, the post-progression utilities identified in the literature (Table 26) are inconsistent with the post-progression utility derived from the ALEX trial (literature values being lower): driven by the adaption in the treatment pathway for ALK-postive NSCLC, with the availability of tyrosine-kinase inhibitors (TKIs) in second line (2L) and beyond.

However, they are not as inconsistent once progression in the CNS is incorporated for the base case analysis.

An additional scenario analysis has been undertaken to explore separate post-progression utilities, based on line of treatment, and post-progression treatment type, utilizing the identified literature (see B.3.4.5). However, this scenario does not account quality of life for progression in the CNS, thus should be interpreted with caution.

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Table 25: Study summary and reported utility data of the relevant study identified in the systematic review

Study	Population details	Method of deriving HSUVs	Countries	Mean HSUVs		
				Pre-progression	Post-progression	Other
Solomon, 2014 (PROFILE 1014)	Locally advanced, recurrent, or metastatic ALK+ NSCLC (N=343)	Instrument: EQ-5D Valuation: NR Elicitation: NR Scale: NR	Australia, Brazil, Bulgaria, Canada, China, France, Germany, Greece, Hong Kong, Hungary, Ireland, Italy, Japan, South Korea, Netherlands, Poland, Russia, Spain, Sweden, Taiwan, UK, US	**Baseline (SD):** • Crizotinib, 0.72 (0.25) • Chemotherapy, 0.69 (0.26) • Docetaxel, 0.67 (0.29) • Pemetrexed, 0.73 (0.24) **During treatment (SE):** • Crizotinib, 0.82 (0.01) • Docetaxel, 0.66 (0.04) • Pemetrexed, 0.74 (0.02)	NA	NA
Felip, 2015 (PROFILE 1014)	Advanced non-squamous ALK+ NSCLC (N=343)	Instrument: EQ-5D (3L version) Valuation: NR (calculated using a standard algorithm) Elicitation: NR Scale: 0-1	NR	**Baseline (SD):** • Crizotinib, 0.72 (0.30) • Chemotherapy, 0.71 (0.26) **During treatment (SD):** • Crizotinib, 0.81 (NR) • Chemotherapy, 0.72 (NR)	NA	NA

ALK+, anaplastic lymphoma kinase-positive; HSUV, health state utility value; NA, not available; NR, not reported; NSCLC, non-small cell lung cancer; SD, standard deviation; SE, standard error; UK, United Kingdom; US, United States.

Table 26: Summary of utilities from identified health technology appraisals

Study	Population details	Mean HSUVs		
		Pre-progression	Post-progression	Other
pCODR crizotinib resubmission 2015 (pCODR, 2015)	Locally advanced or metastatic ALK+ NSCLC	NR	NR	NR
NICE TA406 2016 (NICE, 2016c)	Locally advanced or metastatic ALK+ NSCLC	• Crizotinib: redacted • Pemetrexed + platinum: redacted • Treatment beyond progression with crizotinib: redacted	• Docetaxel (2L): 0.66 • BSC (3L): 0.47	Disutilities associated with AEs: • Elevated transaminases: 0.00 • Neutropenia: 0.09 • Anaemia: 0.07 • Leukopenia: 0.09 • Thrombocytopenia: 0.09
SMC 1152/16 (SMC, 2016)	Advanced ALK+ NSCLC	• Crizotinib: 0.81 • Pemetrexed + platinum: 0.72	• Docetaxel (2L): 0.66 • BSC (3L): 0.47	

2L, second-line; 3L, third-line; AE, adverse event; ALK+, Anaplastic lymphoma kinase positive; NSCLC, non-small cell lung cancer; NR, not recorded

B.3.4.4 Adverse reactions

Adverse event data used in the model were taken directly from the ALEX clinical study. Previous appraisals within this therapy area (NICE, 2016a; NICE, 2016c), have historically utilised all grade ≥3 treatment related AEs with an incidence of ≥5% in either treatment arm in to the economic model. However, for a more robust assessment of the safety profile of both alectinib and crizotinib, all grade 3 and 4 treatment-related AEs with an incidence of ≥3% in either arm of the ALEX trial, and all grade 5 treatment-related AEs irrespective of incidence are included in the base case analysis. The resulting adverse events included in the economic model are shown in Table 27.

Table 27: Adverse events included in the economic model

	Alectinib (n=152)		Crizotinib (n=151)	
	Occurrence	%	Occurrence	%
Alanine aminotransferase increased	7	4%	25	14%
Asparatate aminotransferase increased	10	5%	17	9%
Cardiac Arrest (G5)	0	0%	1	1%
QT interval prolongation	0	0%	6	3%
Neutropenia	0	0%	13	3%
Pneumonitis (G5)	0	0%	3	2%

There are two approaches that could be taken regarding the inclusion of AE impacts on HRQoL:

1. The assumption that any disutility has already been incorporated in to the base case health state utilities through trial derived EQ-5D utilities, and incorporating an additional disutility could be considered double counting;
2. The assumption that averaged trial-derived utilities underestimate disutilities associated with adverse events, and therefore an additional disutility must be applied.

Consistent with the previous appraisal in this indication (TA406 (NICE, 2016c)), the base case analysis takes the former assumption. However, for completeness, a scenario analysis is included exploring quality of life decrements of adverse events. In this scenario, it is assumed increases in alanine/aspartate aminotransferase, and QT interval prolongations have no impact on quality of life, based on clinical expert feedback. In addition, the cardiac arrest AE is assumed to result in an immediate transition to the death health state, thus a utility decrement cannot be applied. As such, the only disutilities included in the scenario were associated with neutropenia and pneumonitis.

In the scenario analysis, the loss of QALYs per adverse event was calculated as the product of the utility decrement and the duration of the AE. The AE decrement applied in the model for neutropenia, along with the assumed duration of event has been derived from Nafees et al, consistent with previous appraisals in NSCLC (NICE, 2016d; NICE, 2016e; NICE, 2017). Conversely, two separate utilities were identified for pneumonitis. Marti et al 2013 (Marti et

al., 2013) classify pneumonia as a marginal -0.008 decrement, whereas Beusterien et al 2010 (Beusterien et al., 2010) classify grade III/IV pneumonia as a -0.2 decrement. As Beusterien classifies the pneumonia grade, and the grade 5 classification incorporated in the ALEX model is more severe, this higher disutility is considered more appropriate, albeit likely still an underestimation of the impact of this AE. However, caution should be exercised as this study was conducted in chronic lymphocytic leukemia (CLL), not NSCLC. It is assumed the duration of pneumonitis is equivalent to neutropenia. Full details can be found in Table 28.

Table 28: Disutilities due to adverse events: scenario analysis

Adverse event	Disutility	Standard error	Duration [days]	Source
Neutropenia	- 0.09	0.02	5	Nafees *et al.*
Pneumonitis	-0.20	0.02	5	Utility: (Beusterien et al., 2010) Duration: assumption, equivalent to neutropenia

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

As HRQoL was collected using the EQ-5D in the ALEX study, consistent with the NICE reference case, these values are utilised as much as possible. However, as described in section B.3.4.3, there are clear benefits of alectinib treatment that are insufficiently captured by the quality of life derived from the EQ-5D in the ALEX study – the benefits demonstrated in progression in the CNS. As such, for the progressed disease health state, a combination of ALEX quality of life data, ALEX progression data (in the CNS and elsewhere), and literature are utilised. See Table 24.

HRQoL has been captured by assessing a multitude of covariates, to determine which can be considered accurate predictors of quality of life. As a result, utility values are applied in line with the model structure, with two distinct health states: PFS, and PD. This methodology is consistent with previous appraisals accepted by NICE for this indication, and other metastatic oncology indications (NICE, 2016a; NICE, 2016c; NICE, 2016b).

Utilities are applied to the model consistently over time, based on the health state a patient is in. With the exception of an additional age-related utility decrement, HRQoL is assumed constant over time.

As an additional scenario analysis, an option has been included to differentiate the post-progression health state utility in to a 2nd and 3rd line treatment utility, driven by the findings of the SLR:

In post-progression (second line treatment), patients are distributed as per the post progression treatments reported in ALEX (for both arms) to either TKI (47%) or non TKI (53%) treatments and attributed to a TKI or non TKI related utility.

The utility value, and duration in which these utilities are applied for is subject to a number of assumptions:

- 2L post-progression survival (PPS) (TKI-treatments):
    - Utilises the same utility value as the base case, as derived from the ALEX trial
    - 2L PPS TKI-utility is applied for a duration equal to the average estimated mean weeks in PFS of alectinib and ceritinib in the crizotinib-failure setting (as derived from the ASCEND 5 and ALUR phase III trials) and crizotinib in the post-chemotherapy setting (as derived from the PROFILE 1007 trial)
- 2L PPS (non–TKI treatments):
    - Utility value derived from the chemotherapy arm of PROFILE 1007 (See B.3.4.3)
    - 2L PPS non-TKI utility is applied for a duration equal to the estimated mean PFS of patients on chemotherapy in the crizotinib-failure setting (as derived from the ALUR trial)
- 3L PPS:
    - Patients are allocated to a best supportive care (BSC) utility as reported in Nafees et al. 2008
    - Utility is applied for the remaining time in post-progression

Table 29 and BSC, best supportive case; PPS, post-progression survival; TKI, tyrosine-kinase inhibitor.

Table 30 for the utility values and time durations the utilities are implemented for in this scenario analysis.

Table 29: Utility estimates (scenario analysis)

Health state	Utility	Variance	Source
Progression-free for TKIs	[redacted]	[redacted]	ALEX mixed model
PPS 2nd line in PPS for TKI	[redacted]	[redacted]	ALEX mixed model

PPS 2nd line in PPS for non TKI	0.660	0.040	PROFILE 1007 - Docetaxel arm
PPS 3rd line in BSC	0.470	0.101	Nafees et al.2008

BSC, best supportive case; PPS, post-progression survival; TKI, tyrosine-kinase inhibitor.

Table 30: Duration of utility estimates (scenario analysis)

PPS Treatment	Duration 2nd line (weeks)	Source
TKI-treatments 2L PPS		
Ceritinib (2L)	41.9	ASCEND-5 PFS
Alectinib (2L)	60.2	ALUR PFS
Crizotinib (2L)	48.1	PROFILE1007 PFS
Average TKI-related duration	50.1	
Non-TKI-treatments 2L PPS		
Chemotherapy (2L)	8.8	ALUR PFS
3L PPS		
BSC (3L)	Remaining time to death	Assumption

BSC, best supportive case; PPS, post-progression survival; TKI, tyrosine-kinase inhibitor.

However, due to the number of assumptions required for this scenario, this is not considered an appropriate base case analysis.

A summary of all utility values implemented in the cost-effectiveness analysis can be found in Table 31.

Table 31: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (SE)	95% CI	Reference in submission (section and page number)	Justification
HS utilities – base case				
Progression-free state	[redacted]	[redacted]	Section B.3.4.1 Table 24	Derived from EQ-5D data collected during ALEX trial. Methodology in-line with NICE reference case
Progressive disease state (alectinib)	[redacted]	[redacted]		EQ5D data combined with ALEX progression data and literature to appropriately represent the quality of life decrement associated with brain metastases
Progressive disease state (crizotinib)	[redacted]	[redacted]		
HS utilities – scenario analysis: ALEX data				
Progression-free state	[redacted]	[redacted]	Section B.3.4.1 Table 23	Derived from EQ-5D data collected during ALEX trial. Methodology in-line with NICE reference case
Progressed disease state	[redacted]	[redacted]		
HS utilities – scenario analysis: 2 post-progression utilities				
Progression-free state	[redacted]	[redacted]	Section B.3.4.5 Table 29	Derived from EQ-5D data collected during ALEX trial. Methodology in-line with NICE reference case
PPS 2nd line in PPS for TKI	[redacted]	[redacted]		
PPS 2nd line in PPS for non-TKI	0.66 (0.040)	0.582 – 0.734		Assumption: value derived from PROFILE 1007 - Docetaxel arm
PPS 3rd line in BSC	0.47 (0.101)	0.271 – 0.669		Assumption: value derived from Nafees et al.2008
AE-related disutilities – Scenario analysis				

Neutropenia	- 0.09 (0.02)	-0.13, -0.051	Section B.3.4.4 Table 27	AE specific disutility derived using standard gamble methodology in the population of interest. Implementation as a scenario consistent with other appraisals (NICE, 2016c)
Pneumonitis	-0.20 (0.02)	-0.24, -0.16	Section B.3.4.4 Table 27	

AE, Adverse event; CI, Confidence interval; HS, Health state; NICE, National institute for Health and Care Excellence; N/R, Not reported; PPS, post-progression survival, TKI, tyrosine-kinase inhibitor.

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

A systematic literature review (SLR) was conducted to identify published evidence regarding the resource use and costs associated with the management and treatment of ALK-positive NSCLC. Detailed descriptions of the search strategy, search terms and abstraction methods are provided in Appendix I.

Summary of identified studies and results

Four health technology appraisals were identified for inclusion. A brief overview is presented in Table 32. See Appendix I for further details.

Table 32 Summary and results of identified studies

Reference, year [Country]	Patient population	Available cost/resource use data	Cost reference year (currency)	Evaluation of costs (brief summary)	Appropriateness for use
TA406, 2016 (NICE, 2016c) UK	Non-squamous ALK-positive advanced NSCLC	• Health state resource use and costs • Palliative care cost • ALK testing cost	NHS reference costs 2014-2015	• Administration costs of oral treatments should be incorporated • Cost per ALK test is between £75-£153	Overall the resource use evidence submitted was considered relevant to the submission, however, the committee and ERG criticised the exclusion of administration costs in the company's base case analysis. In terms of an appropriate cost for ALK testing, the final committee agreed with the lower cost presented by the manufacturer over the higher cost suggested by the ERG Based on the above comments, and the lack of data on ALK found in the SLR, these estimates may be of use for an economic model for an untreated patient population
TA296, 2013 (NICE, 2013), and updated CDF model, TA422, 2016 (NICE, 2016b) UK	Previously treated NSCLC associated with an ALK fusion gene	• Administration costs • ALK testing costs • Acquisition costs	NHS reference costs 2014-2015	Limited information in resubmission	This technology appraisal document includes estimates of resource use, which may be considered relevant from a UK perspective for previously treated patients Overall, estimates of resource use were accepted by the Committee following the update to the original model to include the committee's preferred assumptions Given the lack of resource use evidence for ALK found in the SLR, these estimates may be of use for an economic model

Reference, year [Country]	Patient population	Available cost/resource use data	Cost reference year (currency)	Evaluation of costs (brief summary)	Appropriateness for use
TA395, 2016 (NICE, 2016a) UK	Previously treated ALK positive NSCLC	• Acquisition costs • Health state resource use and costs • Adverse event costs	NHS reference costs 2014-2015	• ALK testing not a consideration • Dosing should be between 82.8% and 100% • Administration cost: £13.60 was assumed to be associated with each prescription. This was based on the cost of 12 minutes of hospital pharmacists time (hourly rate of a hospital pharmacist £68.00÷5 = £13.60; source: PSSRU – Unit costs of Health and Social Care 2014 • Incorporation of costs of 2 blood tests and 2 outpatient visits for managing abnormal blood tests (AEs)	This technology appraisal document discusses estimates of resource use, which may be considered relevant from a UK perspective for previously treated patients However, as assumptions on resource use were from NICE's technology appraisal guidance on erlotinib for NSCLC and for EGFR-TK mutation-positive NSCLC, the generalisability of the findings to patients with ALK is unknown Overall, estimates of resource use were accepted by the Committee, following updates made to include administration costs, and may therefore, be appropriate for use in economic evaluation

AE, adverse event, ALK, anaplastic lymphoma kinase, BSC, best supportive care, CDF, Cancer Drugs Fund; EGFR, epidermal growth factor receptor; ERG, Evidence Review Group; NHS, National Health Service; NSCLC, non-small cell lung cancer; SLR, systematic literature review; TA, technology appraisal; TK, tyrosine kinase.

B.3.5.1 Intervention and comparators' costs and resource use

B.3.5.1.1 Drug acquisition costs – Intervention and comparator

Drug acquisition costs used in the model for the initial treatments are presented in Table 33. Please note, all costs listed are at list price, however alectinib and crizotinib are both associated with confidential patient access schemes.

- Alectinib: As per the SmPC, the recommended dose is 600 mg administered orally twice-daily (total: 1200 mg). The list price of alectinib is £5,032 per pack (consisting of 224 capsules, 150 mg each).

- Crizotinib: As per the SmPC, the recommended dose is 250 mg administered orally twice daily (total: 500 mg). Two doses are available: 250 mg and 200 mg if a dosing reduction is required. However, both are priced equally at £4,689 per pack. Therefore, the model only utilizes the recommended dose.

As both products are oral treatments, in clinical practice, both would be administered as a full pack at a specified lung cancer clinic, with patients then self-dosing until the following clinic appointment. This is incorporated in to the economic model by assuming wastage – i.e. a full pack cost is applied up front, and therefore if a patient dies or discontinues within the specified administration timeframe, the remaining pack is considered 'waste'. Upon consultation with a number of clinical experts, it was determined lung cancer clinics are held every 4 weeks. Therefore, the base case assumes for both products, the full pack cost is implemented every 4 cycles within the model.

For completeness, a scenario analysis is provided assuming no wastage, where the cost per pack is divided across the treatment cycles.

Table 33: Drug acquisition costs used in the cost-effectiveness model

Drug	Pack concentration	Pack volume	Dose per pack	Cost per pack	Source
Alectinib	150 mg	224	33,600 mg	£5,032.00	BNF
Crizotinib	250 mg	60	15,000 mg	£4,689.00	BNF

B.3.5.1.2 Drug acquisition costs – subsequent treatments

The economic model includes costs and resource use of subsequent treatment for patients who have progressed on either alectinib or crizotinib.

At 25 months follow up, approximately 48% of patients were still on treatment with alectinib, and 27% of patients were still on treatment with crizotinib. Subsequent therapies were not routinely captured after a patient discontinued treatment; therefore we do not have a complete data set of post-discontinuation therapies (distribution of treatments, time on subsequent treatment). In total, only 41% of the ALEX population that have progressed have been captured as receiving at least 1 subsequent therapy. In addition, of those captured, a number of subsequent treatments, and the distribution of treatments, are not considered consistent with clinical practice in the UK (see Section B.1.3.2)

Therefore, clinical expert opinion was sought to determine the appropriate distribution of costs and resource use for this population.

As of October 2017, the following treatment options are recommended by NICE for use as second-line treatments for patients with ALK-positive NSCLC:

- Crizotinib is recommended, within its marketing authorisation, as an option for previously treated anaplastic lymphoma kinase-positive advanced non-small cell lung cancer in adults [TA422]

- Ceritinib is recommended, within its marketing authorisation, as an option for treating advanced anaplastic lymphoma kinase positive non-small cell lung cancer in adults who have previously had crizotinib [TA395]

In addition, alectinib also has a marketing authorization in the crizotinib-failure indication (not NICE recommended), and there are a number of other ALK-inhibitors with named patient programmes or clinical trials ongoing in the second line setting either irrespective of 1L treatment, or specifically for treatment after alectinib (ClinicalTrials.gov NCT02513667, 2016; ClinicalTrials.gov NCT01970865, 2017; ClinicalTrials.gov NCT02927340, 2017; ClinicalTrials.gov NCT02584634, 2017; ClinicalTrials.gov NCT02706626, 2017; ClinicalTrials.gov NCT02450903, 2017; ClinicalTrials.gov NCT02292550, 2017). Based on internal market research, approximately 8% of NSCLC patients in the UK enter clinical trials for 2L therapies. It is anticipated this value is higher for ALK-positive NSCLC.

Other second line therapies for the broader NSCLC population include docetaxel, nintedinib+docetaxel, pembrolizumab and nivolumab.

Upon consultation with clinical experts, it was determined subsequent immunotherapies should be excluded due to the limited evidence available demonstrating their benefit in this

population, consistent with the limited usage witnessed in ALEX. In addition, nintedanib was excluded as real world usage of this treatment is significantly limited. Finally, whilst named patient programmes or clinical trials are valid and attractive options for treatment after alectinib or crizotinib failure, without marketing authorization, costs cannot be accrued to these treatments from the NHS or social services perspective.

As such, the remaining subsequent treatment options are ceritinib, crizotinib and docetaxel.

When consulted on with clinical experts, there was considerable uncertainty regarding whether crizotinib was a possible treatment option after alectinib. Many were concerned the crizotinib recommendation was specifically limited to post-chemotherapy and therefore would not apply for use after alectinib. However, given both the marketing authorization and NICE guidance specifically states “previously treated ALK-positive advanced NSCLC” it is assumed this is an appropriate subsequent therapy for alectinib. However, to take account of these concerns, as well as other concerns regarding anticipated MOA interactions, in the base case, subsequent therapy share for alectinib patients is distributed between crizotinib and chemotherapy, again consistent with the ALEX subsequent treatments.

Conversely, clinical experts were unanimous when considering subsequent therapies for use after crizotinib.

The resulting breakdown of the estimated proportion of patients expected to receive each subsequent treatment is given below in Table 34.

Table 34: Base case breakdown of subsequent therapy share

Drug	Alectinib arm	Crizotinib arm
Ceritinib	0%	90%
Crizotinib	60%	0%
Docetaxel	40%	10%

However, it is acknowledged there is considerable uncertainty surrounding these proportions, as demonstrated in clinical expert uncertainty, and particularly due to future anticipated marketing authorizations. Therefore, a number of scenario analyses have been conducted around these values: Firstly, utilizing the alternative distribution highlighted by clinical experts, secondly equalizing the post-TKI proportions across arms, and thirdly utilizing the anticipated distribution that would have been witnessed in the ALEX trial, had

only ceritinib, crizotinib and docetaxel been available (see Table 35). Results can be found in Section B.3.8.

Table 35: Subsequent therapy scenarios

Scenario	Drug	Alectinib arm	Crizotinib arm
1: Clinical expert alternative breakdown of subsequent therapy share	Ceritinib	0%	90%
	Crizotinib	10%	0%
	Docetaxel	90%	10%
2: Equalizing of TKI subsequent therapy share	Ceritinib	0%	90%
	Crizotinib	90%	0%
	Docetaxel	10%	10%
3: Distribution as per ALEX *	Ceritinib	8.9%	79%
	Crizotinib	20.1%	0%
	Docetaxel	71%	21%

* Alectinib: 71% non-TKI, 29% TKI. Of TKIs, ceritinib = 5.9%, crizotinib = 13.2%. Crizotinib: 21% non-TKIs, 79% TKIs.
TKI, tyrosine-kinase inhibitor.

For simplicity purposes, subsequent therapy costs (including acquisition and administration) are applied on a weekly basis, based on the anticipated duration of subsequent therapies.

The costs per cycle for the subsequent therapies included in the model are given below in

Table 36. Please note: all costs provided are at list price. However, ceritinib, alectinib and crizotinib are subject to confidential Patient Access Schemes.

Table 36: Drug acquisition costs (subsequent treatments, list price)

Drug	Dose/vial/pack concentration	Pack size/vial volume	Dose per day	Cost per pack/vial	Cost per cycle	Source
Alectinib	150 mg	224	1200 mg	£5,032	£1,262	UK list price
Crizotinib	250 mg	60	500 mg	£4,689	£1,098	DMD
Ceritinib	150 mg	150	750 mg	£4,923	£1,153	DMD
Docetaxel (w/o vial sharing)	10 mg/ml	1ml	75 mg/m²	£3.85	£20.62	eMIT
		4ml		£12.38		
		7ml		£20.62		
		8ml		£20.44		
Docetaxel (w vial sharing)	10 mg/ml	1ml	75 mg/m²	£3.85	£19.13	eMIT
		4ml		£12.38		
		7ml		£20.62		
		8ml		£20.44		

DMD, Dictionary of Medicines and Devices; eMIT, electronic market information tool; w, with; w/o, without.

These acquisition costs are applied, in combination with the relevant administration costs every cycle for as long as patients are deemed to be on second line therapy.

The duration of time a patient is deemed to be on second line therapy is an additional limitation of the post-discontinuation ALEX data. As the ALEX trial follow-up is not sufficiently long to accurately reflect the length of time on subsequent therapies in clinical practice, assumptions were required. Therefore, the mean weeks of treatment were derived from clinical trials and published literature in the second line setting. This data is given below in Table 37.

Table 37: Subsequent therapies - treatment duration

Drug	Mean weeks of treatment duration	Source
Ceritinib	41.89	ASCEND - 5
Alectinib	60.20	ALUR
Crizotinib	48.14	PROFILE 1007
Docetaxel	8.83	ALUR

B.3.5.1.3 Drug administration costs

Intervention and Comparator

Both alectinib and crizotinib are oral medications: administered as a full pack at a specified lung cancer clinic with patients then self-dosing until the following clinic appointment. Upon consultation with a number of clinical experts, it was determined lung cancer clinics are held every 4 weeks, consistent with the pack size of alectinib. Therefore, consistent with committee-preferred assumptions from previous appraisals in this indication (NICE, 2016c), (NICE, 2016a), an administration cost of pharmacist time is applied every 4 cycles within the model (see Table 38).

Table 38: Drug administration costs: 1L treatments

Drug	Type of administration		NHS reference code	Cost per administration	Source
Intervention					
Alectinib	12 minutes pharmacist time every 4 weeks	Hospital pharmacist (band 6); radiographer cost per working hour	N/A	£46 per hour = £9.20 per administration	PSSRU 2016
Comparator					
Crizotinib	12 minutes pharmacist time every 4 weeks	Hospital pharmacist (band 6); radiographer cost per working hour	N/A	£46 per hour = £9.20 per administration	PSSRU 2016

N/A, Not applicable; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.

Subsequent therapies

For simplicity purposes, subsequent therapy costs (including acquisition and administration) are applied on a weekly basis, based on the anticipated duration of subsequent therapies.

The administration cost of docetaxel is assumed to be that of a simple chemotherapy (as described in the NHS reference costs). This is consistent with other appraisals in 2L NSCLC (NICE, 2011; NICE, 2016d; NICE, 2016e; NICE, 2017). Docetaxel is administered on a 3-weekly cycle.

All three ALK inhibitors are oral therapies, only requiring a cost of pharmacist time per administration (every 4 weeks).

A full breakdown of administration costs for subsequent treatments applied in the model is given in Table 39.

Table 39: Drug administration costs: subsequent treatments

Drug	Type of administration		NHS reference code	Cost per administration	Cost per week	Source
Alectinib	12 minutes pharmacist time every 4 weeks	Hospital pharmacist (band 6); radiographer cost per working hour	N/A	£46 per hour = £9.20 per administration	£2.30	PSSRU 2016
Crizotinib	12 minutes pharmacist time every 4 weeks	Hospital pharmacist (band 6); radiographer cost per working hour	N/A	£46 per hour = £9.20 per administration	£2.30	PSSRU 2016
Ceritinib	12 minutes pharmacist time every 28 days	Hospital pharmacist (band 6); radiographer cost per working hour	N/A	£46 per hour = £9.20 per administration	£2.30	PSSRU 2016
Docetaxel	Deliver simple Parenteral Chemotherapy at first attendance	Outpatient setting	SB12Z	£198.94	£66.31	NHS reference costs 2015-16

N/A, Not applicable; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.

B.3.5.2 Health-state unit costs and resource use

Supportive care costs are applied for both PFS, and PD health states. PD is defined as any progression, irrespective of location. However, as depicted in the literature (Guerin et al., 2015; Peters et al., 2016), and based on clinical expert opinion, there is a considerable extra cost burden if a patient progresses in the CNS. Therefore, two PD costs have been defined, based on progression location, and the overall health state cost is a weighted average, driven by the proportion of progressions witnessed in each location as per the ALEX trial.

The types of resource and frequency of use are derived from the SLR, previous technology appraisals and validated by UK clinicians. Unit costs were derived from NHS reference costs.

Table 40 details the resource use for PFS health state and Table 41 describes the resource use in PD. Table 41 shows the additional resource use for PD health state due to brain metastases. Unit costs are details in Table 43.

Table 40: Resource use for PFS health state

Resource	No. required per month	% of patient requiring resource	Unit cost	Cost per month	Source
Consultant-led outpatient visit / oncologist	0.75	100%	£167.08	£125.31	(NICE, 2016c)
GP visit	1	10%	£45.68	£4.57	(NICE, 2016c)
Cancer nurse	1	50%	£67.30	£33.65	(NICE, 2016c) Further input provided from clinical experts
Full blood test	1	100%	£3.10	£3.10	(NICE, 2016c) Further input provided from clinical experts
Biochemistry	1	100%	£1.18	£1.18	(NICE, 2016c) Further input provided from clinical experts
CT scan	0.5	100%	£118.53	£59.27	(NICE, 2016c) Further input provided from clinical experts
MRI scan	0.2	50%	£202.70	£20.27	Clinical expert opinion
X ray	0.3	50%	£37.30	£5.56	Clinical expert opinion
ECG	1	100%	£71.44	£71.44	Clinical expert opinion
Total cost per month	£324.35				
Total cost per weekly cycle	£74.86				

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

Table 41: Resource use for PD health state (irrespective of progression location)

Resource	No. required per month	% of patient requiring resource	Unit cost	Cost per month	Source
Consultant-led outpatient visit / oncologist	1.25	100%	£167.08	£208.85	(NICE, 2016c) Further input provided from clinical experts
GP outpatient visit	1	50%	£45.68	£22.84	(NICE, 2016c) Further input provided from clinical experts

Cancer nurse	1.5	80%	£67.30	£80.76	(NICE, 2016c) Further input provided from clinical experts
Full blood test	1.5	100%	£3.10	£4.65	(NICE, 2016c) Further input provided from clinical experts
Biochemistry	1.5	100%	£1.18	£1.77	(NICE, 2016c) Further input provided from clinical experts
CT scan	0.75	100%	£118.53	£88.90	(NICE, 2016c) Further input provided from clinical experts
MRI scan	0.5	80%	£202.70	£81.08	Clinical expert opinion
X ray	0.5	60%	£37.30	£11.19	(NICE, 2016c) Further input provided from clinical experts
Total cost per month	£500.04				
Total cost per week	£115.40				

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

Table 42: Additional resource use for PD health state: brain metastases

Product	Resource	% of patient requiring resource	Lifetime exposure limit	Average time in PD	Unit cost	Cost per lifetime exposure	Cost per month
Alectinib	Stereotactic radiotherapy	100%	6 doses	30.7 months	£3,243.60	£19,462	£632.04
Crizotinib				35.1 months			£554.53
Source		Clinical expert opinion		Based on economic model	Table 43	Lifetime exposure * unit cost	Cost per lifetime exposure / average time in PD
Total cost per week: alectinib	+ £146.32						
Total cost per week: crizotinib	+ £127.97						

PD, progressive disease.

Table 43: Unit costs (PFS and PD health states)

Resource	Unit cost	Source
Consultant-led outpatient visit / oncologist	£167.08	NHS reference costs (2015-16) Medical oncology (code: 370), consultant-led appointment

GP visit	£45.68	PSSRU 2016 10.8b: Per patient contact lasting 11.7 minutes, including direct care staff costs, with qualification costs
Cancer nurse	£67.30	NHS reference costs 2014-2015; Nurse cancer relate adult face-t-face (N10AF); Inflated to 2015/16 using PSSRU (2016)
Full blood test	£3.10	NHS reference costs (2015-16) DAPS05: direct access pathology; haematology
Biochemistry	£1.18	DAPS04 NHS reference costs (2015-2016)
CT scan	£118.53	NHS reference costs (2015-16) RD22Z: Computerised Tomography Scan of one area, with pre and post contrast
MRI scan	£202.70	NHS reference costs (2015-16) RD03Z; Magnetic Resonance Imaging Scan of One Area, with Pre- and Post-Contrast
X ray	£37.30	NHS reference costs (2015-16) Diagnostic imaging (code: 812), unit cost (weighted average of consultant-led and non-consultant-led appointments)
ECG	£71.44	NHS reference costs (2015-16) RD51A Simple Echocardiogram, 19 years and over
Stereotactic radiotherapy	£3,243.60	NHS reference costs (2015-2016) AA71A; Stereotactic intracranial radiosurgery for neoplasms or other neurological conditions, with CC score 4+

CC, critical care; CT, computerised tomography; ECG, electrocardiogram; GP, general practitioner; MRI, magnetic resonance imaging; PFS, progression-free survival; PD, progressive disease; PSSRU, Personal Social Services Research Unit.

The total cost per week in the PFS health state is £74.86.

The supportive care cost per week irrespective of progression location is £115.40, with the additional cost per week of a progression in the CNS of £146.32 for alectinib (total: £261.71) and £127.97 for crizotinib (total: £243.37).

The same approach was taken to that described in section B.3.4.3, whereby the total supportive care cost in PD is a weighting of the proportion of patients with CNS progression (74% in crizotinib, 29% in alectinib), and the patients with progression elsewhere, multiplied by the supportive care cost of progression in each location. This resulted in a cost per week of £157 on alectinib, and £210 on crizotinib.

Finally, the resulting PD health state cost per treatment arm is a product of the total supportive care cost per week in PD, the distribution of subsequent therapies (Table 35), the acquisition cost of subsequent therapies (

Table 36), and the administration cost of subsequent therapies (Table 39). Based on the assumptions above, and list prices, the total cost per week in the PD health state for crizotinib is £496.77, and for alectinib is £398.41.

As detailed above, there is uncertainty regarding the distribution of subsequent therapies. Therefore, these figures are explored as a sensitivity analysis.

An end of life/terminal care cost is applied to patients who enter the death state as a one off cost, in line with previous appraisals in NSCLC (NICE, 2011; NICE, 2017; NICE, 2016d; NICE, 2016e; NICE, 2015). The terminal care cost reflects the resource consumption in various care settings, and is weighted by the proportion of patients treated in each setting. This cost is assumed equal for all treatments. Resource use and costs are shown in Table 44 and Table 45. The total cost of end of life is £3,679.37.

Table 44: Resource use for terminal care/end of life

Resource	Number required	Reference	% of patients in each setting	Source
Hospitalisation admission (+excess bed days)	1 (+0.84 excess bed days)	(NICE, 2011; NICE, 2016d; NICE, 2016e; NICE, 2015; NICE, 2017).	55.8%	(NICE, 2011; NICE, 2016d; NICE, 2016e; NICE, 2015; NICE, 2017).
Hospice care	1.00		16.9%	
Macmillan Nurse (home setting)	50	Marie Curie Cancer Care	27.3%	

Table 45: Resource costs for terminal care

Resource	Unit cost	Reference	Weighted unit cost	Total cost of care in each setting
Hospitalisation admission (+excess bed days)	£4051.39 (+ £211.03 for 0.84 excess bed days) =£4,262.42	NHS reference costs 2015-16 (Department of Health 2016) Respiratory Neoplasms without intervention, with CC score 13+ (currency code DZ17S), Non-elective inpatient stay – long stay	£2,378.43	£2,378.43
Macmillan Nurse (home setting)	£29.33 Assumed 2/3 of the cost of a community	(NICE, 2016d; NICE, 2016e; NICE, 2015; NICE, 2017), PSSRU 2016 (10.1)	£8.01	£400.50

	nurse: £44 per working hour, based on average salary of £31,902 equating to Band 6.			
Hospice care	£5,328.03 Assumed 25% increase on hospitalisation setting)	(NICE, 2016d; NICE, 2016e; NICE, 2015; NICE, 2017)	£900.44	£900.44
Total cost				£3,679.37

B.3.5.3 Adverse reaction unit costs and resource use

All grade 3 and 4 treatment-related AEs with an incidence of ≥3% in either the alectinib or crizotinib arms of the ALEX trial (primary population ITT who received any dose), and all grade 5 treatment-related AEs irrespective of incidence are included in the base case analysis.

The costs of treating AEs are per episode. Where possible, the National Schedule of Reference Costs (2015/16) was used to cost AEs. Where there were gaps in the data, costs were sourced from prior NICE submissions and inflated to the appropriate costing year.

The weekly rate of occurrence for each AE is implemented in the model through the overall probability of any patient experiencing the event in any given cycle (see Table 46). This is calculated by using number of AE occurrences divided by the total time (weeks) at risk, which is the sum of the average time on treatment for each patient in the trial. The probability of any patient experiencing the event is then multiplied by the average management costs of the AE to obtain an adverse event cost per patient per week (cycle).

The proportions of patients experiencing each AE are provided in Table 46, while the treatments and associated costs are described in Table 47 to Table 49.

Table 46: Adverse events included in the economic model

	Alectinib		Crizotinib	
Adverse Event	**Events observed**	**Probability of event (per week)**	**Events observed**	**Probability of event (per week)**
Alanine Aminotransferase Increased	7	0.0007	25	0.0035

Aspartate Aminotransferase Increased	10	0.0010	17	0.0023
Cardiac Arrest	0	0.0000	1	0.0001
QT interval prolongation	0	0.0000	6	0.0008
Neutropenia	0	0.0000	13	0.0018
Pneumonitis	0	0.0000	3	0.0004

Table 47: Treatments associated with AEs

Adverse reactions	Treatment	Source
Alanine Aminotransferase Increased	• 2 additional blood tests • 2 outpatient visits	(NICE, 2016a)
Aspartate Aminotransferase Increased	• 2 additional blood tests • 2 outpatient visits	(NICE, 2016a)
Cardiac Arrest	• Hospitalisation	NHS reference costs (2014-15) EB05A: Cardiac Arrest with CC Score 9+
QT interval prolongation	• 2 additional blood tests • 2 ECGs	Clinical expert opinion (NICE, 2016a)
Neutropenia	• Hospitalisation	(NICE, 2016d; NICE, 2016e; NICE, 2017)
Pneumonitis	• Hospitalisation	NHS reference costs (2014/15): DZ11T: Lobar, Atypical or Viral Pneumonia, without Interventions, with CC Score 7-9

CC, critical care; ECG, electrocardiogram; NHS, National Health Service.

Table 48: Unit costs of AE treatments

Resource	Unit cost	Source
Blood test	£3.10	NHS reference costs (2015-16) DAPS05: direct access pathology; haematology
Outpatient visit	£167.08	NHS reference costs (2015-16) Medical oncology (code: 370), consultant-led appointment
ECG	£71.44	NHS reference costs (2015-16) RD51A Simple Echocardiogram, 19 years and over
Cardiac Arrest	£2291.93	NHS reference costs (2014-15) EB05A: Cardiac Arrest with CC Score 9+
Pneumonitis	£2783.99	NHS reference costs (2014/15) DZ11T: Lobar, Atypical or Viral Pneumonia, without Interventions, with CC Score 7-9

CC, critical care; ECG, electrocardiogram; NHS, National Health Service.

Table 49: Summary of adverse reactions and costs used in the economic model

Adverse reactions	Unit cost	Source
Alanine Aminotransferase Increased	£340.36	Table 47, CC, critical care; ECG, electrocardiogram; NHS, National Health Service. Table 48
Aspartate Aminotransferase Increased	£340.36	Table 47, CC, critical care; ECG, electrocardiogram; NHS, National Health Service. Table 48
Cardiac Arrest	£2291.93	Table 47, CC, **critical care; ECG, electrocardiogram; NHS, National Health Service.** **Table 48**
QT interval prolongation	£149.08	Table 47, CC, critical care; ECG, electrocardiogram; NHS, National Health Service. Table 48
Neutropenia	£362.66	(NICE, 2016d; NICE, 2016e; NICE, 2017)
Pneumonitis	£2783.99	Table 47, CC, **critical care; ECG, electrocardiogram; NHS, National Health Service.** **Table 48**

B.3.5.4 Miscellaneous unit costs and resource use

ALK test costs

In the base case, the expected cost per patient to identify one ALK-positive patient from a cohort of all patients with NSCLC is applied to both the ALK inhibitor treatment arms. This is the cost of one test multiplied by the number of patients needed to be tested to identify one ALK-positive patient. Only acquisition costs of the tests were considered, as the NHS already has the infrastructure in place to perform and analyse such tests.

The cost is applied at the beginning of the first cycle in the model alongside drug acquisition costs. Based on a cost per test of £75.00, the resulting cost of identifying a person with the ALK mutation is estimated to be £2,380. This figure was considered within an appropriate range by the committee in the NICE appraisal of crizotinib in the first-line treatment of ALK+ NSCLC (NICE, 2016c). However, as this cost is applied to both treatment arms, there is no impact on the ICER through any variation of this figure.

B.3.6 Summary of base-case analysis inputs and assumptions

B.3.6.1 Summary of base-case analysis inputs

Table 50 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	30 years	Fixed	B.3.2
Discount rate - efficacy	3.5%	Fixed	
Discount rate - costs	3.5%	Fixed	
Population parameters			
Age	55.05 years	Fixed	NR
Body weight	66.60 kg	Fixed	
Height	164.70 cm	Fixed	
Body surface area	1.73 m^2	Fixed	
Clinical inputs			
Assessment of progression	IRC	Fixed	B.3.3
Parametric curves			
PFS – alectinib	KM+Exponential	Multivariate normal	B.3.3
PFS – crizotinib	KM+Exponential	Multivariate normal	
OS – alectinib	Exponential	Multivariate normal	
OS – crizotinib	Exponential	Multivariate normal	
Utilities – base case			
Progression-free	[redacted]	[redacted]	B.3.4.1
Progressed disease (alectinib)	[redacted]	[redacted]	
Progressed disease (crizotinib)	[redacted]	[redacted]	
Utilities – Scenario analysis – ALEX data only			
Progression-free	[redacted]	[redacted]	B.3.4.1
Progressed disease	[redacted]	[redacted]	
Utilities – scenario analysis – 2 post progression utilities			
Progression-free state	[redacted]	[redacted]	B.3.4.5
PPS 2nd line in PPS for TKI	[redacted]	[redacted]	
PPS 2nd line in PPS for non TKI	0.66	0.582 – 0.734 - Beta	
PPS 3rd line in BSC	0.47	0.271 – 0.669 - Beta	
Adverse event disutilities – scenario analysis			
Neutropenia	-0.09	-0.13, -0.051 - Beta	B.3.4.4
Pneumonitis	-0.20	Beta	
Technology acquisition costs per pack (unit costs at list price)			
Alectinib	£5,032.00	Fixed	B.3.5.1
Crizotinib	£4,689.00	Fixed	
Ceritinib	£4,923.00	Fixed	
Docetaxel – 8ml	£20.44	Fixed	
Administration costs: Intervention and Comparator – per administration			
Alectinib	£9.20	Fixed	B.3.5.1
Crizotinib	£9.20	Fixed	
Administration costs: Subsequent therapies – per week			
Alectinib	£2.30	Fixed	B.3.5.1

Crizotinib	£2.30	Fixed	
Ceritinib	£2.30	Fixed	
Docetaxel	£66.31	Fixed	
Supportive care costs			
PFS	£74.86	£60.69 - £89.83 - Normal	B.3.5.2
PD (alectinib)	£398.41	£403.65 - £602.55 - Normal	
PD (crizotinib)	£496.77	£317.41 - £473.81 - Normal	
Terminal care cost			
Terminal care cost	£3,679.37	£1,839.69 - £5,519.06 – Normal	B.3.5.2
Adverse event management costs			
Alanine Aminotransferase inc.	£340.36	Lognormal distribution	B.3.5.3
Aspartate Aminotransferase inc.	£340.36	Lognormal distribution	
Cardiac Arrest	£2,291.93	Lognormal distribution	
QT interval prolongation	£149.08	Lognormal distribution	
Neutropenia	£362.66	Lognormal distribution	
Pneumonitis	£2,783.99	Lognormal distribution	
Subsequent treatment			
Treatment distribution: alectinib	Table 35	Beta	B.3.5.1
Treatment distribution: crizotinib	Table 35	Beta	
Cost of ALK test			
Cost of identifying a person with the ALK mutation	£2,380	Fixed	B.3.5.4

ALK, anaplastic lymphoma kinase; BSC, best supportive care; CI, confidence interval; ECG, Electrocardiogram; Inc., Increase; KM, Kaplan-Meier; OS, Overall survival; PD, Progressive disease; PFS, Progression-free survival; PPS, post-progression survival.

B.3.6.2 Assumptions

Table 51 Key assumptions used in the economic model (base case)

Area	Assumption	Justification
Time horizon	30 years	Life-time equivalent consistent with NICE reference case, reflective of the updated treatment pathway
Comparator	Crizotinib	Based on UK clinical practice and consistent with ALEX data
Clinical efficacy and safety	Efficacy and safety results for alectinib seen in the ALEX study are transferable to UK population	Expert clinical advice suggests the outcomes seen from the study are expected in UK patients given the similarity of patient characteristics between the trial and real-world, and the inclusion of UK sites and patients in ALEX.
Survival: OS	Exponential	Best fit to combined data on AIC / BIC. Provides the second closest estimate of 4 year OS to the long-term PROFILE1014 evidence. Deemed clinically plausible for long-term extrapolation. In line with DSU guidance, separate parametric models of the same type should be fit to each arm, therefore Exponential applied to both arms
Survival: PFS	KM+Exponential	Exponential deemed the most clinically plausible long-term extrapolation for alectinib, with poor fitting to both curves initially, therefore KM utilized for 6 months, and exponential tail added beyond
Treatment duration	Alectinib treatment duration is equivalent to PFS	As per the SmPC, alectinib is administered until disease progression or unacceptable toxicity PFS and TTOT KM data within trial is extremely similar
Supportive care cost: progression in CNS	Additional cost associated with supportive care if a patient progresses in the CNS.	Clinical expert opinion and literature, highlight the additional cost burden for a progression in the CNS, notable: WBRT. Clinical experts confirmed there is a lifetime exposure limit of WBRT, thus the weekly cost applied is a function of cost per lifetime exposure, and the average time a patient is in PD, as detailed in the economic model
Total supportive care cost in PD	Total cost of supportive care in PD is a weighted average of supportive care cost with and without progression in the CNS, based on the proportion of patients with and without progression in the CNS based on ALEX	Alectinib has demonstrated a protective effect of progression in the CNS, resulting in few progressions in the CNS, as opposed to progression elsewhere. As such, the total supportive care cost in PD is lower than crizotinib
End of life cost	Based on previous NICE TAs	Applied as a one off cost for all patients who die to take into consideration the added expense of terminal care

HRQoL	Based on EQ-5D data collected in ALEX, varied by health state	Consistent with previous appraisals
	Lower utility applied to the proportion of patients who progress in the CNS	Unable to capture decrement in ALEX EQ-5D data, but is a significant driver of quality of life, therefore literature utilised to capture the full benefits of alectinib
	Omission of AE disutilities in the base case analysis	The disutility associated with AEs was assumed to have been captured in the EQ-5D responses in ALEX. This is in-line with the approach taken in past appraisals in this disease area. See section B.3.4.4 for more details.
Safety	Grade 3 and 4 treatment related adverse events experienced by ≥ 3% of patients in either arm of ALEX, and all grade 5 treatment related AE irrespective of incidence are included in the analysis	Conservative approach
Subsequent treatment	Adaptation of captured subsequent therapies from ALEX to those most relevant to UK clinical practice	In line with clinical expert feedback
	Proportion of patients receiving a subsequent treatment in clinical practice	Clinical experts gave estimates of the proportion of patients who would receive each type of intervention as a second line therapy in clinical practice.

AE, adverse event; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; CNS, central nervous system; DSU, Decision Support Unit; KM, Kaplan-Meier; OS, overall survival; PD, progressive disease; PFS, progression-free survival; TTOT, time to off-treatment; UK, United Kingdom; WBRT, whole brain radiotherapy.

B.3.7 Base-case results

B.3.7.1 Base-case incremental cost-effectiveness analysis results

Base-case results of the economic model are presented below.

Alectinib provided a QALY gain of 3.73, and a life-year gain of 5.11, at a total drug cost of £172,025, and total overall cost of £239,894 at list price. In contrast, crizotinib provides a QALY gain of 2.70, and a life-year gain of 4.25, at a total cost of £169,665 at list price.

As such, the resulting ICER versus crizotinib is £68,146 per QALY gained. [redacted] However, crizotinib is associated with a PAS, at an unknown level of discount; therefore the analysis could not be conducted at the with-PAS price level.

See Table 52 for a summary of the base case results.

It should be highlighted: caution should be exercised when analysing the resulting ICERs, as a considerably conservative assumption of the overall survival benefit of alectinib has been taken, driven by the immature data , as discussed in section B.3.3.4,.

Table 52: Base-case results (without PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Crizotinib	£169,665	4.25	2.70				
Alectinib	£239,894	5.11	3.73	£70,229	0.86	1.03	£68,146

ICER, incremental cost-effectiveness ratio; Incr, incremental; LYG, life years gained; QALYs, quality-adjusted life years

B.3.8 Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

To assess the uncertainty surrounding the variables included in the cost-effectiveness model, a probabilistic sensitivity analysis (PSA) was undertaken using 1,000 samples. The mean values, distributions around the means, and sources used to estimate the parameters are detailed in section B.3.6.

Results of the PSA compared to deterministic results are presented in Table 53. The scatterplot in ICERs, incremental cost-effectiveness ratios; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years.

Figure 18 shows the iterations and the cost effectiveness acceptability curve is shown in Figure 19.

The analyses below are based on the list price of alectinib. Please see the confidential PAS Appendix (Appendix N) for PSA results incorporating the alectinib PAS. Crizotinib is associated with a confidential patient access scheme, thus analyses could not be conducted on this.

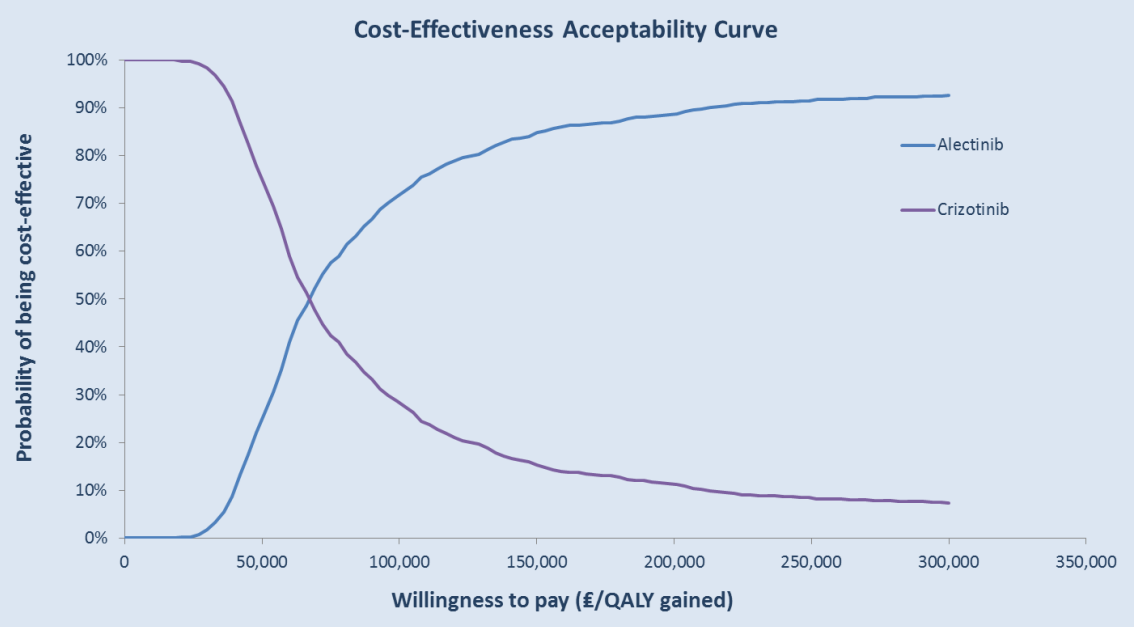
Table 53: PSA results compared to base-case (without PAS)

	Costs		QALYs		ICERs	
	Base case	PSA	Base case	PSA	Base case	PSA
Crizotinib	£169,665	£167,253	2.70	2.71		
Alectinib	£239,894	£238,023	3.73	3.75	£68,146	£67,703

ICERs, incremental cost-effectiveness ratios; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years.

Figure 18: Cost-Effectiveness Plane

Figure 19: Cost-Effectiveness Acceptability Curve



B.3.8.2 Deterministic sensitivity analysis

The choice of parameters to include in univariate analysis was considered a-priori, and further informed by the results in section B.3.7, with focus on the parameters providing greatest impact on the percentage increment in costs or QALYs, thus having the greatest impact on the resulting ICER. The parameter values used in the analyses which had the greatest impact on the results can be found in Table 54 below. Generally, the base case

value of parameters were varied across a +/- 50% range, with the exception of the utility values. Results of the analyses using alectinib list price are displayed in Figure 20.

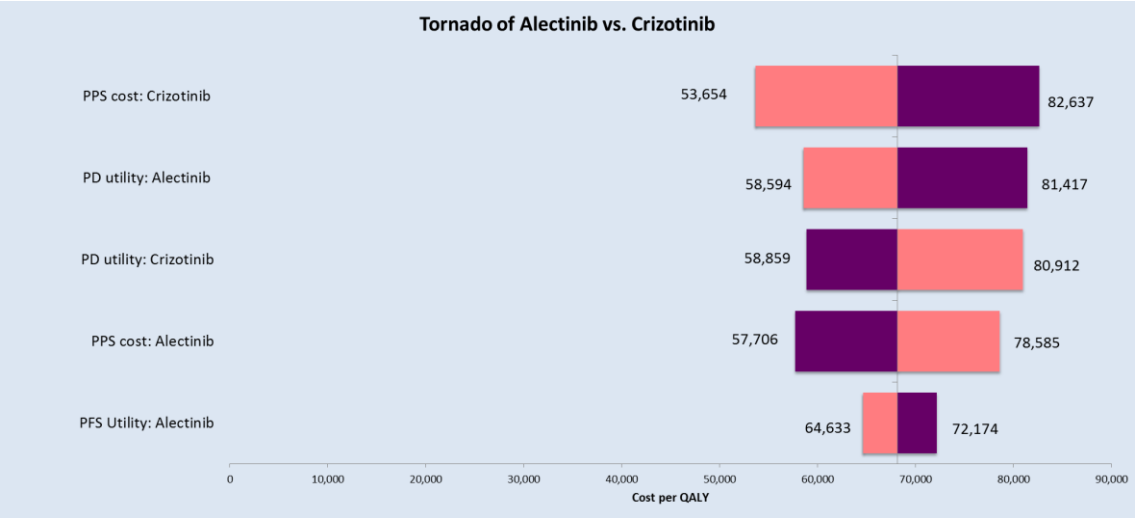
For the results of the deterministic sensitivity analysis with-PAS, please see the confidential PAS Appendix (Appendix N).

Table 54: Parameter values for univariate sensitivity analysis

Parameter	Base case value	Lower value	Higher value
PFS Utility: Alectinib	0.81	0.791	0.836
PFS Utility: Crizotinib	0.81	0.791	0.836
PD utility: Alectinib	0.666	0.600	0.733
PD utility: Crizotinib	0.573	0.516	0.631
PFS cost: Alectinib	£74.86	£60.06	£89.66
PFS cost: Crizotinib	£74.86	£60.06	£89.66
PPS cost: Alectinib	£394.88	£316.82	£472.94
PPS cost: Crizotinib	£479.50	£384.72	£574.29
Terminal care cost	£3679.37	£1839.69	£5519.06
Administration cost: Crizotinib	£9.20	£4.60	£13.80
Administration cost: Alectinib	£9.20	£4.60	£13.80
ALK test cost: Alectinib	£2380.00	£1190	£3570
AE cost: Alectinib	£0.60	£0.30	£0.90
AE cost: Crizotinib	£4.13	£2.07	£6.20

AE, adverse event; ALK, anaplastic lymphoma kinase; PD, progressive disease; PFS, progression-free survival; PPS, post-progression survival.

Figure 20: Tornado diagram



B.3.8.3 Scenario analysis

Scenario analyses were conducted to assess uncertainty around structural assumptions of the model. Without-PAS results are shown in Table 55 (for with-PAS, please see the confidential PAS Appendix – Appendix N) for the following scenarios exploring parameter changes:

- Alternative wastage assumptions (see B.3.2.3)
- Alternative plausible OS Extrapolations (see B.3.3.4)
- Capping of OS benefit (see B.3.3.4)
- Alternative plausible PFS Extrapolations (see B.3.3.5)
- PFS as assessed by investigators (INV) (see B.3.3.5)
- Alternative utilities (see B.3.4.5)
- Alternative subsequent therapy distributions (see B.3.5.1)
- Disutility for AEs (see B.3.5.3)

Table 55: Scenario analyses

		Alectinib			Crizotinib			Alectinib vs Crizotinib
	Description	Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Total costs	ICER
Wastage	Wastage (base case)	5.11	3.73	£239,894	4.25	2.70	£169,665	£68,146
	No wastage	5.11	3.73	£238,586	4.25	2.70	£162,996	£73,348
OS distribution	Exponential (base case)	5.11	3.73	£239,894	4.25	2.70	£169,665	£68,146
	Weibull	5.83	4.26	£245,840	3.11	2.08	£162,946	£38,037
	Log-normal	7.91	6.01	£267,790	5.06	3.13	£174,422	£32,408
	Gamma	7.13	5.35	£259,971	5.72	3.48	£178,232	£43,572
	Log logistic	7.04	5.31	£259,784	4.49	2.82	£171,021	£35,617
Capping of OS and PFS treatment effect duration	No cap (base case)	5.11	3.73	£239,894	4.25	2.70	£169,665	£68,146
	3 years	4.63	3.35	£208,809	4.25	2.70	£169,665	£60,343
	5 years	4.80	3.49	£224,306	4.25	2.70	£169,665	£69,231
	7 years	4.91	3.58	£231,921	4.25	2.70	£169,665	£70,956
	10 years	5.01	3.65	£236,730	4.25	2.70	£169,665	£70,440
PFS distribution	KM+ Exponential (base case)	5.11	3.73	£239,894	4.25	2.70	£169,665	£68,146
	Exponential	5.11	3.76	£250,228	4.25	2.70	£169,741	£76,306
	Weibull	5.13	3.86	£296,751	4.25	2.67	£162,478	£113,168
	KM+Weibull	5.13	3.83	£283,252	4.25	2.67	£161,329	£105,128

PFS endpoint	INV (base case)	5.11	3.73	£239,894	4.25	2.70	£169,665	£68,146
	IRC	5.11	3.74	£241,888	4.25	2.71	£172,477	£67,800
Utility scenarios	One PPS utility (base case)	5.11	3.73	£239,894	4.25	2.70	£169,665	£68,146
	One PPS utility, ALEX data only	5.11	3.88	£239,894	4.25	3.13	£169,665	£93,764
	2nd & 3rd line PPS utilities	5.11	3.25	£239,894	4.25	2.43	£169,665	£85,111
Subsequent treatment distributions (see Table 35)	Base case	5.11	3.73	£239,894	4.25	2.70	£169,665	£68,146
	Scenario 1	5.11	3.73	£213,094	4.25	2.70	£169,665	£42,140
	Scenario 2	5.11	3.73	£255,975	4.25	2.70	£169,665	£83,749
	Scenario 3	5.11	3.73	£222,859	4.25	2.70	£164,428	£56,697
AE disutility	No (Basecase)	5.11	3.73	£239,894	4.25	2.70	£169,665	£68,146
	Yes	5.11	3.73	£239,894	4.25	2.70	£169,665	£68,131

AE, adverse event; ICER, incremental cost-effectiveness ratio, INV, investigator; IRC, Independent Review Committee; KM, Kaplan-Meier; LYs, life years; OS, overall survival; PFS, progresison-free survival; PPS, post-progression survival; QALYs, quality-adjusted life years.

B.3.8.4 Summary of sensitivity analyses results

As seen in the probabilistic sensitivity analysis scatterplots, alectinib is associated with a clear clinical benefit over crizotinib. This is further validated in the one-way sensitivity analyses and scenario analyses whereby a change in the plausible OS parametric distributions consistently has a favourable effect on the ICER.

The main drivers of the economic analysis include utility estimates (not accounting for CNS QoL), the overall survival distribution utilised (reflecting the conservative assumption used in the base case analysis), PFS extrapolation (driven by the likelihood of Weibull crossing OS), and the exploration of an OS treatment benefit cap. However, an OS treatment benefit cap provides an arbitrary cut off, not supported by evidence. Given the extrapolation presented is already deemed significantly conservative towards alectinib, it is not considered appropriate to utilise such a cap.

The results included above have been conducted on the list price of alectinib and crizotinib. However, crizotinib is associated with a confidential PAS, and similarly a PAS for alectinib has been submitted to Patient Access Schemes Liaison Unit (PASLU), hence the above results do not accurately reflect the true cost-benefit of alectinib. For the with-alectinib PAS results, please see the confidential PAS Appendix (Appendix N).

B.3.9 Subgroup analysis

No subgroup analyses were performed. ALK-positive NSCLC is a small population, with limited ability to restrict further in clinical practice. In addition, clinical benefit was observed in all subgroups of patients in the ALEX study. As such no analyses were conducted on restricted populations as compared to the anticipated indication.

B.3.10 Validation

B.3.10.1 Validation of cost-effectiveness analysis

Selection of the appropriate distributions has been driven by statistical fit to the data, visual fit to the KM and, importantly, clinical plausibility of the outcomes. All outcomes of the alectinib and crizotinib arms of the economic model have been extensively compared to and validated against all available evidence for these products to assess the accuracy of the modelled survival (See Appendix J). Based on this, it is deemed a conservative estimate of the relative benefit of alectinib has been utilised as the base case analysis.

The economic model was constructed specifically from the UK-NHS perspective. The structure is consistent with other oncology models and previous NSCLC submissions to NICE and all costs are sourced from UK published literature. In addition, the model approach and inputs were validated by a number of UK clinical experts to ensure the model was reflective of clinical practice. This includes, but is not limited to: resource use; health state methodologies; OS projections and extrapolation techniques.

Internal quality control and validation of the model was conducted by an external consultancy. Cell by cell validation was conducted which included formula checking, cell references and all aspects of model functionality. A number of 'pressure tests' were conducted, often using extreme values. The results of the model using these values were then compared to expected outputs to assess functionally accuracy.

B.3.11 Interpretation and conclusions of economic evidence

This is the first economic evaluation focused on assessing the cost-effectiveness of alectinib for the first-line treatment of patients with ALK-positive advanced NSCLC.

The economic evaluation utilises the data available from the ALEX trial: A phase III open label RCT conducted in 98 centres in 29 countries, including the UK. The baseline characteristics of patients within the ALEX trial have been validated by clinical experts and can be considered representative of the UK population. Therefore the population included in the economic evaluation can be considered relevant to clinical practice in England and Wales. In addition, the UK-NHS perspective has been taken throughout, with all costs from published UK sources.

Alectinib provided 5.11 life-years, an increase of 0.86 compared to crizotinib. Based on the extrapolations chosen, this is considered a conservative estimate of the survival benefit that alectinib is anticipated to provide over the current standard of care, crizotinib.

Alectinib provides an incremental gain of 1.03 QALYs over the current standard of care, crizotinib. The utility differential is derived entirely from the PFS health state, further supportive of the conservative estimate of survival presented as the base case.

The base-case ICER comparing alectinib and crizotinib at list price is £68,146 per QALY gained. [redacted] Nevertheless, it is acknowledged crizotinib also have a confidential PAS, thus the analysis could not be completed at the accurate price level for the comparator.

Extensive sensitivity analyses were conducted to test how robust the model results were to change in parameter values, and to consider alternative approaches or sources related to the estimation of QALYs, costs, and clinical inputs.

The key strengths associated with the cost-effectiveness analysis surround its use of the best available evidence to inform the model:

- Head-to-head data from the ALEX trial comparing alectinib to the standard of care, crizotinib was used in the economic evaluation for overall survival, PFS and safety
- Utility values were obtained from EQ-5D ALEX data, using the UK tariff
- Resource utilisation and unit costs used in the analysis are reflective of UK clinical practice and were mainly derived from previous NICE appraisals
- Extensive sensitivity and scenario analyses were conducted to inform the uncertainty around the above limitations, which helped understand what key variables could potentially have a major impact on the cost-effectiveness results.

Nevertheless, as with all economic evaluations conducted early in the product life-cycle, long term data are limited. The ALEX trial is ongoing, with significantly immature OS data. Extrapolation of OS and PFS was required for the AUC partitioned survival approach taken for the economic model. All extrapolations are subject to limitations as the aim is to predict future benefits for treatments. However, a robust and comprehensive approach has been conducted, which result in conservative estimates of the relative benefit of alectinib.

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Single technology appraisal

Alectinib for untreated anaplastic lymphoma kinase positive advanced non-small- cell lung cancer [ID925]

Dear Jessica,

The Evidence Review Group, BMJ-TAG, and the technical team at NICE have looked at the submission received on 24 October 2017 from Roche. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **10am on Friday 1 December 2017**. Your response and any supporting documents should be uploaded to NICE Docs.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Anna Brett, Technical Lead (Anna.Brett@nice.org.uk). Any procedural questions should be addressed to Kate Moore, Project Manager (Kate.Moore@nice.org.uk).

Yours sincerely

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Encl. checklist for confidential information

Section A: Clarification on effectiveness data

Overall survival

A1. **Priority question**: The company submission (CS) states, "Subsequent therapies were not routinely captured after a patient discontinued treatment" however, the clinical study report (CSR) for ALEX states (on page 1969) that, "After disease progression, patients will be treated at the discretion of the investigator according to local practice. Information regarding the nature and the duration of subsequent therapies will be collected" and that, "Data for subsequent therapy will be collected for the analysis of OS."

a. Please complete the following table for the subset of the ALEX population whose subsequent therapies were captured.

b. Please provide mean and median overall survival (OS) for patients who received any subsequent tyrosine kinase inhibitor (TKI) in the alectinib group, and the same for the crizotinib group.

c. Please provide mean and median OS for patients who received any subsequent non-TKI in the alectinib group, and the same for the crizotinib group.

	Alectinib		**Crizotinib**	
	1st subsequent treatment, n (%)	**≥2nd subsequent treatment, n (%)**	**1st subsequent treatment, n (%)**	**≥2nd subsequent treatment, n (%)**
Any anti-cancer therapy				
Any TKI				
Alectinib				
Crizotinib				
Ceritinib				
Brigatinib				
Lolatinib				
[complete others]				
Any non-TKI				
Docetaxel				
Nivolumab				
[complete others]				

A2. The CS states that, "only 41% of the ALEX population who have progressed have been captured as receiving at least 1 subsequent therapy". Please confirm that the

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remaining 59% of patients who have progressed on randomised therapy have not had subsequent therapies captured.

A3. Please list the countries and number of sites where crossover is known to have occurred from crizotinib to alectinib, and vice versa.

A4. **Priority question**: Please provide OS Kaplan-Meier (KM) plots and the respective OS KM data (in Excel format) for the following subgroups in ALEX:

a. For alectinib patients who received any subsequent anti-cancer therapy versus those who have not;

b. For crizotinib patients who received any subsequent anti-cancer therapy versus those who have not;

c. For alectinib-treated patients who received a subsequent tyrosine kinase inhibitor (TKI) versus those who have not;

d. For crizotinib-treated patients who received a subsequent tyrosine kinase inhibitor (TKI) versus those who have not;

e. Hazard ratios (HRs) and 95% confidence intervals (CIs) for OS for the analyses described in a), b), c) and d).

A5. **Priority question**: Please provide a subgroup analysis for OS and the respective KM plots and KM data (in Excel format) for the following in ALEX:

a. For alectinib patients with versus without central nervous system (CNS) metastases at baseline;

b. For crizotinib patients with versus without CNS metastases at baseline;

c. HRs and 95% CIs for OS for the analyses described in a) and b).

A6. **Priority question**: Please conduct a regression analysis to explore the relationship between CNS progression and OS for alectinib and crizotinib in ALEX.

CNS Progression

A7. **Priority question**: For time to CNS progression, please provide an explanation of the competing risk analysis, including reasons for censoring.

A8. **Priority question**: Peters 2017 states, “Patients with isolated asymptomatic CNS progression could receive, at the investigator’s discretion, a local therapy followed by continued trial treatment until systemic disease progression, symptomatic CNS

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progression, or both". For the alectinib and crizotinib groups separately, please provide:

a. the number of patients whose CNS progression by independent review committee (IRC) was asymptomatic;

b. for any patients who had asymptomatic CNS progression before having symptomatic CNS progression, the mean and 95% CI months between these events.

A9. **Priority question**: Please provide the following:

a. The number of patients who had a CNS progression event (IRC) before having systemic progression by independent review (IRC) (and the mean time between the events)

b. The number of patients who had a CNS progression event (IRC) before having systemic progression by investigator-assessment (INV) (and the mean time between the events)

c. The number of patients who had a CNS progression event after having systemic progression (and the mean time between the events)

d. The number of patients who had a CNS progression that was considered a systemic progression event

A10. **Priority question**: Please provide KM curves and KM data in Excel format for time to CNS progression for alectinib and crizotinib separately (regardless of CNS metastases at baseline and whether they had a non-CNS related progression event).

A11. **Priority question**: Please clarify how many of the 18 CNS progressions in the alectinib group and 68 CNS progressions in the crizotinib group were in patients who had CNS metastases at baseline.

Progression-free survival

A12. **Priority question**: Please provide subgroup analyses (smoking status, baseline Eastern Cooperative Oncology Group performance score (ECOG PS), CNS metastases at baseline as determined by IRC, and prior brain radiation) for PFS by IRC assessment, including KM curves, underlying KM data in excel format and HRs between treatments with 95% CIs for each level of the categorical variable

A13. Table 9 of the CSR [redacted]

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[redacted] For those with disease progression, please provide a similar breakdown of number and site of lesions when progression was documented.

Health-related quality of life data

A14. Please provide more detailed results from ALEX for all EORTC QLQ-LC13 and EORTC QLQ-Core 30 (mean and standard deviations over time and at end of treatment for each group, including the number of responses at each timepoint).

Baseline characteristics

A15. Please clarify whether patients with an ECOG PS of 2 were eligible for ALEX. CS Table 5 (pg 23) shows that 7% of each group had ECOG PS 2 and CS page 18 states that randomisation was stratified by 0 to 1 versus 2, but the inclusion criteria on page 19 states only those with a score of 0 or 1 were eligible.

A16. Please provide the number of patients in each group with ECOG PS of 0 and 1 separately.

A17. Please provide the number of patients in each group whose CNS metastases at baseline were symptomatic.

Study design and quality assessment

A18. Please provide justifications for the risk of bias judgements presented in CS Appendix D1.3.

A19. Please explain why ALEX was designed as open label rather than double-blind.

A20. Given the open-label design of ALEX, please explain:

d. why INV PFS was chosen as the primary outcome and used in the company base-case, rather than PFS assigned by the IRC.

e. why objective response rate was based on INV but CNS progressions were by IRC.

A21. Please confirm whether safety assessments were made by the treating physician who was aware of treatment assignment.

Section B: Clarification on cost-effectiveness data

Model structure and approach

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B1. **Priority question.** Given the company's rationale for one of alectinib's main advantages being in delaying CNS progression, please consider restructuring the economic model to explicitly incorporate CNS progression, so appropriate costs and benefits can be more accurately estimated. If the company decides not to restructure the model, please justify why it was considered unnecessary.

B2. **Priority question.** Please undertake a formal assessment of the existence (or not) of proportional hazards (PHs) for the OS and PFS (including INV- and IRC- assessed) data in ALEX, using the guidance outlined in DSU 14 (such as using log-cumulative hazard plots and assessing the clinical plausibility of the assumption).

B3. **Priority question.** In light of the conclusions reached as a result of question B2, please explore the following:

a. Using the log-cumulative hazard plots, please assess the methodological and clinical plausibility of using exponential distributions to model OS and PFS in the model, and therefore assume a constant hazard for survival and progression outcomes for the entire period of analysis for OS (and for the extrapolation part of the PFS curves);

b. Please explore the additional rationale underlying the methodological assumption in using exponential distributions to model OS and PFS, even when independently fitting exponential models to each treatment arm, that PHs exist because the hazards are constant throughout time, and thus so is the ratio between the hazards across treatment arms.

B4. **Priority question.** Please provide (in Excel format) the KM data for time to off-treatment (TTOT) shown in Figure 8, page 56 of the CS.

B5. Please clarify if the sentence on page 52 of the CS, "whereas most previous appraisals have not distinguished between progression locations, the model structure utilised in this submission does", refers to the costs and QALYs in the economic model being weighted by the proportion of patients observing CNS progression with alectinib and crizotinib, respectively.

Treatment effectiveness

B6. **Priority question.** The ERG used the KM data for alectinib and crizotinib from ALEX, provided in the economic model, to fit and extrapolate survival curves for OS and PFS (fitted independently for the two treatment arms). The ERG found a few discrepancies between its results and the company's, in terms of assessment of fit. Therefore, can the company please consider re-running the statistical models in order to:

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a. Re-assess the lack of convergence of the Gompertz model for OS and PFS outcomes for alectinib. When the ERG ran the survival analysis, not only did the Gompertz model converge, but it was also the best fitting model (regardless of clinical plausibility of the extrapolated curves) for OS and PFS outcomes for alectinib. If the Gompertz model does not reach convergence, please explain why;

b. Re-assess the relative fit of the exponential model for OS for alectinib according to AIC values. In the ERG's initial analysis (and indeed in the visual fit exercise of the curves provided in the company's economic model), the exponential curve seems to be the worst-fitting one, but was still chosen to model OS for alectinib;

c. Similar to alectinib, the exponential model is among the worst-fitting models for the OS curve for crizotinib. If, for clinical plausibility reasons, the company considers that the exponential tails are the most clinically plausible ones to model OS, please state such rationale, and consider using a similar approach to that taken to modelling PFS curves (i.e. fitting a parametric tail to the OS KM curve for both alectinib and crizotinib), given the poor fit of exponential curves to the OS KM data in ALEX;

d. Please explain the methodological difference between the piecewise exponential models and the KM + exponential curve models, included in the economic model.

B7. **Priority question.** In case of model convergence, please include Gompertz curves in the economic model for OS and PFS outcomes for alectinib.

B8. **Priority question.** Please clarify if the Gompertz curves included for OS and PFS for alectinib in the economic model are indeed Gompertz curves (considering the statements included in the CS about the non-convergence, and therefore non-inclusion of Gompertz models).

B9. **Priority question.** With regards to the KM data referred to on pages 62-63 of the CS, pertaining to the OS curve for PROFILE 1014, please provide the OS KM data (in Excel format) for PROFILE 1014, used to compare survival predictions from ALEX.

B10. **Priority question.** Please undertake an exercise of assessment of fit and clinical plausibility of extrapolated curves with the IRC-assessed PFS data from ALEX, similar to the one provided for the INV-assessed PFS data in the CS. Please investigate if the survival analysis undertaken originally by the company for the IRC-assessed PFS needs re-assessing, similar to what has been described in question B6.

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B11. **Priority question.** The model incorporates the very strong assumption that all patients will have CNS progression on the first cycle after they move to the disease progression health state. As an alternative analysis, please include a scenario analysis in the model using the clinical data requested in A10 to estimate CNS progression and the impact of CNS progression in patients' quality of life and on resource use.

B12. **Priority question.** Please provide the proportion of patients who were allowed to cross-over treatment arms in ALEX. For example, page 314 of the CSR reports that a patient initially allocated to alectinib, was subsequently treated with crizotinib.

B13. **Priority question.** In light of question B12, please justify if OS outcomes from ALEX need adjustment due to cross-over in the trial.

Health-related quality of life

B14. **Priority question.** Please undertake and report the results (step by step) of a stepwise approach, in order to select the variables included as predictors of patients' utility in the mixed model described on page 71 of the CS.

B15. **Priority question.** Please clarify how the utility estimates in Table 23 were calculated. If those estimates were obtained from the mixed model in Table 22, please clarify which covariates were included.

B16. **Priority question.** Table 22 in the CSR seems to report the variables included in the mixed model for predicting patients' quality of life. Please present the model results if only statistically significant variables are included in the model (determined through the process described in question B14). Please justify the decision to include non-statistically significant variables, if that remains the approach taken for the company's base case analysis.

B17. **Priority question.** In accordance with the guidance outlined in DSU TSD 10, please provide descriptive statistics for the EQ-5D data captured in ALEX. More specifically, please provide:

a. Mean (SD), median and inter-quartile range at baseline and at end of study;

b. Mean change from baseline to end of study, with respective 95% CIs and number of observations at baseline and at end of study;

c. Mean (SD) and number of observations collected at each time point of QoL collection;

d. Mean age of responders.

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B18. **Priority question.** Please clarify why different utility estimates were applied to TKI and non-TKI treatments, in the scenario analysis considering subsequent therapies.

B19. **Priority question.** In the scenario analysis considering subsequent therapies, patients are distributed into subsequent therapies (for both arms) to either TKI (47%) or non-TKI (53%) treatments and attributed to a TKI or non-TKI related utility. However, in Table 35 of the CS, the distribution reported in ALEX for each treatment arm is provided: alectinib, 71% non-TKI, 29% TKI; crizotinib, 21% non-TKIs 79% TKIs. Please change this in the model to reflect the different types of subsequent therapies received in the two treatment arms in ALEX and justify why this approach was not taken in the base case analysis.

B20. **Priority question.** Please undertake a subgroup analysis of the EQ-5D data collected in ALEX for the group of patients experiencing CNS progression.

B21. Please clarify how sources of utility values for CNS (Roughley *et al.* 2014, Mulvenna *et al.* 2016, Peters *et al.* 2016) were chosen and identified and why a systematic review to identify utility values associated with CNS was not performed.

B22. Please provide the full texts for Solomon 2014 and Felip 2015 included in Table 25 of the CS. The reference for Solomon 2014 provided relates to Solomon 2016. Please ensure the HSUVs provided in Table 25 are those reported in the sources provided.

B23. Please clarify how sources of utility decrements associated with adverse events were chosen and identified (Marti *et al.* 2013, Beusterien *et al.* 2010, Nafees *et al.* 2008, Peters *et al.* 2016, Roughley *et al.* 2014, Mulvenna *et al.* 2016) and why a systematic review to identify utility decrements associated with adverse events and CNS was not performed.

B24. Please provide the number of patients in ALEX with bone metastases at data cut off as per the IRC endpoint by treatment arm.

B25. Please extract the Blackhall 2014 paper and add the extraction to Table 25 of the CS as a new row.

Resource use and costs

B26. **Priority question.** Please include a scenario analysis in the model (through a drop-down menu option) that estimates the costs of treating CNS metastasis with steroids (Mulvenna *et al.* 2016), instead of stereotactic radiotherapy.

B27. **Priority question.** Clinical expert opinion given to the ERG explained that docetaxel is not the only chemotherapy agent used to treat ALK+ NSCLC in the UK. It was reported that pemetrexed or docetaxel are usually given as single therapies or that

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pemetrexed in combination with carboplatin (or cisplatin) are given as combination therapies. Please consider including a "basket" of chemotherapies as subsequent treatments in the model, and costing this treatment accordingly.

B28. **Priority question.** Please include a scenario analysis in the model (selectable from a drop-down menu) which estimates the costs of subsequent therapies according to the information given in response to question A2 b (and respective table included).

B29. Please clarify why the cost of concomitant drugs was not considered in the model.

B30. It would appear that the cost of docetaxel (which should be given in every 21-day cycle) is being applied weekly in the model ('Cost Inputs'K113). Please correct this in the model.

B31. Please clarify how sources of subsequent treatment duration (ASCEND-5, ALUR and PROFILE 1007) were identified and chosen. Please provide the full-texts of those papers.

Adverse events

B32. Please clarify why adverse events for patients receiving second line treatments are not considered in the model in terms of impact on quality of life and costs.

Section C: Textual clarifications and additional points

C1. The ERG has found discrepancies between the variables reported in Table 50 of the CS and the model.

a) Please clarify where/how adverse event management costs are varied in PSA as only deterministic values can be identified in the model;

b) Please provide the standard errors of all variables included in PSA (where appropriate), including the respective sources (i.e. if the estimates were assumed or taken from literature);

c) Table 50 in the CS states the cost of ALK testing is fixed, but this variable is included in PSA in the model 'Cost Inputs'L72. Please amend Table 50 to reflect this;

d) The submission reports a beta distribution for utility values whilst the model is informed by a gamma distribution 'Model Inputs'J38:Q50. Please update Table 50 accordingly.

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C2. Please provide a table containing the 21 studies excluded from the original HRQoL search Appendix H.

C3. Are the utility values extracted from Solomon 2014 in Table 25 the utility values reported in Blackhall 2014?

C4. Table 50 of the CS refers to the KM PFS data from ALEX used in the base case analysis being IRC-assessed, whereas Table 55 refers to the base case being INV-assessed. Please confirm whether what is stated in Table 50 is a typo.

C5. Please revise the number of studies in Figure 6 of Appendix G to reflect the 21 unique studies as Figure 6 currently sums to 22.

C6. Please provide the text related to* in Figure 5 of Appendix G.

C7. Please clarify the number of studies identified from the cost-effectiveness update search and HRQoL update search. Please report the number of studies including and excluding duplicates from the original search and including and excluding additional studies identified from hand searches. Please fill in the table below for both searches.

Cost-effectiveness		
	Additional studies from hand searches included	Additional studies from hand searches excluded
Duplicates from original search included		
Duplicated from original search excluded		
HRQoL		
	Additional studies from hand searches included	Additional studies from hand searches excluded
Duplicates from original search included		
Duplicated from original search excluded		

C8. Please clarify why a quality assessment of the included studies such as the Critical Appraisal Skills Programme (CASP) assessment as recommended by the DSU (TSD document 9) was not undertaken on the included HRQoL evidence.

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Peters S, Camidge DR, Shaw AT, Gadgeel S, Ahn JS, Kim D-W, et al. Alectinib versus Crizotinib in Untreated ALK-Positive Non–Small-Cell Lung Cancer. New England Journal of Medicine. 2017;377:829-38.

Single technology appraisal

Alectinib for untreated anaplastic lymphoma kinase positive advanced non-small- cell lung cancer [ID925]

Dear Kate,

Please find enclosed responses to the majority of clarification questions.

As per my email dated 27th November, the following clarification questions are currently outstanding, and will be provided by COB 15th December:

A6, A10, A13, B1, B10 (if curve updates required with updated modelling), B11, B19, B20, B24, B27, B28, B30, C1.

Please let me know if you have any questions.

Kind regards,

Jessica Purchase

Health Economist
Roche Products Ltd

Section A: Clarification on effectiveness data

Overall survival

A1. **Priority question**: The company submission (CS) states, “Subsequent therapies were not routinely captured after a patient discontinued treatment” however, the clinical study report (CSR) for ALEX states (on page 1969) that, “After disease progression, patients will be treated at the discretion of the investigator according to local practice. Information regarding the nature and the duration of subsequent therapies will be collected” and that, “Data for subsequent therapy will be collected for the analysis of OS.”

a. Please complete the following table for the subset of the ALEX population whose subsequent therapies were captured.

This has been provided in Table 3.

b. Please provide mean and median overall survival (OS) for patients who received any subsequent tyrosine kinase inhibitor (TKI) in the alectinib group, and the same for the crizotinib group.

It is imperative to note, this is a non-randomised analysis, subject to considerable selection bias. As such, assessing the numbers in isolation is misleading and not encouraged.

18 patients in the alectinib arm and 34 patients in the crizotinib arm are known to have received a subsequent TKI.

In addition to the bias generated by a non-randomised analysis, the low patient numbers requires this analysis to be interpreted with caution.

Table 1: mean and median overall survival (OS) subsequent TKIs

	Alectinib	Crizotinib
Mean (months)	[redacted]	[redacted]
Median (months)	[redacted]	[redacted]

c. Please provide mean and median OS for patients who received any subsequent non-TKI in the alectinib group, and the same for the crizotinib group.

It is imperative to note, this is a non-randomised analysis, subject to considerable selection bias. As such, assessing the numbers in isolation is misleading and not encouraged.
13 patients in the alectinib arm and 6 patients in the crizotinib arm are known to have received a subsequent non-TKI.

In addition to the bias generated by a non-randomised analysis, the low patient numbers requires this analysis to be interpreted with caution.

Table 2: mean and median overall survival (OS) subsequent non-TKIs

	Alectinib	Crizotinib
Mean (months)	[redacted]	[redacted]
Median (months)	[redacted]	[redacted]

Table 3: First and second or further subsequent treatments after trial treatment discontinuation

	Alectinib		Crizotinib	
Treatment	**First subsequent (n=68)***	**Second or further subsequent (n=68)***	**First subsequent (n=105)***	**Second or further subsequent (n=105)***
Total number of patients with at least one treatment	31 (45.6%)	9 (13.2%)	40 (38.1%)	4 (3.8%)
TYROSINE KINASE INHIBITORS				
Total number of patients with at least one treatment	13 (19.1%)	5 (7.4%)	33 (31.4%)	3 (2.9%)
Ceritinib	2 (2.9%)	2 (2.9%)	13 (12.4%)	1 (1.0%)
Alectinib	0 (0.0%)	0 (0.0%)	8 (7.6%)	2 (1.9%)
Crizotinib	6 (8.8%)	3 (4.4%)	2 (1.9%)	0 (0.0%)
Loratinib	4 (5.9%)	1 (1.5%)	2 (1.9%)	0 (0.0%)
Brigatinib	1 (1.5%)	0 (0.0%)	4 (3.8%)	0 (0.0%)
Gefitinib	0 (0.0%)	0 (0.0%)	2 (1.9%)	0 (0.0%)
Entrectinib	0 (0.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)
Erlotinib	0 (0.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)
PLATINUM COMPOUNDS				
Total number of patients with at least one treatment	16 (23.5%)	3 (4.4%)	6 (5.7%)	0 (0.0%)
Cisplatin	7 (10.3%)	0 (0.0%)	5 (4.8%)	0 (0.0%)
Carboplatin	9 (13.2%)	3 (4.4%)	1 (1.0%)	0 (0.0%)
ANTIMETABOLITES				
Total number of patients with at least one treatment	14 (20.6%)	3 (4.4%)	6 (5.7%)	0 (0.0%)
Pemetrexed	8 (11.8%)	2 (2.9%)	5 (4.8%)	0 (0.0%)
Pemetrexed disodium	4 (5.9%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
Gemcitabine	2 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Gemcitabine hydrochloride	0 (0.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)
TAXANES				

Total number of patients with at least one treatment	3 (4.4%)	0 (0.0%)	0 (0.0%)	1 (1.0%)
Paclitaxel	3 (4.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Docetaxel	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.0%)
IMMUNOSTIMULANTS				
Total number of patients with at least one treatment	0 (0.0%)	2 (2.9%)	0 (0.0%)	0 (0.0%)
Nivolumab	0 (0.0%)	2 (2.9%)	0 (0.0%)	0 (0.0%)
ANGIOGENESIS INHIBITORS				
Total number of patients with at least one treatment	2 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Bevacizumab	2 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
ALKYLATING AGENTS				
Total number of patients with at least one treatment	1 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cyclophosphamide	1 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
ANTINEOPLASTIC AGENTS NEC				
Total number of patients with at least one treatment	0 (0.0%)	1 (1.5%)	1 (1.0%)	0 (0.0%)
Antineoplastic agent NOS	0 (0.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)
FAZ053 (Anti PD−L1)	0 (0.0%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
CYTOTOXIC ANTIBIOTICS				
Total number of patients with at least one treatment	1 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Doxorubicin	1 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
VINCA ALKALOIDS				
Total number of patients with at least one treatment	1 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Vincristine	1 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

* 68 alectinib, and 105 crizotinib treated patients have permanently discontinued study treatment

A2. The CS states that, “only 41% of the ALEX population who have progressed have been captured as receiving at least 1 subsequent therapy”. Please confirm that the remaining 59% of patients who have progressed on randomised therapy have not had subsequent therapies captured.

Subsequent therapies were not systematically captured as part of the ALEX study. The ERG is correct in its interpretation, but Roche would like to clarify: 41% of the ALEX population who have permanently discontinued study treatment have been captured as receiving at least 1 subsequent treatment. In summary, the subsequent therapies of the remaining 59% of patients who have permanently discontinued study treatment were not documented.

A3. Please list the countries and number of sites where crossover is known to have occurred from crizotinib to alectinib, and vice versa.

Overall 10 patients in the crizotinib arm received alectinib, and 9 patients in the alectinib arm received crizotinib after they had permanently discontinued the assigned trial treatment. Note neither of these switches are due to protocol defined crossover but rather the use of available subsequent treatments in clinical practice at the investigators discretion.

Locations of the 10 patients who received subsequent alectinib include: Israel, Great Britain (2 sites), Canada, USA (4 sites) and Hong Kong.

Locations of the 9 patients who received subsequent crizotinib include: Italy, Hong Kong, Switzerland, Portugal, Singapore, Korea, Costa Rica and Taiwan.

A4. **Priority question**: Please provide OS Kaplan-Meier (KM) plots and the respective OS KM data (in Excel format) for the following subgroups in ALEX:

The KM data requested are included in the Excel file “NICE CQs supplementary data”, sheet “A4”. The KM plots can be found below.

a. For alectinib patients who received any subsequent anti-cancer therapy versus those who have not;

It is imperative to note, this is a non-randomised analysis, subject to considerable selection and immortal time bias. Therefore, all analyses should be interpreted with care and caution.

Following the clarification call, Roche understood this question to be requesting an analysis of any patient who has discontinued study treatment and received a subsequent anti-cancer therapy, versus any patient who has not received a subsequent anti-cancer therapy. As such, this analysis explores:

- 31 alectinib treated patients who have been captured as having received any subsequent anti-cancer therapy
- 121 alectinib treated patients who have not been captured as receiving any subsequent anti-cancer therapy

However, two considerations are critical:

- A high proportion of the 121 patients captured here as having no subsequent therapy were still on study treatment (alectinib) at data cut off as are still progression free

- Of those who have discontinued study treatment, a subsequent therapy has not been captured in the analysis. However, it is assumed a high proportion will have received a subsequent therapy, in line with clinical practice in the respective countries.

As such, this analysis should be interpreted with caution.

Figure 1: Alectinib: any subsequent anti-cancer therapy versus those who have not

b. For crizotinib patients who received any subsequent anti-cancer therapy versus those who have not;

It is imperative to note, this is a non-randomised analysis, subject to considerable selection and immortal time bias. Therefore, all analyses should be interpreted with care and caution.

Following the clarification call, Roche understood this question to be requesting an analysis of any patient who has discontinued study treatment and received a subsequent anti-cancer therapy, versus any patient who has not received a subsequent anti-cancer therapy. As such, this analysis explores:

- 40 crizotinib treated patients who have been captured as having received any subsequent anti-cancer therapy

- 111 crizotinib treated patients who have not been captured as receiving any subsequent therapy.

However, two considerations are critical:

- A high proportion of the 111 patients captured here as having no subsequent therapy were still on study treatment (crizotinib) at data cut off as are still progression free

- Of those who have discontinued study treatment, but a subsequent therapy has not been captured in the analysis, it is assumed a high proportion will have received a subsequent therapy, in line with clinical practice in the respective countries.

As such, this analysis should be interpreted with caution.

Figure 2: Crizotinib: any subsequent anti-cancer therapy versus those who have not

c. For alectinib-treated patients who received a subsequent tyrosine kinase inhibitor (TKI) versus those who have not;

It is imperative to note, this is a non-randomised analysis, subject to considerable selection bias. Therefore, all analyses should be interpreted with care and caution.

Following the clarification call, Roche understood this question to be requesting an analysis of any patients who have discontinued study drug and received any subsequent TKI (irrespective of first, second or further lines of subsequent treatments) versus those patients who have discontinued study drug and received no subsequent TKI (irrespective of first, second or further lines of subsequent treatments). As such, this analysis explores:

- 18 patients who have been captured as receiving any subsequent TKI
- 13 patients who have been captured as exclusively receiving no subsequent TKI

In addition to the considerable selection bias this analysis captures, the small patient numbers captures further supports the need for this analysis to be interpreted with care and caution.

Figure 3: Alectinib: subsequent tyrosine kinase inhibitor (TKI) versus those who have not

d. For crizotinib-treated patients who received a subsequent tyrosine kinase inhibitor (TKI) versus those who have not;

It is imperative to note, this is a non-randomised analysis, subject to considerable selection bias. Therefore, all analyses should be interpreted with care and caution.

Following the clarification call, Roche understood this question to be requesting an analysis of any patients who have discontinued study drug and received any subsequent TKI (irrespective of first, second or further lines of subsequent treatments) versus those patients who have discontinued study drug and received no subsequent TKI (irrespective of first, second or further lines of subsequent treatments). As such, this analysis explores:

- 34 patients who have been captured as receiving any subsequent TKI
- 6 patients who have been captured as exclusively receiving no subsequent TKI

In addition to the considerable selection bias this analysis captures, the small patient numbers captures further supports the need for this analysis to be interpreted with care and caution.

Figure 4: Crizotinib: subsequent tyrosine kinase inhibitor (TKI) versus those who have not

e. Hazard ratios (HRs) and 95% confidence intervals (CIs) for OS for the analyses described in a), b), c) and d).

As detailed above the analyses requested and provided are non-randomised analyses, subject to considerable selection and immortal time bias. In addition to the bias generated by a non-randomised analysis, the low patient numbers requires the analyses to be interpreted with care and caution: assessing the numbers in isolation is misleading and not encouraged.

Table 4: Subgroups by subsequent treatments summary statistics

	Alectinib HR (CI)	Crizotinib HR (CI)
Patients who received any subsequent anti−cancer therapy vs those who did not	[redacted]	[redacted]
Patients who received a subsequent tyrosine kinase inhibitor (TKI) vs those who did not	[redacted]	[redacted]

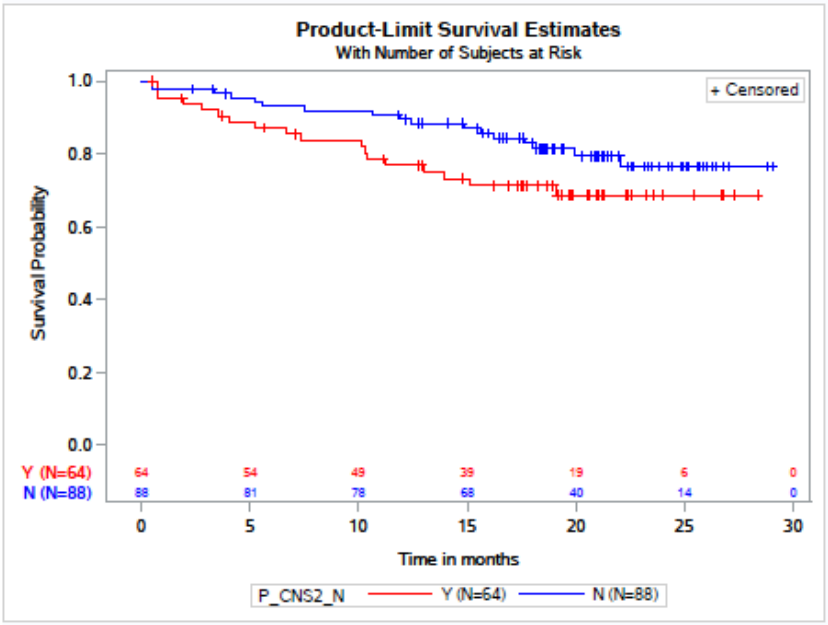
A5. **Priority question**: Please provide a subgroup analysis for OS and the respective KM plots and KM data (in Excel format) for the following in ALEX:

The KM data requested are included in the Excel file “NICE CQs supplementary data”, sheet “A5”. The KM plots can be found below.

a. For alectinib patients with versus without central nervous system (CNS) metastases at baseline;

64 patients had CNS metastases at baseline, as opposed to 88 patients who did not.

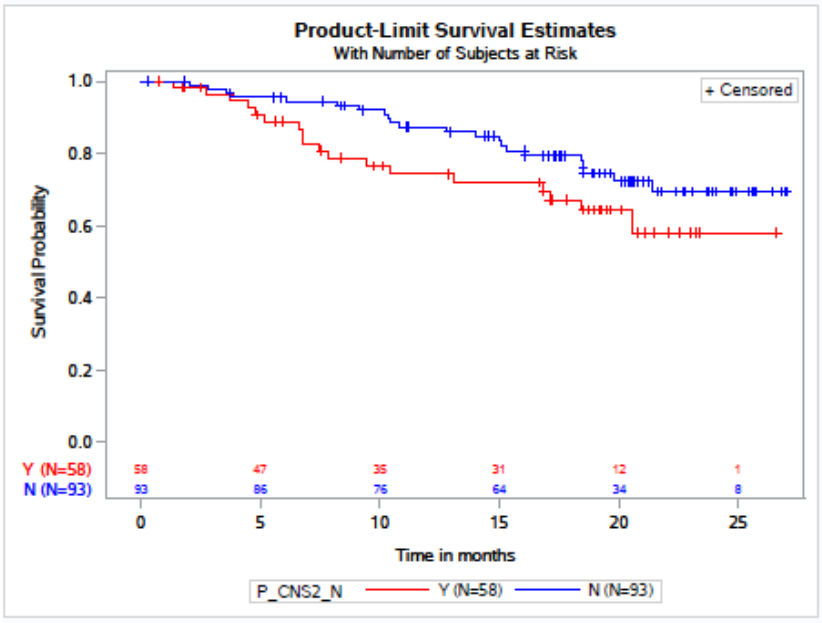
Figure 5: Alectinib: With vs. without CNS at baseline



b. For crizotinib patients with versus without CNS metastases at baseline;

58 patients had CNS metastases at baseline, as opposed to 93 patients who did not.

Figure 6: Crizotinib: With vs. without CNS at baseline



c. HRs and 95% CIs for OS for the analyses described in a) and b).

Table 5: Subgroups by CNS metastases at baseline summary statistics

	Alectinib HR (CI)	Crizotinib HR (CI)
Patients who had CNS metastases at baseline vs those who did not	0.59 (0.30, 1.14)	0.60 (0.32, 1.13)

A6. **Priority question**: Please conduct a regression analysis to explore the relationship between CNS progression and OS for alectinib and crizotinib in ALEX.

Given the immaturity of overall survival, it is not possible to conduct a regression analysis to explore the relationship between CNS progression and OS for alectinib and crizotinib in ALEX. Therefore, an alternative analysis has been conducted: a landmark analyses for 6 and 12-month CNS progressive disease as a predictor of OS. The landmark analysis approach is described in Anderson et al 1983 (Anderson et al., 1983). Anderson uses the landmark method as a valid approach for evaluating survival by tumour response by selecting a fixed time after the initiation of therapy as a landmark for conducting the analysis. Those patients still on study at the landmark time are separated into two response categories according to whether they have responded before that time. Patients are then followed forward in time to ascertain whether survival from the landmark depends on the patients' response status at the landmark. Patients who go off protocol before the time of landmark evaluation are excluded from the analysis and patients are analysed according to their response status at the landmark time regardless of any subsequent shifts in tumour response status. Thus, probability estimates and statistical tests are conditional on the response status of patients at the landmark time.

This analysis has been conducted for two populations (see response to A10 for further details on the populations):

1. CNS progressors as classified by the RECIST or CNS-RECIST criteria (CNS-PFS (IRC), Figure 1-4)

2. CNS progressors as classified by the RECIST only criteria (adapted CNS-PFS (IRC), Figure 5-8)

As shown from the below curves, patients who progress in the CNS have a poorer prognosis, and poorer survival expectation than those who do not. However, at this stage, patient numbers are too small to allow a real comparison of impact between arms. In particular on the alectinib arm, due to the small number of patients with CNS progression, each death in this arm triggers a deep drop in the KM curve. Further, these analyses are likely to capture 'early progressors' who could be subject to a more aggressive progression, particularly in the alectinib arm. Thus caution should be exercised to ensure appropriate interpretation of the curves. As such, longer term data is required to draw meaningful conclusions on these analyses.

This analysis does not impact the economic modelling approach as outcomes are not directly linked. This data are limited, biased and too variable to be implemented in the economic model.

CNS-PFS (IRC)

6 month landmark analysis

Figure 7: CNS-PFS (IRC, RECIST + CNS-RECIST): 6 month landmark analysis: CNS progression as a predictor of OS: Alectinib

Figure 8: CNS-PFS (IRC, RECIST + CNS-RECIST): 6 month landmark analysis: CNS progression as a predictor of OS: Crizotinib

12 month landmark analysis

Figure 9: CNS-PFS (IRC, RECIST + CNS-RECIST): 12 month landmark analysis: CNS progression as a predictor of OS: Alectinib

Figure 10: CNS-PFS (IRC, RECIST + CNS-RECIST): 12 month landmark analysis: CNS progression as a predictor of OS: Crizotinib

Figure 11: Adapted CNS-PFS (IRC, RECIST): 6 month landmark analysis: CNS progression as a predictor of OS: Alectinib

Figure 12: Adapted CNS-PFS (IRC, RECIST): 6 month landmark analysis: CNS progression as a predictor of OS: Crizotinib

12 month landmark analysis

Figure 13: Adapted CNS-PFS (IRC, RECIST): 12 month landmark analysis: CNS progression as a predictor of OS: Alectinib

Figure 14: Adapted CNS-PFS (IRC, RECIST): 12 month landmark analysis: CNS progression as a predictor of OS: Crizotinib

A7. **Priority question**: For time to CNS progression, please provide an explanation of the competing risk analysis, including reasons for censoring.

The IRC time to CNS progression endpoint utilises two criteria: RECIST, and CNS-RECIST, a modified RECIST scale assessed by a separate IRC to that of the PFS IRC.

The CNS progression analyses was performed using “competing risk” methods with minor statistical differences for the Cumulative Incidence Rates of CNS Progression and the Time to CNS Progression analysis. Similar to standard PFS and OS analyses, survival analysis models were used, but there were differences in the way events were counted and how long patients were kept in the analyses.

The analysis takes into consideration the possibility that at the time of analysis a patient may have one of the following events (if any – the patient may still be on treatment), and counts only the first one to have occurred:

- Progression in the CNS (with or without systemic progression)
- Non-CNS progression (progression outside of the CNS)
- Death

Given that in the analysis the above events are mutually exclusive, they are “competing” with each other and a patient may only have one of them. The CNS analysis performed considers the risk of a patient having a progression in the CNS as the first event occurring, while it does not count the other risks (non-CNS progression and death).

If patients had a non-CNS PD as first progression or died without prior progression (competing events) they were censored. In addition, patients who had not experienced disease progression or death at the time of analysis were censored at the last tumour assessment date either during study treatment or during follow-up. Patients with no post-baseline tumour assessment were censored at the date of randomization.

A8. **Priority question**: Peters 2017 states, “Patients with isolated asymptomatic CNS progression could receive, at the investigator’s discretion, a local therapy followed by continued trial treatment until systemic disease progression, symptomatic CNS progression, or both”. For the alectinib and crizotinib groups separately, please provide:

    a. the number of patients whose CNS progression by independent review committee (IRC) was asymptomatic;

This response was submitted early, in a letter dated 23rd November 2017. It is copied below for reference.

Roche would like to clarify a perceived misunderstanding in the trial design and data collection for the ALEX trial.

Tumour evaluation by RECIST (version 1.1) was performed by investigators (INV) every 8 weeks until disease progression. This included systematic brain imaging in all patients. Conversely, the blinded Independent Review Committee (IRC) conducted two assessments: one for overall systemic disease (RECIST) and a second IRC solely evaluated CNS endpoints

(CNS-RECIST). Therefore, both INV and IRC were able to determine CNS progression. However, time to CNS progression as measured by INV was not captured as an endpoint in the ALEX trial, whereas time to CNS progression by IRC was[1].
As progression in the CNS was measured as part of the INV tumour evaluation; subsequently, patients with isolated asymptomatic CNS progression could be given a local therapy (e.g., stereotactic radiotherapy or surgery) followed by continuation of either alectinib (in alectinib arm) or crizotinib (in crizotinib arm) at the investigator's discretion, when they believed that the patient would benefit from continuing study treatment. Despite continuing study treatment, it's important to note, the isolated asymptomatic CNS progression event was still considered the appropriate event for the PFS analysis. In this circumstance, 40 crizotinib patients were deemed to have an isolated asymptomatic CNS progression, of which 30 continued to receive crizotinib treatment, as opposed to 5 alectinib patients who were deemed to have an isolated asymptomatic CNS progression, all of whom continued treatment.

However, the IRC was a blinded analysis, where only RECIST results such as MRI and CT scans were available, with no additional clinical data. As such, the IRC did not have the information to assess if the CNS progression was asymptomatic or not, therefore it is not possible to determine the answer to this question. Nevertheless, given the similarities in the PFS endpoint between INV and IRC assessment, it is reasonable to assume a similar alignment in the CNS progression classification.

Finally, it's imperative to note, this analysis emphasises a pivotal discrepancy between the trial design, and the anticipated license for alectinib. Whilst a patient with asymptomatic isolated CNS progressive disease could, at the discretion of the investigator, remain on treatment in the ALEX trial, there are no such criteria in the anticipated license of alectinib. As such, in UK clinical practice, all patients will discontinue treatment at progressive disease, irrespective of symptoms.

b. for any patients who had asymptomatic CNS progression before having symptomatic CNS progression, the mean and 95% CI months between these events.

This response was submitted early, in a letter dated 23rd November 2017. However, further evidence is now provided:

As per protocol, for the patients with isolated asymptomatic CNS progression who continued study treatment, tumour assessment was required to be performed every 8 weeks until symptomatic CNS progression or systemic (non-CNS) progression. However if the patient or physician did not see further benefit from continuing study treatment, study treatment could be discontinued before symptomatic CNS progression or systemic progression was determined.

Of the 5 patients in the alectinib arm in this subgroup, 3 patients were still under study treatment without any non-CNS progression at the time of the clinical cut-off for the primary

[1] Primary endpoint: Investigator (INV) assessed progression free survival (PFS). Secondary endpoints tested in the following sequence: independent review committee (IRC) assessed PFS, time to IRC–assessed CNS progression according to RECIST criteria, INV-assessed response rate, overall survival (OS).

analysis (09 February 2017), 1 patient had systemic progression 110 days after asymptomatic CNS progression, and 1 patient discontinued study treatment before any symptomatic CNS or non-CNS progression could be detected based on investigator assessment.

Of the 30 patients in the crizotinib arm in this subgroup, 8 patients were still under study treatment without any non-CNS progression at the time of clinical cutoff, 6 patients had systemic progression between 55 and 209 days after asymptomatic CNS progression (55, 112, 112, 145, 202, 209 days) and 16 patients discontinued study treatment or died before any symptomatic CNS or non-CNS progression could be detected based on investigator assessment.

A9. **Priority question**: Please provide the following:

a. The number of patients who had a CNS progression event (IRC) before having systemic progression by independent review (IRC) (and the mean time between the events)

It should be noted, after the first progression event, further progression events have not been systematically captured. In order to report this, more than one event must have been captured. Therefore this analysis is subject to uncertainty.

A total of 28 patients had a CNS progression event before a systemic progression by IRC: 4 in the alectinib arm, 24 in the crizotinib arm. In the alectinib arm, the mean time between events was 43 days, as opposed to 71 days in the crizotinib arm.

b. The number of patients who had a CNS progression event (IRC) before having systemic progression by investigator-assessment (INV) (and the mean time between the events)

It should be noted, after the first progression event, further progression events have not been systematically captured. Therefore this analysis is subject to uncertainty.

A total of 39 patients had a CNS progression event before a systemic progression by INV: 5 in the alectinib arm, 34 in the crizotinib arm. In the alectinib arm, the mean time between events was 70 days, as opposed to 127 days in the crizotinib arm.

c. The number of patients who had a CNS progression event after having systemic progression (and the mean time between the events)

It should be noted, after the first progression event, further progression events have not been systematically captured. Therefore this analysis is subject to uncertainty.

A total of 7 patients (3 in alectinib, 4 in crizotinib) had a CNS progression after having a systemic progression by INV.

A total of 11 patients (5 in alectinib, 6 in crizotinib) had a CNS progression after having a systemic progression by IRC.

d. The number of patients who had a CNS progression that was considered a systemic progression event

In the ALEX study, the independent review of CNS disease (namely CNS RECIST review) was performed by a panel of independent reviewers, which did not assess extra-cranial CNS disease. Meanwhile, a different panel of independent reviewers evaluated the response of systemic disease including CNS disease as per RECIST (IRC RECIST review).

For alectinib: at the primary analysis, 18 patients in the alectinib arm were identified as having CNS progression without prior non-CNS progression. These patients were primarily identified by CNS RECIST review with the exception of two patients, who were identified by IRC RECIST review. Since CNS RECIST review only assessed intra-cranial CNS disease, the patients with concurrent extra-cranial progression were identified from the IRC RECIST review, based on the evaluation of systemic disease (including CNS disease) of the 18 patients. Of those 18 patients, 6 patients had systemic progression at the time of the CNS progression.

For crizotinib: at the primary analysis, 68 patients in the crizotinib arm were identified as having CNS progression without prior non-CNS progression. These patients were primarily identified by CNS RECIST review with the exception of 5 patients which were identified by IRC RECIST review. Since CNS RECIST review only assessed intra-cranial CNS disease, the patients with concurrent extra-cranial progression were identified from the IRC RECIST review, based on the evaluation of systemic disease (including CNS disease) of the 68 patients. Of those 68 patients, 8 patients had systemic progression at the time of the CNS progression.

A10. **Priority question**: Please provide KM curves and KM data in Excel format for time to CNS progression for alectinib and crizotinib separately (regardless of CNS metastases at baseline and whether they had a non-CNS related progression event).

Two KM curves have been made available:

1. CNS-PFS (IRC) utilising the same two criteria: RECIST or CNS RECIST to capture CNS-progression or death (Figure 15). Any patient who experiences a non-CNS-progression prior to CNS-progression is followed until the first of CNS progression or death or loss to follow up.

    - Utilising the RECIST or CNS-RECIST criteria allows for the most complete and robust analysis of the impact of CNS metastases. However, to ensure internal consistency, the PFS (IRC) endpoint must also be adapted to incorporate the CNS-RECIST criteria. This analysis captures all CNS progressions; however this may be earlier than would be in clinical practice, as CNS-RECIST is not routinely used in the NHS.

2. An adapted version of CNS-PFS (IRC) (Figure 16). This utilises only the RECIST criteria, consistent with the PFS endpoints of the trial. Patients with a worsened CNS non-target lesion or a new CNS lesion are classified as CNS PD, whereas all other PD found on the general RECIST scale without any indication that this PD was

based on CNS are classified as non-CNS PD. Any patient who experiences a non-CNS-progression prior to CNS-progression is followed until the first of CNS progression or death or loss to follow up.

- Whilst this analysis is more consistent with the PFS endpoints, it is worth highlighting, due to the mechanism of assessing target and non-target lesions using RECIST, some CNS progressions are not captured in the analysis. Thus, this should be interpreted as a conservative assessment of CNS progression events.

The KM data are included in the Excel file “NICE CQs supplementary data_Updated response”, sheet “A10”, and the KM curves can be found below.

Figure 15: CNS-PFS KM (IRC, RECIST + CNS-RECIST)

Figure 16: Adapted CNS-PFS KM (IRC, RECIST)

A11. **Priority question**: Please clarify how many of the 18 CNS progressions in the alectinib group and 68 CNS progressions in the crizotinib group were in patients who had CNS metastases at baseline.

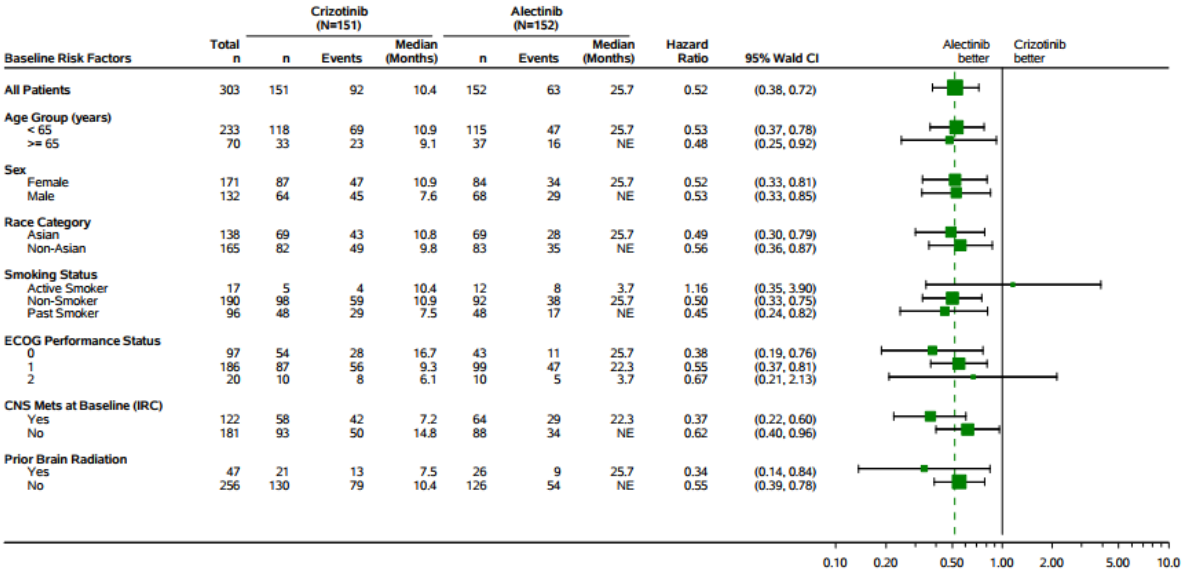
Of the 18 and 68 patients in the alectinib and crizotinib arms who had CNS progression without prior non-CNS progression by IRC, 12 (66.7%) and 33 (48.5%) had CNS metastases at baseline (IRC).

Progression-free survival

A12. **Priority question**: Please provide subgroup analyses (smoking status, baseline Eastern Cooperative Oncology Group performance score (ECOG PS), CNS metastases at baseline as determined by IRC, and prior brain radiation) for PFS by IRC assessment, including KM curves, underlying KM data in excel format and HRs between treatments with 95% CIs for each level of the categorical variable

The KM data requested are included in the Excel file “NICE CQs supplementary data”, sheet “A12”. The KM curves and summary statistics can be found below.

Figure 17: Summary of subgroup analyses



Baseline Risk Factors	Total n	Crizotinib (N=151) n	Crizotinib (N=151) Events	Crizotinib (N=151) Median (Months)	Alectinib (N=152) n	Alectinib (N=152) Events	Alectinib (N=152) Median (Months)	Hazard Ratio	95% Wald CI
All Patients	303	151	92	10.4	152	63	25.7	0.52	(0.38, 0.72)
Age Group (years)									
< 65	233	118	69	10.9	115	47	25.7	0.53	(0.37, 0.78)
>= 65	70	33	23	9.1	37	16	NE	0.48	(0.25, 0.92)
Sex									
Female	171	87	47	10.9	84	34	25.7	0.52	(0.33, 0.81)
Male	132	64	45	7.6	68	29	NE	0.53	(0.33, 0.85)
Race Category									
Asian	138	69	43	10.8	69	28	25.7	0.49	(0.30, 0.79)
Non-Asian	165	82	49	9.8	83	35	NE	0.56	(0.36, 0.87)
Smoking Status									
Active Smoker	17	5	4	10.4	12	8	3.7	1.16	(0.35, 3.90)
Non-Smoker	190	98	59	10.9	92	38	25.7	0.50	(0.33, 0.75)
Past Smoker	96	48	29	7.5	48	17	NE	0.45	(0.24, 0.82)
ECOG Performance Status									
0	97	54	28	16.7	43	11	25.7	0.38	(0.19, 0.76)
1	186	87	56	9.3	99	47	22.3	0.55	(0.37, 0.81)
2	20	10	8	6.1	10	5	3.7	0.67	(0.21, 2.13)
CNS Mets at Baseline (IRC)									
Yes	122	58	42	7.2	64	29	22.3	0.37	(0.22, 0.60)
No	181	93	50	14.8	88	34	NE	0.62	(0.40, 0.96)
Prior Brain Radiation									
Yes	47	21	13	7.5	26	9	25.7	0.34	(0.14, 0.84)
No	256	130	79	10.4	126	54	NE	0.55	(0.39, 0.78)

Figure 18: Patients Who Are Active Smokers

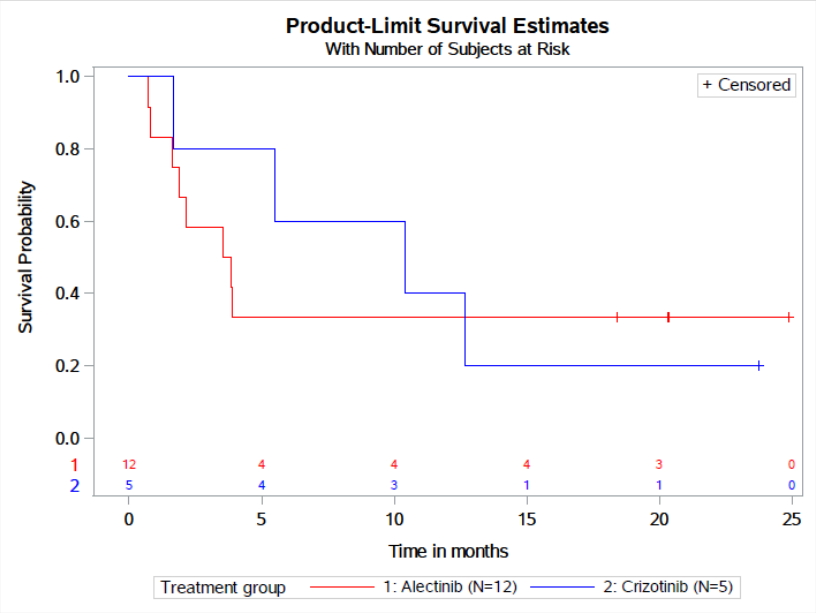


Figure 19: Patients Who Are Non-Smokers

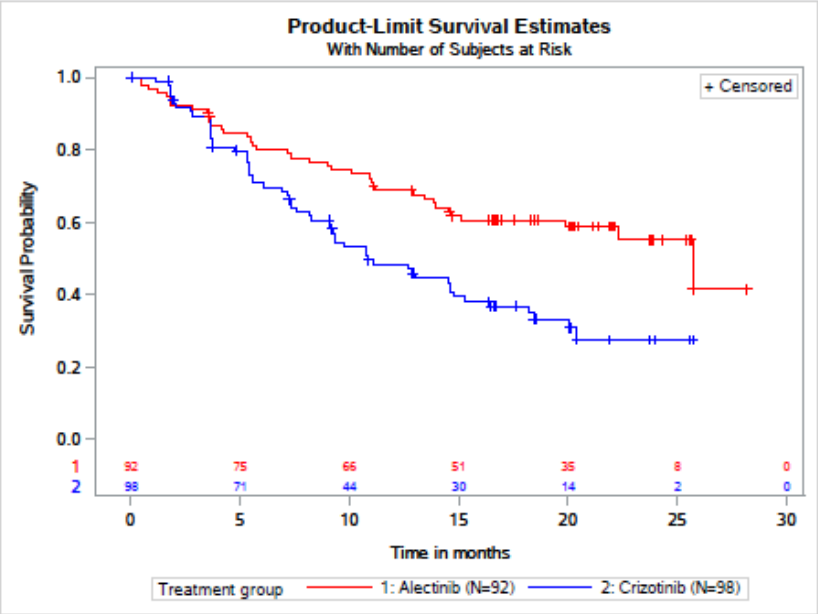


Figure 20: Patients Who Are Past Smokers

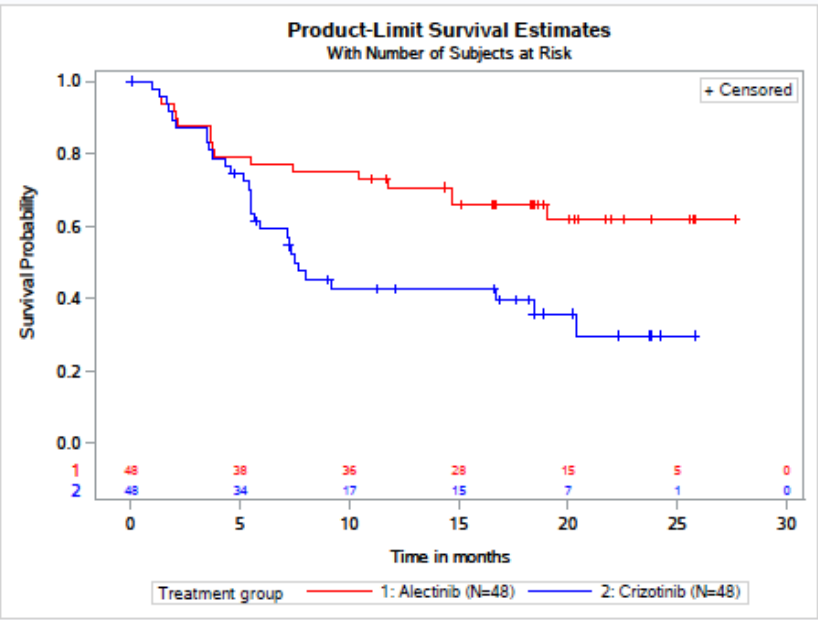


Figure 21: Patients With ECOG PS 0

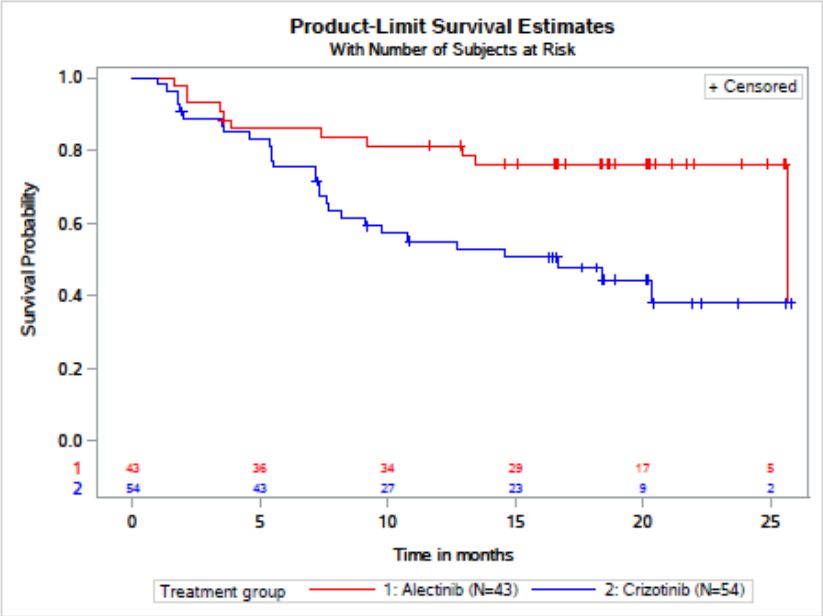


Figure 22: Patients With ECOG PS 1

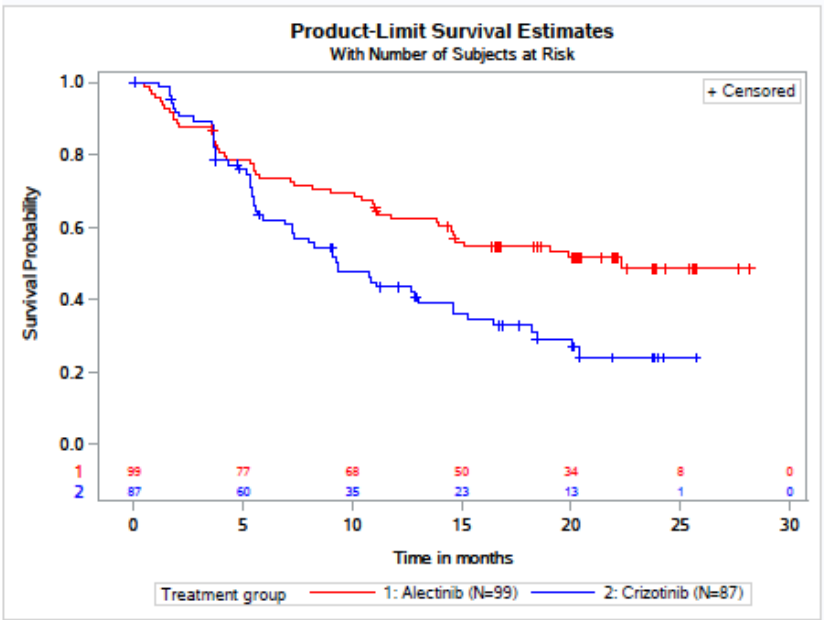


Figure 23: Patients With ECOG PS 2

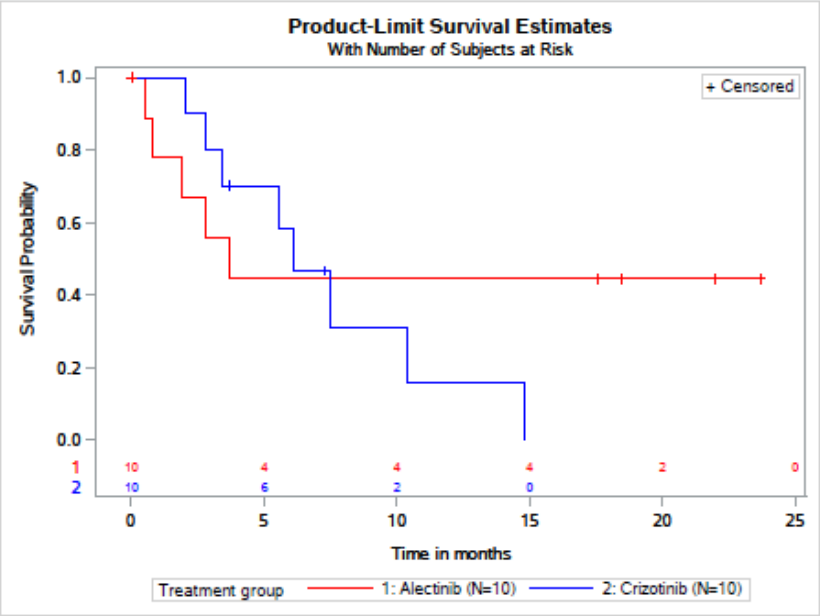


Figure 24: Patients With CNS Metastases at Baseline (IRC)

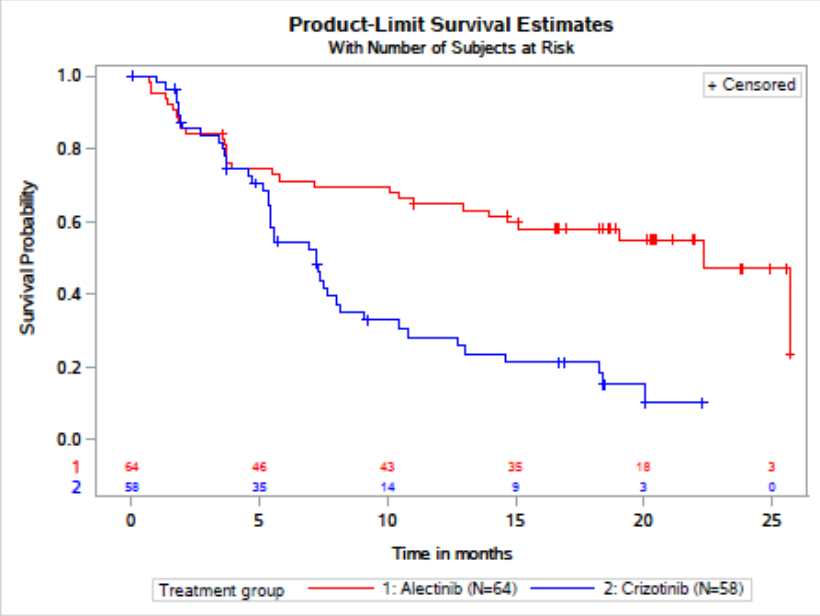


Figure 25: Patients With No CNS Metastases at Baseline (IRC)

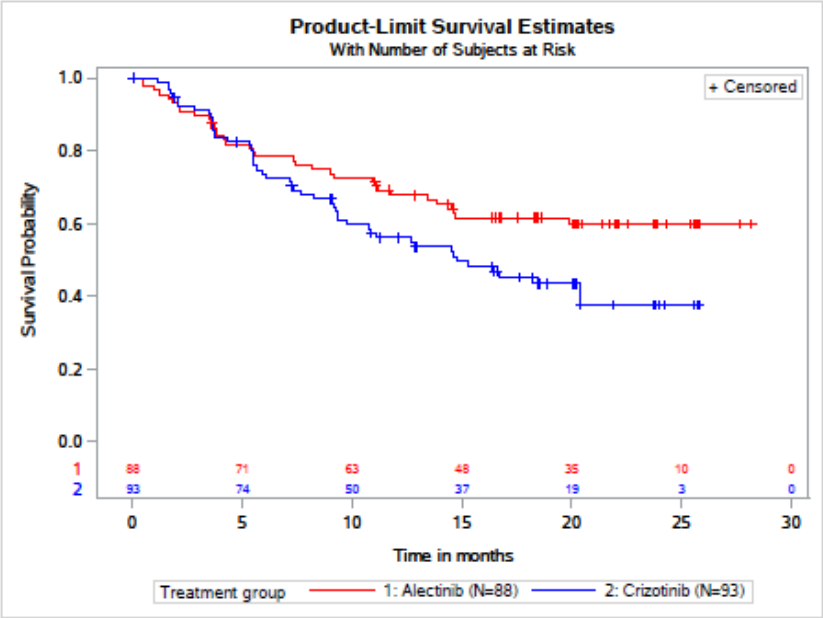


Figure 26: Patients With Prior Brain Radiation

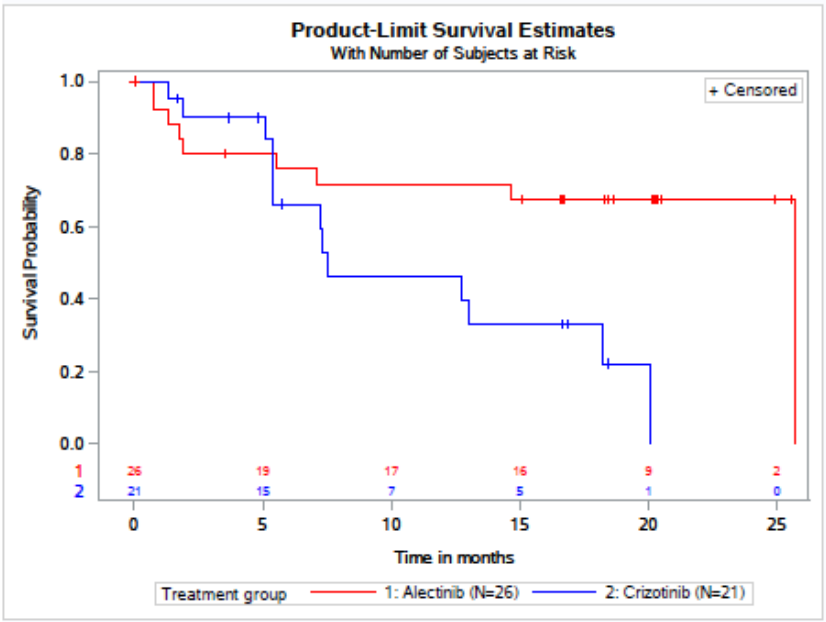
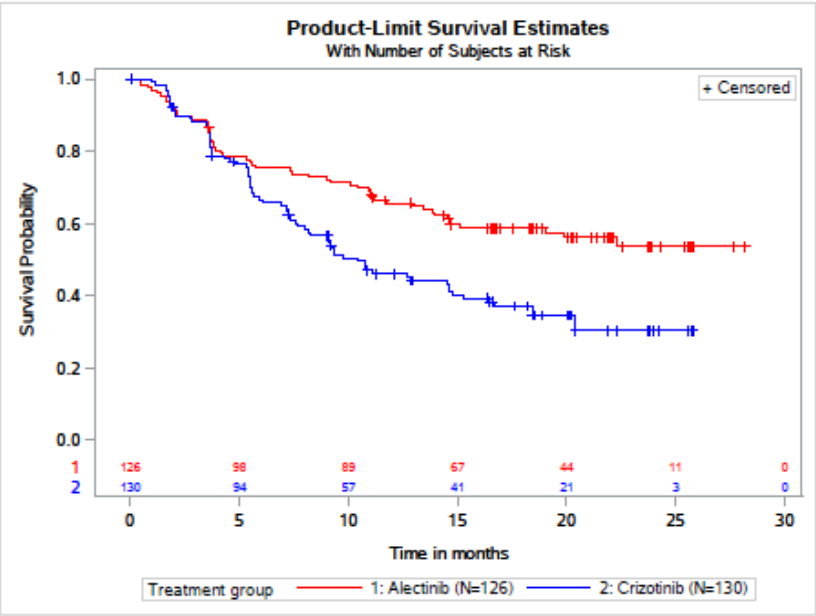


Figure 27: Patients With No Prior Brain Radiation



A13. Table 9 of the CSR [redacted] For those with disease progression, please provide a similar breakdown of number and site of lesions when progression was documented.

This analysis has not yet been processed from the data, thus cannot be provided at this time.

Health-related quality of life data

A14. Please provide more detailed results from ALEX for all EORTC QLQ-LC13 and EORTC QLQ-Core 30 (mean and standard deviations over time and at end of treatment for each group, including the number of responses at each timepoint).

25 files detailing mean and standard deviations over time, including the number of responses at each time point, and change from baseline by visit have been provided alongside this response.

Baseline characteristics

A15. Please clarify whether patients with an ECOG PS of 2 were eligible for ALEX. CS Table 5 (pg 23) shows that 7% of each group had ECOG PS 2 and CS page 18 states that randomisation was stratified by 0 to 1 versus 2, but the inclusion criteria on page 19 states only those with a score of 0 or 1 were eligible.

The inclusion criteria on page 19 include an error: patients with ECOG PS 0-2 were eligible for inclusion.

A16. Please provide the number of patients in each group with ECOG PS of 0 and 1 separately.

Table 6: ECOG PS patient numbers

	Alectinib	Crizotinib
ECOG PS 0	43	54
ECOG PS 1	99	87

A17. Please provide the number of patients in each group whose CNS metastases at baseline were symptomatic.

This analysis is not available. However, the CSR states: "Prior brain or leptomeningeal metastases allowed if asymptomatic (e.g., diagnosed incidentally at study baseline). Asymptomatic CNS lesions might have been treated at the discretion of the investigator as per local clinical practice. If patients had neurological symptoms or signs due to CNS metastasis, patients needed to complete whole brain radiation or gamma knife irradiation treatment. In all cases, radiation treatment must have been completed at least 14 days before enrolment and patients must have been clinically stable." Therefore it can be assumed no, or very few patients with CNS metastasis at baseline were symptomatic.

Study design and quality assessment

A18. Please provide justifications for the risk of bias judgements presented in CS Appendix D1.3.

The Cochrane critical appraisal justifications are provided in Table 7, and the NICE critical appraisal justifications for the same studies are provided in Table 8.

Table 7: Cochrane risk of bias assessment

	Random sequence generator		Allocation concealment		Blinding of participants and personnel		Blinding of outcome assessment		Incomplete outcome data		Selective reporting		Any other source of bias	
Author, Year	Y/N/?	Justification	Y/N/?	Justification	Y/N/?	Justification	Y/N/?	Justification	Y/N/?	Justification	Y/N/?	Justification	Y/N/?	Justification
Solomon, 2014a	Low risk of bias	Randomisation was stratified, suggesting randomisation sequence generated adequately	Unclear risk of bias	Method of concealment not described	Low risk of bias	Study was open-label, but all scans were assessed by central IRR by radiologists unaware of group assignments. Lack of blinding does not appear to have resulted in larger number of withdrawals in the comparator arm.	Low risk of bias	Outcome assessed by central IRR by radiologists unaware of group assignments	Low risk of bias	No missing outcome data	Low risk of bias	Study protocol not available but all pre-specified outcomes are reported in publications and/or registry	High risk of bias	When the study was designed the standard comparator was considered PEM+platinum-based chemotherapy. The comparator arm was based on this strategy. Since then there is evidence that adding PEM maintenance therapy after the maximum of 6 cycles of CHEMO can have additional benefit. There was no maintenance therapy in this study and the treatment duration for CRZ was, therefore, much longer

														(median 10.9 mths) than that of CHEMO (median 4.1 mths). Only one outcome (rate of AEs associated with cardiac failure) was adjusted for treatment duration differences. The choice of platinum chemotherapy was made by the investigator. 23% of patients in each arm had brain metastases at BL (all treated with brain radiotherapy and neurologically stable and BIRC assessed)
Lu, 2016a (abstract) and registry entry	Low risk of bias	Randomisation was stratified, suggesting randomisation sequence generated adequately	Unclear risk of bias	Method of concealment not described	Unclear risk of bias	Study was open-label. Scans were assessed by IRR but not reported in registry or abstract (no	Unclear risk of bias	Study was open-label. Scans were assessed by IRR but not reported in	Unclear risk of bias	Withdrawals due to AEs or lack of efficacy has not been reported, nor has	Low risk of bias	Study protocol not available but all pre-specified outcomes are reported in publications and/or registry	Unclear risk of bias	When the study was designed the standard comparator was considered PEM+platinu

						full paper yet published) whether assessment was performed at a central lab or whether radiologists were blind to treatment assignment		registry or abstract (no full paper yet published) whether assessment was performed at a central lab or whether radiologists were blind to treatment assigneme nt		treatment dose changes or interruption s.				m-based chemotherap y. The comparator arm was based on this strategy. Since then there is evidence that adding PEM maintenance therapy after the maximum of 6 cycles of CHEMO can have additional benefit. There was no maintenance therapy in this study and the treatment duration for each arm was not reported. All pts with BMs at BL had BMs that were treated with brain radiotherapy and neurologically stable in order to be eligible. 20% and 31% in CRZ and CHEMO arms respectively

														had brain metastases at BL, an imbalance that could favour CRZ
Soria, 2017	Low risk of bias	Randomisation was stratified, suggesting randomisation sequence generated adequately	Low risk of bias	Randomisation assigned by interactive response technology	High risk of bias	Study was open-label - patients and investigators were not masked to treatment - but most study sponsor personnel were blind to treatment assignment. As response outcomes were assessed by BIRC, it is unlikely that the open-label nature of the study would have influenced outcome assessment. However, it may have influenced withdrawals potentially: withdrawal due to lack of efficacy was higher in the CHEMO arm	Low risk of bias	As response outcomes were assessed by BIRC, it is unlikely that the open-label nature of the study would have influenced outcome assessment.	Low risk of bias	No missing outcome data	High risk of bias	Grouped Serious Adverse Event data were not reported. Full paper does indicate that serious adverse drug reactions were similar in both treatment groups but no data are given	High risk of bias	Relative dose intensity of ceritinib was 78.4% vs. 93.8-99.2%, which may make the comparative assessment more conservative. The CHEMO comparative arm allowed maintenance therapy with PEM, meaning that the comparative assessment would be more conservative compared to use of a CHEMO regimen consisting of a maximum of 6 cycles. Withdrawal due to lack of efficacy was higher in the CHEMO arm

						(94/187, 50%) than in the ceritinib arm (51/189, 27%) and withdrawals for any reason were also higher with CHEMO (157/187, 84%) than with ceritinib (94/189, 50%).							(94/187, 50%) than in the ceritinib arm (51/189, 27%) and withdrawals for any reason were also higher with CHEMO (157/187, 84%) than with ceritinib (94/189, 50%). Assessment of intracranial response may differ from other studies as RECIST 1.1 was modified to be more rigorous: "a maximum of five target lesions in the brain could be selected (if the minimum size of the longest diameter was 10mm) at baseline and evaluated at each subsequent timepoint" 31% and 33% of pts in CER

														or CHEMO arms respectively had brain metastases. BM (INV-assessed) were neurologically stable, symptomatic or non-symptomatic, and with/without previous brain radiation (59% of patients with BM did not have prior brain radiotherapy, in contrast to PROFILE 1014 where patients with BM had treated BM).
Peters, 2014	Low risk of bias	Randomisation was stratified using a block-stratified randomisation procedure, suggesting randomisation sequence	Low risk of bias	Randomisation was performed centrally via interactive voice or web-based response system	High risk of bias	Study was open-label. IRC corroborated INV assessments, and IRC assessments of secondary endpoints PFS and TTP outcomes	High risk of bias	The primary outcome was PFS assessed by INV, and this could have been affected by the lack of blinding, as	Low risk of bias	No missing outcome data for primary and key secondary outcomes	Unclear risk of bias	All primary and key secondary outcomes reported (data in confidence). Of the secondary outcomes listed in clinicaltrials.gov data	Low risk of bias	Baseline characteristics well balanced and there were no protocol violations. All patients randomised were treated as planned. Mean dose

		generated adequately				were made blind, so these are unlikely to have been affected. IDMC meetings were conducted blind to the sponsor. The primary outcome was PFS assessed by INV, and this could have been affected potentially by the lack of blinding, however. Discontinuation from treatment (any reason) was higher in the CRZ control arm (105/151, 69.5%) than in the ALEC arm (68/152, 44.7%), as was withdrawal by subjects (11/151, 7.3% with CRZ vs. 3/152, 2% with ALEC)		could ORR (also assessed by INV), hence high risk of bias. Secondary endpoints (PFS, Time to CNS progression) were assessed by blinded IRC so these are associated with a low risk of bias. OS would also be associated with a low risk of bias.				regarding pharmacokinetic endpoints and HRQoL (time to deterioration in QLQ-C30 or in QLQ-LC13, QLQ-C30 scores, QLQ-LC13 scores) have not yet been reported.		intensity was 92.4% with CRZ and 95.6% with ALEC 38% and 42% had BM at BL (IRC assessed), and 38% and 40% (INV assessed) for CRZ and ALEC, respectively. These %s, although balanced within the study, are higher than in PROFILE 1014, PROFILE 1029 and ASCEND-4, which could influence inter-study comparisons. Whether it could affect the comparison of relative effects is not known.

Table 8: NICE critical appraisal of RCTs

	Was randomisation carried out appropriately?		Was the concealment of treatment allocation adequate?		Were the groups similar at the outset of the study in terms of prognostic factors?		Were the care providers, participants and outcome assessors blind to treatment allocation?		Were there any unexpected imbalances in drop-outs between groups?		Is there any evidence to suggest that the authors measured more outcomes than they reported?		Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	
Author, Year	Y/N/ unclear/ NA	Justification	Y/N/ unclear/ NA	Justification	Y/N/ unclear/ NA	Justification	Y/N/ unclear/ NA	Justification	Y/N/ unclear/ NA	Justification	Y/N/ unclear/ NA	Justification	Y/N/ unclear/ NA	Justification
Solomon, 2014a	Yes	Randomisation was stratified, suggesting randomisation sequence generated adequately	Unclear	Method of concealment not described	Yes	Baseline characteristics were similar between treatment arms. 23% of patients in each arm had brain metastases at BL (all treated with brain radiotherapy and neurologically stable and BIRC assessed)	No	Study was open-label, but all scans were assessed by central IRR by radiologists unaware of group assignments. Lack of blinding does not appear to have resulted in larger number of withdrawals in the comparator arm.	Yes	Discontinuation from treatment was higher in CRZ arm (92/172, 53%) compared with CHEMO arm (61/171, 36%). The difference was mostly due to PD in CRZ arm	No	Study protocol not available but all pre-specified outcomes are reported in publications and/or registry	Unclear	The efficacy analysis was on an ITT basis (all randomised) The safety analysis included all patients who were randomised and received ≥ 1 dose of the assigned treatment. No reporting of methods applied for missing data
Lu, 2016a (abstract) and registry entry	Yes	Randomisation was stratified, suggesting randomisation sequence	Unclear	Method of concealment not described	No	Baseline characteristics were similar between treatment arms. All pts	No	Study was open-label. Scans were assessed by IRR but not reported in registry or	No	Discontinuation was similar in CRZ arm (39/104, 38%) compared with CHEMO	No	Study protocol not available but all pre-specified outcomes are reported in	Unclear	At the time of this assessment, the trial design was not reported in full.

		generated adequately				with BMs at BL had BMs that were treated with brain radiotherapy and neurologically stable in order to be eligible. 20% and 31% in CRZ and CHEMO arms respectively had brain metastases at BL, an imbalance that could favour CRZ		abstract (no full paper yet published) whether assessment was performed at a central lab or whether radiologists were blind to treatment assignment		arm (43/103, 42%)		publications and/or registry		
Soria, 2017	Yes	Randomisation was stratified, suggesting randomisation sequence generated adequately	Yes	Randomisation assigned by interactive response technology	Yes	Baseline characteristics were similar between treatment arms. 31% and 33% of pts in CER or CHEMO arms respectively had brain metastases. BM (INV assessed) were neurologically stable,	No	Study was open-label - patients and investigators were not masked to treatment - but most study sponsor personnel were blind to treatment assignment. As response outcomes were assessed by BIRC, it is	Yes	Discontinuations were higher with CHEMO (157/187, 84%) than with ceritinib (94/189, 50%).	Yes	Grouped Serious Adverse Event data were not reported. Full paper does indicate that serious adverse drug reactions were similar in both treatment groups but no data are given	Unclear	The efficacy analysis was on an ITT basis (all randomised) The safety analysis included all patients who were randomised and received ≥ 1 dose of the assigned treatment. No reporting of methods applied for

						symptomatic or non-symptomatic, and with/without previous brain radiation		unlikely that the open-label nature of the study would have influenced outcome assessment. However, it may have influenced withdrawals potentially: withdrawal due to lack of efficacy was higher in the CHEMO arm (94/187, 50%) than in the ceritinib arm (51/189, 27%) and withdrawals for any reason were also higher with CHEMO (157/187, 84%) than with ceritinib (94/189, 50%).						missing data, patients with missing subgroup information were not included in analysis of PFS according to subgroups
Peters, 2014	Yes	Randomisation was stratified using a block-stratified randomisation procedure, suggesting	Yes	Randomisation was performed centrally via interactive voice or web-based response system	Yes	Baseline characteristics were similar between treatment arms. 38% and 42% had BM at	No	Study was open-label. IRC corroborated INV assessments, and IRC assessments of secondary		Discontinuation from treatment was higher in the CRZ control arm (105/151, 69.5%) than in the ALEC	Unclear	All primary and key secondary outcomes reported (data in confidence). Of the secondary	Yes	Both efficacy and safety analyses were on an ITT basis (all randomised). For PFS

		randomisation sequence generated adequately				BL (IRC assessed), and 38% and 40% (INV assessed) for CRZ and ALEC, respectively		endpoints PFS and TTP outcomes were made blind, so these are unlikely to have been affected. IDMC meetings were conducted blind to the sponsor. The primary outcome was PFS assessed by INV, and this could have been affected potentially by the lack of blinding, however. Discontinuation from treatment (any reason) was higher in the CRZ control arm (105/151, 69.5%) than in the ALEC arm (68/152, 44.7%), as was withdrawal		arm (68/152, 44.7%)		outcomes listed in clinicaltrials.gov data regarding pharmacokinetic endpoints and HRQoL (time to deterioration in QLQ-C30 or in QLQ-LC13, QLQ-C30 scores, QLQ-LC13 scores) have not yet been reported.		and OS, patients with no post-BL assessments were censored at date of randomisation; for ORR and DCR, patients without post-BL assessments were regarded as non-responders.

								by subjects (11/151, 7.3% with CRZ vs. 3/152, 2% with ALEC)						

A19. Please explain why ALEX was designed as open label rather than double-blind.

An open-label study design was selected for patients enrolled in this study for a number of reasons. Firstly, for a blinded study design, all enrolled patients would be required to take five large capsules twice per day. This high pill count results from the difference in capsule size between crizotinib (size 0) and alectinib (size 1). Each dose would comprise one 250-mg capsule of crizotinib or matching placebo and four 150-mg capsules of alectinib or matching placebo. In order to blind, crizotinib capsules must be over-encapsulated. That further increases the size of a capsule from size 0 to size 00. Size 00 is usually the largest capsule size used orally for humans. For some patients, size 00 capsules are too large to swallow. The number and also the large size of the capsules could have increased the risk non-compliance.

Furthermore, a blinded study would increase the complexity of standard dose reductions. Dose interruption or dose reduction may be required on the basis of individual safety and tolerability. The standard dose reductions for crizotinib would be 200 mg BID (different capsule, size 1), followed by 250 mg QD. Dose reductions for alectinib would occur in 150-mg steps. In a double-blind study, these multiple step dose reductions introduce a high level of complexity and potential for error.

Additional steps have been taken to ensure the validity of the data in an open-label study design. These include performing a supportive analysis of efficacy on the basis of determining progression by an IRC, performing sensitivity analyses to demonstrate the robustness of the primary endpoint, defining progression using established response evaluation criteria (RECIST v1.1), performing tumour assessment at the same frequency in both arms and adhering to protocol-defined schedules, and finalizing the strategy for the final analysis of the primary endpoint before trial start, including developing predefined methods for handling missing data and censoring rules. Efficacy analyses will only be performed at the pre-specified analysis timepoints in the protocol (final analysis once 170 PFS events have occurred and survival follow-up analysis at 143 events).

A20. Given the open-label design of ALEX, please explain:

a. why INV PFS was chosen as the primary outcome and used in the company base-case, rather than PFS assigned by the IRC.

The selection of investigator-assessed PFS as the primary endpoint was made following discussions with the Health Authorities (including the US Food and Drug Administration) about its acceptability as the primary endpoint for the study.

Logistically, it would have been challenging to use IRC assessments for the primary analysis of PFS. The analysis of PFS was event driven, with tumour assessments conducted every 8 weeks until disease progression, as per the study protocol. In contrast, IRC assessments were centralised and not performed in real time, resulting in a delay between the tumour imaging and the completion of the IRC assessment. Therefore, it was not feasible to monitor the number of PFS events and plan the timing of the primary analysis around IRC assessments. Therefore it was agreed with the FDA to define investigator-assessed PFS as

the primary endpoint, with IRC-assessed PFS as a key secondary endpoint tested to confirm the results of the primary analysis.

In line with the regulatory decisions regarding the primary outcome INV PFS is presented in the company base-case, however, IRC PFS is also presented within the company submission.

b. why objective response rate was based on INV but CNS progressions were by IRC.

The decision to assess CNS endpoints using an independent review committee (IRC) was made in order to add validity to the interpretation of these results particularly as this assessment, by nature, is independent of investigator assessments and was also blinded. This was considered to be particularly important as specific CNS endpoints e.g. time to CNS progression was considered to be one of the key secondary endpoints of the clinical trial.

By contrast objective response rate (ORR) was not considered to be as important as a secondary endpoint and was therefore assessed by the investigator. However, data regarding ORR as assessed by the IRC in patients who had measurable disease at baseline was performed as an exploratory analysis in order to support the analysis or investigator-assessed ORR. The analysis of ORR assessed by the IRC in the ITT population showed comparable results.

A21. Please confirm whether safety assessments were made by the treating physician who was aware of treatment assignment.

Roche can confirm as an open label study the treating physicians, who were conducting the safety assessments, were aware of treatment assignment.

Section B: Clarification on cost-effectiveness data

Model structure and approach

B1. **Priority question.** Given the company's rationale for one of alectinib's main advantages being in delaying CNS progression, please consider restructuring the economic model to explicitly incorporate CNS progression, so appropriate costs and benefits can be more accurately estimated. If the company decides not to restructure the model, please justify why it was considered unnecessary.

Whilst exploring this further, Roche identified an error in the original submission. Throughout the submission, CNS progression is referenced as coming from the RECIST criteria, used in both the INV and IRC PFS endpoint. However, it has now come to our attention that IRC CNS progression was in fact measured by two criteria: RECIST and CNS RECIST. Whilst this approach ensures a complete and robust analysis of the important impact of CNS metastases, the number of patients with an event of CNS progression cannot be interpreted as a function of all PFS events as per IRC, as we have depicted in our submission.

Therefore, in order to restructure the model as the ERG have requested, one of the endpoints (PFS or CNS-PFS) was required to be adapted, to ensure internal consistency of the partitioned survival model. Three options were available:

i. Add CNS-RECIST to the PFS (IRC) endpoint (see Excel file "NICE CQs supplementary data_Updated response", sheet "B1")

ii. Separate RECIST and CNS-RECIST from the CNS-PFS endpoint, and only capture CNS progression as per RECIST (see Figure 16 and Excel file "NICE CQs supplementary data_Updated response", sheet "A10")

iii. Conduct both analyses, to capture the uncertainty associated with each approach

Roche have pursued the third option in the updated economic model.

The structure of the model has been overhauled to provide the user with a choice between a model with the original modelling approach, and two new approaches. The below table lists the options now available in the model. These are selectable from cell 'Model Inputs'!$F$19 (named range pfs_def) within the model:

Table 9: Model options

Option in named range pfs_def	Data source for PFS	Data source for CPFS	Censoring rules for CPFS
Original	Original model information	% in the original model	
RECIST and CNS RECIST	New analysis using PFS as per IRC (based on both RECIST and CNS-RECIST)	New analysis using CPFS as per IRC (based on both RECIST and CNS-RECIST)	CNS progression = event Death = event Lost to follow-up = censor Time was the first of: - Measured CNS progression - Death - Lost to followup
RECIST only	Original KM data as per the model originally submitted to NICE	New analysis using CPFS as per IRC (based on RECIST)	

The first option is the original approach to survival analysis, whilst the other two use two different sets of assumptions regarding the survival analysis of CNS progression free survival.

The RECIST and CNS-RECIST analysis has been chosen as the new base case analysis as this analysis is the most robust option available as it incorporates all identified CNS progressions (in line with the competing risks analysis presented in the CSR). The RECIST plus CNS RECIST analysis also has the added benefit of allowing greater potential capture of CNS progressions due to the 2 measures being incorporated, as follow-up for additional progressions was not routinely conducted once the first progression was seen on RECIST.

RECIST only assessment is presented to allow model sensitivity to the measure chosen to be assessed.

Consideration was given to whether or not non CNS progression should be censored given that follow-up for additional progressions was not routinely conducted once the first progression was seen on RECIST. When such censoring was applied, the CPFS curves crossed the OS curves, which produce implausible outcomes (negative population of the CPFS health state), given the partitioned survival model structure. Patients were therefore followed until the first of CNS progression, death or loss to follow-up regardless of whether a non-CNS progression was observed.

As the new approaches involved extensive changes to the model, a description of survival, cost and HRQL implications is provided in the below list. Further, all major changes within the updated CE model are highlighted in yellow so that they may be conveniently located by the ERG.

1. Post-progression survival with and without CNS metastases have been added to the survival model. Patients in PFS can transition into PPS without CNS progression, PPS with CNS progression or death. Patients with progression but no CNS progression can then subsequently progress into either progression with CNS progression or death. Finally, patients in PPS with CNS progression can transition only to death. Therefore, the underlying model structure remains similar, and the flow of calculations has been kept as similar to the original model as possible.

2. The cost associated with CNS progression in comparison to any other progression has been added in the form of a marginal cost associated with additional procedures and resource usage. That is, CNS metastasis costs are treated as additive to the subsequent treatment drug costs which are associated with progression (applied as a one-off cost on progression). As such, treatments provided to post-progression patients are assumed to be the same with or without CNS metastasis, except for the new costs added for CNS metastasis specific treatments. The costing of CNS metastases has been revised in line with ERG question response (Question B26) to match the Novello et al guidelines and now has the capacity to include corticosteroids (dexamethasone), stereotactic radiosurgery (SRS), whole-brain radiotherapy, and resection surgery rather than just SRS. Explanations for costs and justifications for assumptions are provided below.

3. The health-state utility value (HSUV) associated with CNS metastasis is the same value as used in the original submission of 0.52. This value is active in the models separating PPS with and without CNS metastasis, unless the options for progressed utility in the named range Utility_Option ('Model Inputs'!F49) is designated to be “2nd & 3rd line PPS utility”, in which case these values take precedence and CNS metastasis is therefore assumed to only affect costs of providing care, and not patient HRQL. The 0.52 value is derived from works by Roughley *et al*. (2014). The S.E. for this value is assumed to be 10% of the mean value (0.052), and the deterministic value is varied using a beta distribution in the PSA, in line with other utilities.

Explanation of survival modelling assumptions for CNS metastasis

As previously, the selection of the survival curve used within the economic model was based upon statistical goodness of fit, visual fit to the KM and clinical plausibility in the long term.

The AIC and BIC statistics indicated that there is no meaningful difference in goodness of fit to the trial data for both treatment arms between the log-normal, log-logistic and gamma parametric fits to the CPFS curve using either of the two new survival modelling strategies (see Table 10 and Table 11). Gamma was selected for the extrapolation, due to the levelling off of cumulative CNS metastasis incidence in the long term, demonstrated by the poster presented by Betts et al. at the 2016 AMCP Managed Care & Specialty Pharmacy Annual Meeting in San Francisco (Betts, 2016). It should be noted, however, that this poster likely underestimates CNS progression considerably for crizotinib given the healthier population included.

Table 10: CPFS (IRC, RECIST + CNS RECIST) parametric fits

	Alectinib		Crizotinib	
Distribution	AIC	BIC	AIC	BIC
Exponential	298.93	301.95	372.19	375.21
Weibull	299.56	305.61	368.48	374.51
Log-normal	297.25	303.29	353.97	360.01
Gamma	298.98	308.05	352.46	361.51
Log-logistic	298.89	304.94	358.53	364.57
Gompertz	300.93	306.98	373.87	379.90

Table 11: Adapted CPFS (IRC, RECIST) parametric fits

	Alectinib		Crizotinib	
Distribution	AIC	BIC	AIC	BIC
Exponential	273.12	276.14	322.43	325.45
Weibull	274.41	280.46	319.79	325.83
Log-normal	273.51	279.56	312.96	318.99
Gamma	275.51	284.58	313.97	323.02
Log-logistic	274.16	280.21	316.30	322.33
Gompertz	275.12	281.16	323.54	329.57

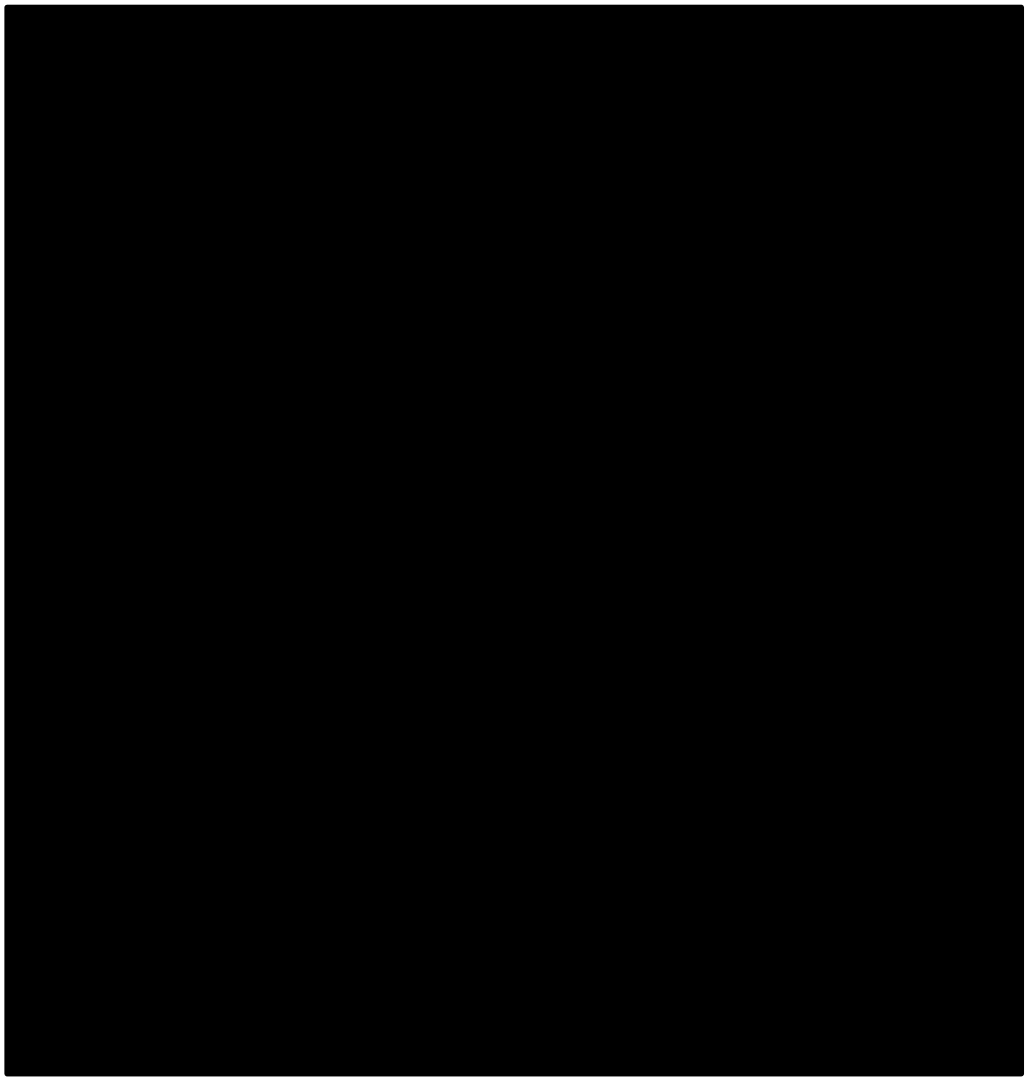
As CPFS using RECIST + CNS-RECIST was selected as the base case, it was necessary to also update the PFS (IRC) endpoint, to also include CNS-RECIST, to ensure internal consistency of the economic model. However, if selecting the adapted-CPFS, using RECIST only as a scenario analysis, this is updated back to the original PFS (IRC) endpoint. IRC is used in both cases to be consistent with the newly incorporated measures of CNS progression. The updated PFS curve (IRC, RECIST + CNS RECIST) has also been projected using KM + exponential for consistency with previous modelling of PFS and as this still provided a good fit to this endpoint.

Figure 28: Updated PFS (IRC, RECIST + CNS-RECIST)

The overall survival base case modelling/extrapolation assumptions have not changed compared to the original base case model. Overall survival remains an exponential fit.

The proportion of transitions out of CPFS which were and were not deaths from the ALEX trial was used to track the proportion of patients in each cycle which enter the progressed and CNS progressed state. These proportions are located in the CE model in cells 'Model Inputs'!D142:E143, and the data was taken from table 15 of the CSR (see Table 12). This is assumed to be a fixed proportion throughout the model, as no other information on this is available and stratified analyses would lead to excessive subdivision of the data and result in biased analyses.

Table 12: Table 15 from CSR



In the event that KM + extrapolation is selected for the CPFS curve, the starting point to apply the parametric extrapolation was selected using the log-hazard plot (see Figure 29).

Figure 29: CPFS (IRC, RECIST + CNS-RECIST) log hazard plot

A graphical representation of the two different KMs is provided in Figure 30, and in the model inputs sheet, to allow for simple comparison of CPFS survival estimates when using RECIST only or RECIST + CNS RECIST. As is intuitive, CNS + CNS RECIST is associated with higher failure rates for CPFS in both arms than RECIST only, which is less likely to detect CNS metastasis than both measures combined.

Figure 30: CPFS endpoints: RECIST + CNS-RECIST, versus RESIST only

The KM data are included in the Excel file “NICE CQs supplementary data_Updated response”, sheet “A10” and “B1”. Log cumulative hazard plots for all curves can also be found in sheet “LCHP”.

Explanation of costing assumptions for CNS metastasis specific treatments

In the base case in the originally submitted model, at progression, all patients were assumed to either immediately CNS progress or never CNS progress. In the updated base-case, this does not happen. Patients at CNS progression are now assigned the marginal cost associated with CNS progression. Thus, one simplifying assumption of the updated model is that other than the CNS metastasis specific resource usage currently captured, there is no difference in the cost per week associated with a patient that has progressed but does or does not also have CNS metastasis.

The marginal cost associated with CNS progression in the updated model is assumed to be incurred at the point of CNS progression. Patients which CNS progress but do not die in a model cycle are assigned the cost of a course of SRS treatment, of identical cost to the cost used in the original submission (Table 42 in document B). In addition to this, patients CNS progressing are assigned the cost of 4mg of dexamethasone daily, in line with the recommendations made by Novello *et al (Novello et al., 2016).* The cost for this dexamethasone are taken from the most recent eMIT publication (Health., 2017).

The costs of resection surgery and whole-brain radiotherapy (WBRT) have also been added into the model. Following consultation with Roche clinical experts, the opinion was that approximately 77% of patients receive WBRT, 23% of patients receive SRS and resection

surgeries are very rare. These proportions are applied in scenario analyses rather than being used in the base-case, as no other values are available against which to validate this information, and a recent UK publication states that WBRT has "little additional clinically significant benefit for this patient group" (Mulvenna et al., 2016). However, the impact on the ICER is marginal. As described in answer to question B26, provision of steroids only is not recommended, so this has not been included as the base case, or as a scenario analysis.

In the updated model, all patients with CNS progression receive symptomatic treatment, based on clinical opinion that asymptomatic CNS progression patients are likely to quickly progress to symptomatic and require treatment.

New base-case results

Updated base-case results are supplied in a separate document, alongside this response.

B2. **Priority question.** Please undertake a formal assessment of the existence (or not) of proportional hazards (PHs) for the OS and PFS (including INV- and IRC- assessed) data in ALEX, using the guidance outlined in DSU 14 (such as using log-cumulative hazard plots and assessing the clinical plausibility of the assumption).

The log cumulative hazard plots for OS and PFS (by INV and IRC) can be found in Figure 31, Figure 32, and Figure 33 respectively.

Figure 31: OS log cumulative hazard plots

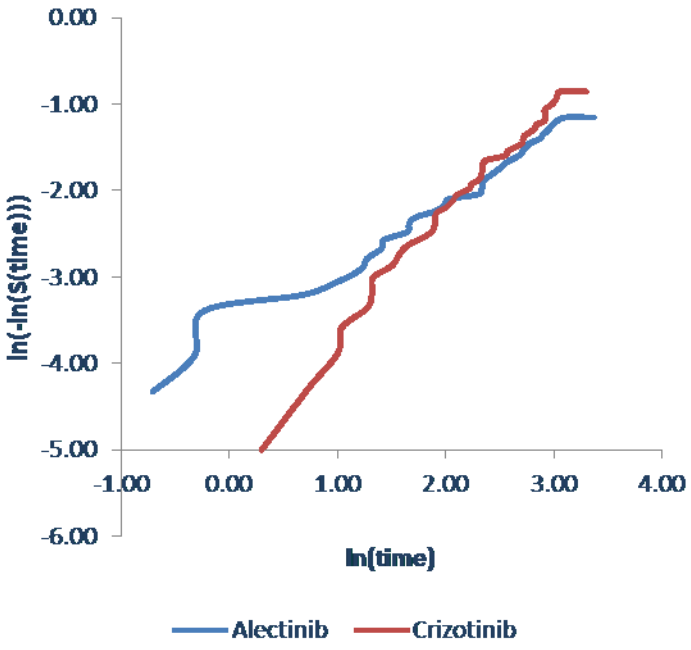


Figure 32: PFS INV log cumulative hazard plots

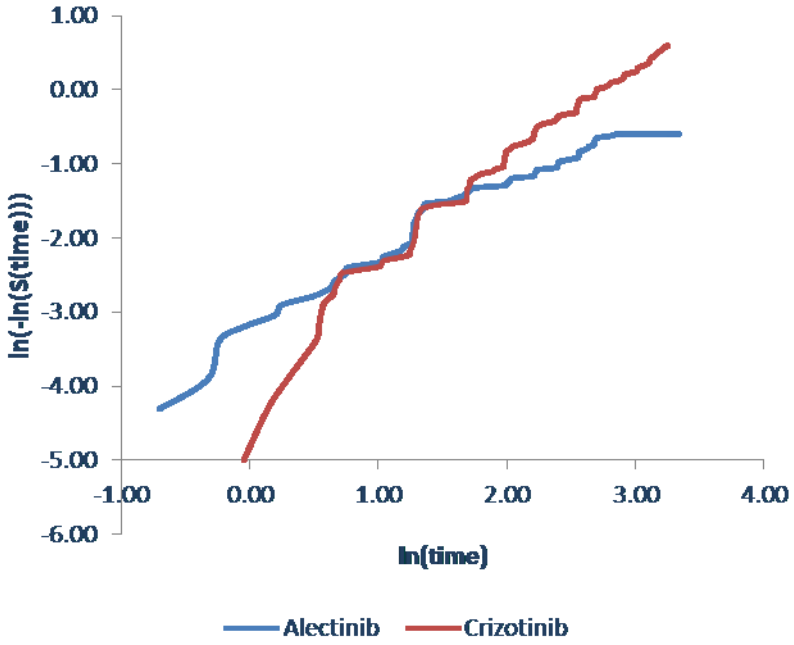
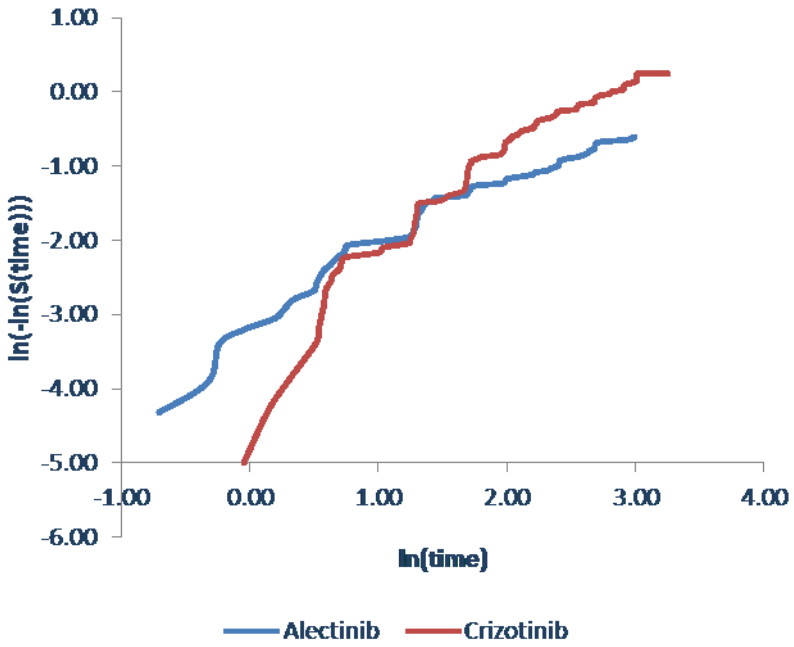


Figure 33: PFS IRC log cumulative hazard plots



As demonstrated, the proportional hazards assumption is not met, validating the approach taken in the company submission in the fitting of separate parameterisations to each treatment arm, and applying separate parametric models of the same type, to both crizotinib and alectinib, as recommended by DSU guidance (Latimer, 2013).

B3. **Priority question.** In light of the conclusions reached as a result of question B2, please explore the following:

a. Using the log-cumulative hazard plots, please assess the methodological and clinical plausibility of using exponential distributions to model OS and PFS in the model, and therefore assume a constant hazard for survival and progression outcomes for the entire period of analysis for OS (and for the extrapolation part of the PFS curves);

The exponential parametric model was selected for both treatment arms based on: statistical fit, visual inspection, and clinical plausibility, as per the NICE recommendation. In addition, clinical expert advice validated the chosen distributions as appropriate.

From a technical stance, we recognize that use of exponential distribution where the hazard is constant, leads inevitably to proportional hazards assumption that does not hold, at least initially, based on the log cumulative hazard plots. It is recommended that if the log cumulative hazards are crossing, as seen here, then each arm should be analysed separately (Latimer, 2013). It is, however, not sufficient to exclude a parametric distribution solely on the basis of the log cumulative hazard plots. The choice should also be based on:

- clinical plausibility of the model predictions
- whether the log-cumulative hazard plots are relatively straight lines (implies that a Weibull model would be appropriate)
- closeness to a gradient of 1 (implies an exponential model would be appropriate)
- whether they indicate radical fluctuations or shifts that require piecewise or more flexible models
- whether each model sufficiently fits the observed data both statistically and visually

Taking these elements into account, the exponential was considered as an appropriate option for OS extrapolation and PFS extrapolation after 18 months, despite its limitations.

Note we supply data for PFS using the KM plus exponential in the base case due to the crossing of KMs and hazard functions up to 18 months, for OS a similar KM plus exponential option is supplied as scenario analysis within the CS, and will also be provided in the response including the model updates for question B1.

b. Please explore the additional rationale underlying the methodological assumption in using exponential distributions to model OS and PFS, even when independently fitting exponential models to each treatment arm, that PHs exist because the hazards are constant throughout time, and thus so is the ratio between the hazards across treatment arms.

This question has been answered as part of the response to B3a.

B4. **Priority question.** Please provide (in Excel format) the KM data for time to off-treatment (TTOT) shown in Figure 8, page 56 of the CS.

The KM data requested are included in the Excel file "NICE CQs supplementary data", sheet "B4".

B5. Please clarify if the sentence on page 52 of the CS, "whereas most previous appraisals have not distinguished between progression locations, the model structure utilised in this submission does", refers to the costs and QALYs in the economic model being weighted by the proportion of patients observing CNS progression with alectinib and crizotinib, respectively.

The ERG's interpretation here is correct. For additional clarity, further explanation has been included below:

Two costs and utilities have been utilised in the progressive disease state, in order to reflect the difference between a CNS and non CNS-related progression. Supportive care costs and health state utilities have then been weighted according to the proportion of patients who experience a CNS-related progression (as reported in ALEX) across both treatment arms. Ultimately, a single cost and utility (for each treatment arm) is applied to the progressive disease health state in the model.

However, as per question B1, Roche have requested an extension to update the structure of the economic model, therefore this is subject to change.

Treatment effectiveness

B6. **Priority question.** The ERG used the KM data for alectinib and crizotinib from ALEX, provided in the economic model, to fit and extrapolate survival curves for OS and PFS (fitted independently for the two treatment arms). The ERG found a few discrepancies between its results and the company's, in terms of assessment of fit. Therefore, can the company please consider re-running the statistical models in order to:

Roche have re-explored the extrapolations, and are confident the results incorporated in the economic model, and our company submission are accurate. The reason for the discrepancy is two-fold:

1. Times for censored patients have not been provided in dataset included in the economic model, which the ERG has used to rerun the analysis. As such, the ERG must be making assumptions on censoring, which will impact the results being provided, we are not clear what these assumptions are but they will not produce the same results as the actual data.

2. The difference in statistical programs used: Roche has conducted these analyses using SAS 9.4, whereas the ERG confirmed they have used R. These packages have different methods to calculate AIC, therefore will produce different results.

    - R calculates AIC as: -2*log-likelihood + 2*npar. The maximum log-likelihood function is calculated with the optim function and the default method is Nelder and Mead (1965) in flexsurvreg.

- In SAS, PROC LIFEREG is used for PSM and the same formula is used for AIC: -2*log-likelihood +2*npar. However here maximum log-likelihood is calculated using the Newton-rapheson method.
    - This could lead to some minor differences in the calculated AICs but the most likely source of the difference between the ERG's estimates and those in the submission is the assumptions the ERG have used for censoring times (compared to use of actual data).

It is worth highlighting, the SAS program has a standard package to conduct this analysis, whereas R has a number of packages, and a number of different assumptions that can be implemented, which will inherently change the results. As SAS is a program that is endorsed and recommended by NICE, Roche feel it is unnecessary to rerun this analysis in R, for the benefit of the ERG.

a. Re-assess the lack of convergence of the Gompertz model for OS and PFS outcomes for alectinib. When the ERG ran the survival analysis, not only did the Gompertz model converge, but it was also the best fitting model (regardless of clinical plausibility of the extrapolated curves) for OS and PFS outcomes for alectinib. If the Gompertz model does not reach convergence, please explain why;

In the SAS analysis there is insufficient data to estimate the theta of the Gompertz model. As such, a distribution is provided, however it is closely approximated to the exponential. In addition, a PSA is unable to be conducted as the variance/covariance matrix doesn't converge. This analysis was therefore not included in the economic validation exercise.

b. Re-assess the relative fit of the exponential model for OS for alectinib according to AIC values. In the ERG's initial analysis (and indeed in the visual fit exercise of the curves provided in the company's economic model), the exponential curve seems to be the worst-fitting one, but was still chosen to model OS for alectinib;

As discussed in the company submission (section B.3.3.2), and as detailed in TSD14 (Latimer, 2013), extrapolation of curves should be based on: statistical analyses (AIC and BIC), visual inspection, and clinical plausibility. TSD14 also details that whilst AIC/BIC tests are useful to determine which models fit the observed data best, they do not tell us anything about how suitable a parametric model is for the time period beyond the final trial follow-up. This is of particular importance for the appraisal of alectinib, where only 50% of the PFS curve and 27% of the overall survival curve has available KM data. As such, it is important to utilise other means to validate the model predictions.

Assessment of model fit by AIC only is not an academically robust analysis. However, a table has been incorporated below, demonstrating that as per the SAS outputs, exponential is still the best fitting curve for alectinib OS. However, as addressed in the company submission, the AIC estimates are very close, demonstrating a number of the distributions

are similarly plausible, thus the importance of visual assessment and clinical plausibility to determine the optimal distribution.

Table 13: Best statistical fit by AIC: alectinib OS

Distribution	AIC	Ranking of fit
Exponential	246.59	1
Weibull	247.98	4
Log-normal	247.97	3
Gamma	249.79	6
Log-logistic	247.91	2
Gompertz	248.59	5

c. Similar to alectinib, the exponential model is among the worst-fitting models for the OS curve for crizotinib. If, for clinical plausibility reasons, the company considers that the exponential tails are the most clinically plausible ones to model OS, please state such rationale, and consider using a similar approach to that taken to modelling PFS curves (i.e. fitting a parametric tail to the OS KM curve for both alectinib and crizotinib), given the poor fit of exponential curves to the OS KM data in ALEX;

As detailed in question B6b, assessment of model fit by AIC only is not an academically robust analysis. However, a table has been incorporated below. Whilst exponential is not one of the best fitting curves to the available data, it is pivotal to highlight two key considerations:

1. The numerical difference between the best statistically fitting curve (the log-normal) and the worst statistically fitting curve (the Gompertz) is 3.85 points. When assessing the best statistical fit a difference of 5 or more is generally considered important. Therefore it is clear all of the distributions are similarly plausible fits

2. KM data is only available for 35% of the overall survival curve. As such, it is important to utilise other means to validate the model predictions.

Table 14: Best statistical fit by AIC: crizotinib OS

Distribution	AIC	Ranking of fit
Exponential	234.24	5
Weibull	232.71	3
Log-normal	230.88	1
Gamma	232.79	4
Log-logistic	232.10	2
Gompertz	234.72	6

As described in the company submission (section B.3.3.2), beyond statistical fit, visual fit and clinical plausibility of the resulting model tails were assessed for all distributions to determine the appropriate extrapolation. Further, longer term evidence for crizotinib (PROFILE 1014) was sought, to validate survival predictions of all distributions.

Accounting for the more favourable patient characteristics of the PROFILE 1014 trial, the exponential provided the second best fit to the long term evidence available for crizotinib based upon digitised data (second to the gamma, which, when applied to the alectinib arm, in line with DSU guidance (Latimer, 2013), provided a long term survival estimate that was questioned on clinical plausibility grounds). As such, it was deemed the exponential was the most appropriate distribution to utilise.

Nevertheless, Roche accepts, and highlighted within our submission, that the exponential fit to the available data for both treatment arms is not optimal. Roche originally did not fit a parametric tail to the OS KM curve for both alectinib and crizotinib given the immaturity of the data, however if the ERG prefers to utilise KM data, and apply the distribution to the tail, there is a minimal difference in the resulting ICER and improved visual fit. A scenario accounting for this will be added to the updated economic model when provided (extension requested until COB 15h December).

d. Please explain the methodological difference between the piecewise exponential models and the KM + exponential curve models, included in the economic model.

Please see below the description of each option:

a) KM + parametric tail (exponential in our case) allows the model to use the observed KM data until any time point of the observational period (user defined cut-off time) and apply an extrapolation parametric model after that time point. The parametric tail is based on the fit to the entire dataset (before and after the user defined time point). This allows us to utilise all available evidence up to the point of extrapolation, to inform the shape of the curve, and only replace the end 'tail' of the data where censoring increases.

b) The piecewise option that often is required from ERGs, allows the application of a constant hazard after any point that the user of the model believes there is a difference in the trend of the hazard during the observational period. That option then isolates the latest part of the hazard where there is a shift in the hazard trends and applies an exponential extrapolation based on that.

Given the cumulative hazard plot graphs, we could not identify any major shift in the hazard trend at any time point, therefore did not deem it appropriate to use the piecewise approach.

To note: a small error has been identified in the macro associated with the piecewise distribution. Therefore, this will be updated in the updated version of the economic model (extension requested until COB 15th December).

B7. **Priority question.** In case of model convergence, please include Gompertz curves in the economic model for OS and PFS outcomes for alectinib.

As discussed in response to question A6, the source of the discrepancy has been identified. The SAS analysis provided in the economic model, and company submission is correct. The Gompertz model is included in the economic model, although there was insufficient data to

calculate theta, therefore this distribution acts as an exponential, and a PSA cannot be conducted on it.

B8. **Priority question.** Please clarify if the Gompertz curves included for OS and PFS for alectinib in the economic model are indeed Gompertz curves (considering the statements included in the CS about the non-convergence, and therefore non-inclusion of Gompertz models).

The Gompertz distribution is a generalization of the exponential distribution and can accommodate monotonically increasing (γ>1) or decreasing hazards (γ<1) over time, defaulting to a constant hazard for specific values of the shape parameter (λ). The hazard function of Gompertz is therefore: h(t) = exp(exp(λ) + γt).

If, as in our case, the data do not allow the estimation of the γ, then the Gompertz behaves as an exponential.

B9. **Priority question.** With regards to the KM data referred to on pages 62-63 of the CS, pertaining to the OS curve for PROFILE 1014, please provide the OS KM data (in Excel format) for PROFILE 1014, used to compare survival predictions from ALEX.

As specified in the company submission (section B.3.3.2), the PROFILE 1014 KM curve was digitised using Engauge Digitizer 9.8. Therefore, the KM data that can be provided is not robust patient level data, thus is subject to uncertainty. The KM data requested are included in the Excel file “NICE CQs supplementary data”, sheet “B9”. As also described in section B.3.3.2, we would like to highlight the significant differences in baseline characteristics between the PROFILE 1014 and ALEX trials. Of note, patients in the PROFILE 1014 were generally younger, with a lower proportion of brain metastases at baseline, and a higher proportion of patients had received prior treatment for brain metastases at baseline (see Appendix M of company submission). Thus, in total, patients were generally healthier in the PROFILE 1014 study, and therefore could be expected to perform better. This is further supported when reviewing the NICE appraisal of crizotinib (TA409) where results were adjusted to a real world population, acknowledging the favourable patient population in the trial (NICE, 2016). We hope the ERG do not plan to conduct a naïve treatment comparison utilising the provided KM data.

B10. **Priority question.** Please undertake an exercise of assessment of fit and clinical plausibility of extrapolated curves with the IRC-assessed PFS data from ALEX, similar to the one provided for the INV-assessed PFS data in the CS. Please investigate if the survival analysis undertaken originally by the company for the IRC-assessed PFS needs re-assessing, similar to what has been described in question B6.

This was already provided in Appendix L of the company submission. However, for ease it has also been included below.

Following the response to B6, this analysis has not been re-assessed for the endpoints currently included in the economic model. However, if updates are required following the

model structure update, as requested in B1, this will be provided in parallel (requested extension to COB 15th December).

Parametric distribution fitting to PFS by IRC

The AIC and BIC goodness of fit for PFS IRC can be found in Table 15.

Table 15: Summary of goodness of fit for PFS: alectinib and crizotinib

	Alectinib		Crizotinib	
Parametric distribution	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	381.93	384.96	384.40	387.42
Weibull	378.95	385.00	384.30	390.34
Log-normal	371.85	377.90	370.73	376.77
Gamma	369.76	378.83	369.26	378.31
Log-logistic	376.07	382.12	375.01	381.04
Gompertz	383.93	389.98	386.40	392.44

Figure 34 shows the visual fit of all PFS distributions to the ALEX KM data. As the Gompertz did not converge for alectinib, visual assessment of PFS clinical plausibility for the remaining curves can be found in Figure 35.

Similarly to PFS by INV, the top 3 distributions by the combined best statistical fit (Log-normal, Gamma and Log-logistic) are clinically implausible, as the PFS curves meet the OS curves, and are subsequently capped (i.e. if the cap was not implemented, PFS would cross OS). Weibull also appears to come close to crossing, and, similarly to the PFS INV endpoint, produces clinically implausible long term PFS estimates for alectinib, based on consultation with clinical experts (10 years = 10% patients still in PFS).

Therefore, the rankings presented in section B.3.3.3 of the company submission (see Table 16) are consistent across endpoints, and the exponential is the best fitting curve, irrespective of endpoint utilized.

Figure 34: Visual fit of PFS distributions to KM data

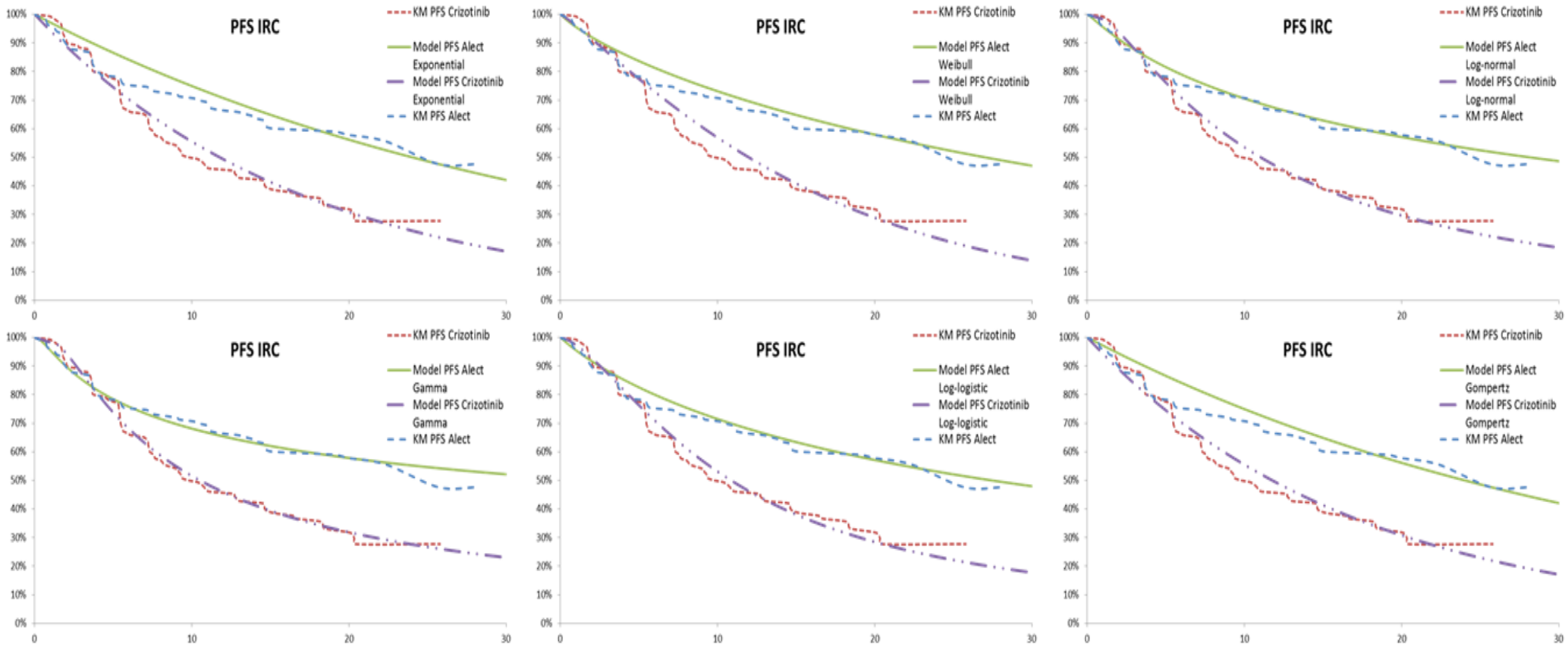


Figure 35: Visual assessment of PFS clinical plausibility

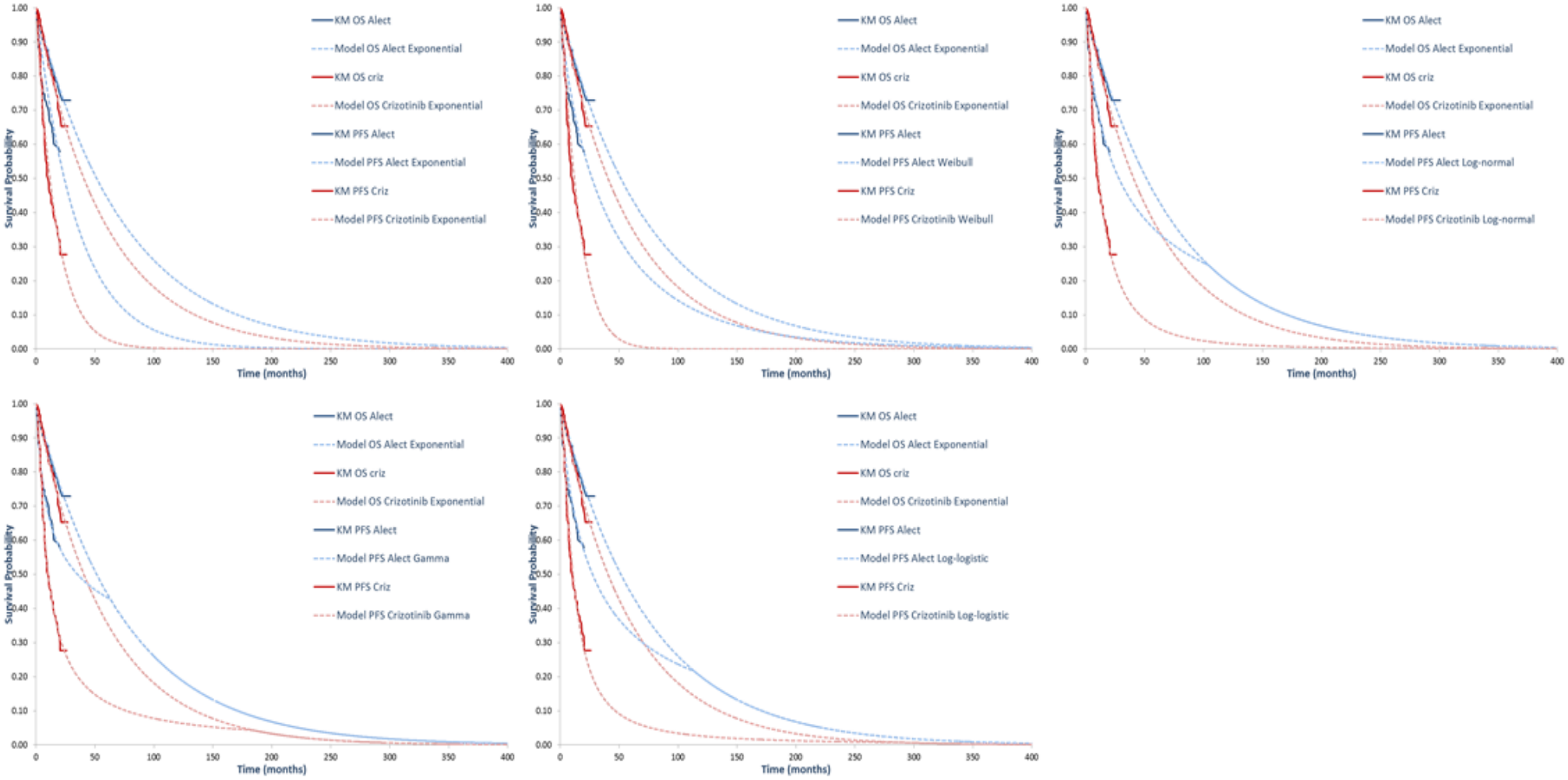


Table 16: Ranking of PFS distributions based on combined AIC/BIC, visual fit and clinical plausibility

Parametric distribution	Alec/criz combined AIC	Alec/criz combined BIC	Visual fit to KM	Clinical plausibility	Ranking
Exponential	754.47	760.51	×	✓	1
Weibull	746.09	758.18	~	~	2
Log-normal	732.27	744.36	✓	××	3
Gamma	733.09	751.21	✓	××	3
Log-logistic	738.09	750.17	✓	××	3
Gompertz	755.70	767.78	×	-	4

No updates were made to either RECIST only PFS IRC or OS fits. New PFS and CPFS fit information is supplied in answer to B1.

B11. **Priority question.** The model incorporates the very strong assumption that all patients will have CNS progression on the first cycle after they move to the disease progression health state. As an alternative analysis, please include a scenario analysis in the model using the clinical data requested in A10 to estimate CNS progression and the impact of CNS progression in patients' quality of life and on resource use.

As discussed in question B1, the model has been updated utilising CNS progression as a function of all progressions.

B12. **Priority question.** Please provide the proportion of patients who were allowed to cross-over treatment arms in ALEX. For example, page 314 of the CSR reports that a patient initially allocated to alectinib, was subsequently treated with crizotinib.

Overall 10 patients in the crizotinib arm received alectinib, and 9 patients in the alectinib arm received crizotinib after they had permanently discontinued the assigned trial treatment. Note neither of these switches are due to protocol defined crossover but rather use of available subsequent treatments in clinical practice at the investigators discretion.

B13. **Priority question.** In light of question B12, please justify if OS outcomes from ALEX need adjustment due to cross-over in the trial.

In lieu of a naïve per-protocol analysis, we used a discount method approach to assess the potential impact of treatment switching on the intention to treat (ITT) comparison for OS (White, 2005). This was explored to determine if crizotinib-treated patients who switch onto alectinib and benefit from the new treatment, could lead to an underestimation of the OS advantage of alectinib.

To assess the potential impact of treatment switching, we therefore multiplied (discounted) the observed survival time after the first dose of alectinib until censoring or death by 0.1 to 1.2 for the 10 patients in the crizotinib arm that switched onto alectinib and calculated the hazard ratio (HR) between treatment arms with the total duration (for the crizotinib arm, time to first dose of alectinib + multiplied observed time until censoring or death and for the alectinib arm, time to event without any adjustment).

As at the data cut-off of 9 February 2017, the median time on alectinib was 5.2 months (interquartile range 2.3, 7.9) for patients switching from crizotinib. If we assumed that the treatment effect of alectinib after switching from crizotinib was as large as a HR of 0.2, the estimated (stratified) OS HR for the ITT comparison was 0.75 (95% CI 0.47, 1.18) as compared with an estimated (stratified) OS HR of 0.76 (95% CI 0.48, 1.20) when ignoring treatment switching.

As such it was not deemed necessary at this time point to perform an adjustment for treatment switching at this stage. However, this will be reassessed once more long-term OS data become available.

Health-related quality of life

B14. **Priority question.** Please undertake and report the results (step by step) of a stepwise approach, in order to select the variables included as predictors of patients' utility in the mixed model described on page 71 of the CS.

Roche conducted two analyses in order to derive the company base case. The variables included were considered exhaustive as predictor variables for quality of life in patients with ALK-positive NSCLC after discussions with both the clinical team within Roche, and clinical experts. In summary, the models were built based on clinical reasoning. The clinically relevant predictors included were: age and sex (basic demographics), race and CNS metastasis at baseline (IRC) (stratification variables used for analysis), treatment group and progressed vs non-progressed health state.

We did not conduct a step wise approach as often such an approach leads to overfitting of the data if a large number of candidate predictors are considered and the final model does not take the model building process in to account.

Roche are confident the appropriate variables as predictors of patients' utility have been captured in the current analysis. Therefore in conducting this stepwise analysis, only these variables have been incorporated.

Variables were excluded based on a p-value > 0.1.

The first model from the stepwise approach can be found in Table 17. This is consistent with the initial mixed model referred to in the company submission.

Table 17: First model: stepwise approach (Initial mixed model from CS)

Covariate	Estimate	St. Error	DF	P value
Intercept	0.9055	0.05829	241	<.0001
Treatment (crizotinib)	0.01990	0.02317	237	0.3912
Sex (Female)	-0.02640	0.02325	236	0.2573
Age	-0.00181	0.000916	240	0.0496
Race (Asian)	0.04780	0.02307	235	0.0393
CNS metastasis at baseline (yes)	-0.02354	0.02358	238	0.3191
Disease Progressed (Yes)	-0.08934	0.009550	4351	<0.0001

The first covariate to be removed is treatment type. The following model in the stepwise approach can therefore be found in Table 18.

Table 18: Second model: stepwise approach (Final mixed model from CS)

Covariate	Estimate	St. Error	DF	P value
Intercept	0.9208	0.05541	239	<.0001
Sex (Female)	-0.02641	0.02322	237	0.2566
Age	-0.00189	0.000910	239	0.0385
Race (Asian)	0.04726	0.02303	236	0.0412
CNS metastasis at baseline (yes)	-0.02446	0.02352	239	0.2995
Disease Progressed (Yes)	-0.08911	0.009547	4357	<0.0001

The second covariate to be removed is CNS metastasis at baseline. The following model in the stepwise approach can therefore be found in Table 19.

Table 19: Third model: stepwise approach

Covariate	Estimate	St. Error	DF	P value
Intercept	0.9123	0.05469	239	<.0001
Sex (Female)	-0.02585	0.02317	237	0.2656
Age	-0.00192	0.000907	239	0.0353
Race (Asian)	0.04760	0.02298	236	0.0394
Disease Progressed (Yes)	-0.08928	0.009546	4360	<0.0001

The final covariate removed, based on a p-value > 0.1 is sex. Therefore the final model can be found in Table 20.

Table 20: Final model: stepwise approach

Covariate	Estimate	St. Error	DF	P value
Intercept	0.8956	0.05270	240	<.0001
Age	-0.00190	0.000909	241	0.0380

Race (Asian)	0.04857	0.02300	237	0.0357
Disease Progressed (Yes)	-0.08918	0.009546	4361	<0.0001

B15. **Priority question.** Please clarify how the utility estimates in Table 23 were calculated. If those estimates were obtained from the mixed model in Table 22, please clarify which covariates were included.

As discussed above, the initial mixed model (see Table 17) considered the following predictor variables:

- Treatment (Alectinib vs. Crizotinib),
- Gender (Male vs. Female),
- Age,
- Race (Asian vs. non-Asian),
- CNS metastasis at baseline (Yes vs. No)
- Progressed Disease (Yes vs. No)

Given the lack of significance in the treatment type (alectinib vs. crizotinib) it was deemed that there should be no distinction in the utility per treatment arm and the mixed model was limited to the remaining variables.

The final mixed model (Table 18) includes:

- Progressed Disease (Yes vs. No)
- CNS at baseline
- Race (Asian vs. non-Asian)
- Age
- Sex

Therefore, the resulting utility estimates (Table 21) are derived from the final mixed model as shown in Table 14.

Table 21: Final utility estimates (CS)

Health state	Utility	St. Error
Progression-free Survival	[redacted]	[redacted]
Progressed Disease	[redacted]	[redacted]

B16. **Priority question.** Table 22 in the CSR seems to report the variables included in the mixed model for predicting patients' quality of life. Please present the model results if only statistically significant variables are included in the model (determined through the process described in question B14). Please justify the decision to include non-statistically significant variables, if that remains the approach taken for the company's base case analysis.

Based on the process followed in B14, the resulting utilities if only statistically significant variables are included can be found in Table 22. As demonstrated, these are very comparable to the final utilities utilised in the base case of the company submission (Table 21), and therefore are unlikely to have any impact on the cost effectiveness analysis.

Table 22: Final utility estimates (stepwise approach)

Health state	Utility	St. Error
Progression-free Survival	[redacted]	[redacted]
Progressed Disease	[redacted]	[redacted]

B17. **Priority question.** In accordance with the guidance outlined in DSU TSD 10, please provide descriptive statistics for the EQ-5D data captured in ALEX. More specifically, please provide:

a. Mean (SD), median and inter-quartile range at baseline and at end of study;

Table 23: EQ5D in ALEX: Mean (SD), median and inter-quartile range at baseline and last observation

Treatment	Variable	Mean (SD)	Median	Interquartile range
Alectinib	Utility (baseline)	[redacted]	[redacted]	[redacted]
	Utility (last observation)	[redacted]	[redacted]	[redacted]
Crizotinib	Utility (baseline)	[redacted]	[redacted]	[redacted]
	Utility (last observation)	[redacted]	[redacted]	[redacted]

b. Mean change from baseline to end of study, with respective 95% CIs and number of observations at baseline and at end of study;

Table 24: EQ5D in ALEX: Mean change from baseline to end of study

Treatment	Variable	N	Mean (SD)	95% CI
Alectinib	Utility (baseline)	[redacted]	[redacted]	[redacted]
	Utility (last observation)	[redacted]	[redacted]	[redacted]
	Change from baseline	[redacted]	[redacted]	[redacted]
Crizotinib	Utility (baseline)	[redacted]	[redacted]	[redacted]

	Utility (last observation)	[redacted]	[redacted]	[redacted]
	Change from baseline	[redacted]	[redacted]	[redacted]

c. Mean (SD) and number of observations collected at each time point of QoL collection;

Table 25: EQ5D in ALEX: Mean (SD) and number of observations collected at each time point

	Alectinib			Crizotinib		
Analysis Visit Window	Number of observations	Mean	Std Dev	Number of observations	Mean	Std Dev
BASELINE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 32	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 44	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 52	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 56	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 60	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 64	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 68	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 72	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 76	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 80	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 84	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 88	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 92	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 96	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 100	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 104	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 108	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Week 112	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 116	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 120	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 124	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

d. Mean age of responders.

As discussed in the company submission, baseline questionnaire compliance rates were moderate for both treatment arms in the ITT population, with 94 (61.8%) alectinib-treated patients and 78 (51.7%) crizotinib-treated patients completing their baseline assessment, due to suboptimal initial site training to introduce electronic device to the patients.

However, thereafter there was generally a low level of missing data; therefore the mean age of responders can be considered equivalent to the mean age of the trial: 55 years.

B18. **Priority question.** Please clarify why different utility estimates were applied to TKI and non-TKI treatments, in the scenario analysis considering subsequent therapies.

The scenario analysis differentiating utility by type of subsequent therapy was explored following the SLR outputs, where it was identified from PROFILE 1007 that second line chemotherapy was associated with a lower utility estimate than second line TKI, and lower than the post-progression utility estimate derived from the ALEX trial. As a proportion of patients on both crizotinib and alectinib could receive subsequent chemotherapy in clinical practice, it was deemed appropriate to conduct a scenario exploring the impact of such an analysis.

B19. **Priority question.** In the scenario analysis considering subsequent therapies, patients are distributed into subsequent therapies (for both arms) to either TKI (47%) or non-TKI (53%) treatments and attributed to a TKI or non-TKI related utility. However, in Table 35 of the CS, the distribution reported in ALEX for each treatment arm is provided: alectinib, 71% non-TKI, 29% TKI; crizotinib, 21% non-TKIs 79% TKIs. Please change this in the model to reflect the different types of subsequent therapies received in the two treatment arms in ALEX and justify why this approach was not taken in the base case analysis.

Subsequent therapies were not routinely captured after a patient discontinued treatment; therefore the complete data set of post-discontinuation therapies is not available (distribution of treatments, time on subsequent treatment). In total, only 41% of the ALEX population that have permanently discontinued trial treatment have been captured as receiving at least 1 subsequent therapy. Further, of those captured, the distribution of subsequent therapies within the trial is unlikely to be reflective of clinical practice, as noted within the submission (see section B.3.5.1.1):

1. Products not being recommended by NICE in the appropriate setting (for example, alectinib in the crizotinib-failure indication; bevacizumab in NSCLC),

2. Usage in the trial of a number of unlicensed products (for example, lorlatinib and brigatinib),

3. General UK clinician preferences as opposed to Global clinician preferences

Finally, the distribution from the trial is naturally biased by time, both due to the higher proportion of patients still on treatment with alectinib over crizotinib and through the possible differences between early- and later progressors. Both therefore bias the distribution and split of subsequent treatments per arm.

Given that quality of life data is not directly available from the trial on progression by type of subsequent therapy received (note, very low patient numbers impact such an analysis – see answer to question A4), differentiating utility by type of subsequent therapy was explored only as scenario analysis following the SLR outputs, where it was identified subsequent chemotherapy was associated with lower utility estimates. This was only presented as a scenario analysis for a number of reasons:

1. The scenario analysis does not account for the impact of CNS metastases

2. Utilising literature only is not best practice where patient specific data is available

3. A vast number of assumptions are required to determine the duration of time for which each utility should be applied

Therefore, as described in the company submission, it was not deemed appropriate to use this analysis as the base case.

Further, given the distribution of subsequent therapies by arm within the trial is unlikely to be reflective of clinical practice, and the inferred bias of as discussed above, it was deemed more appropriate to conduct the analysis where patients are distributed into subsequent therapies based on data for both arms, which was considered more reflective of clinical practice, in line with NICE preferences (Lee et al.).

A scenario analysis has been provided in the updated economic model, as requested, however Roche would like to emphasise the considerable limitations to such an analysis, thus encourage the ERG and committee to only consider this a scenario analysis.

B19. **Priority question.** Please undertake a subgroup analysis of the EQ-5D data collected in ALEX for the group of patients experiencing CNS progression.

Similarly to the base case utility analysis, the mixed model considers the following predictor variables:

- Treatment (Alectinib vs. Crizotinib),

- Gender (Male vs. Female),

- Age,

- Race (Asian vs. non-Asian),

- CNS metastasis at baseline (Yes vs. No)
- Progressed Disease (Yes vs. No)

However in this case, progressed disease is specific to CNS progression.

Further, as depicted in our response to A6, A10, B1: two CNS PFS analyses have been made available: CPFS (IRC, RECIST + CNS-RECIST) and adapted-CPFS (IRC, RECIST). Results for both have been reported.

CPFS (IRC, RECIST + CNS-RECIST)

Table 26: Mixed model 1: CPFS (IRC, RECIST + CNS-RECIST)

Covariate	Estimate	St. Error	DF	P value
Intercept	0.9008	0.05829	241	<.0001
Treatment (crizotinib)	0.01904	0.02320	238	0.4126
Sex (Female)	-0.02459	0.02325	237	0.2913
Age	-0.00179	0.000916	240	0.0518
Race (Asian)	0.04693	0.02307	236	0.0430
CNS metastasis at baseline (yes)	-0.02567	0.02358	239	0.2773
CNS Disease Progressed (Yes)	-0.03433	0.009164	4419	0.0002

As treatment was not a statistically significant variable, the mixed model was rerun:

Table 27: Mixed model 2: CPFS (IRC, RECIST + CNS-RECIST)

Covariate	Estimate	St. Error	DF	P value
Intercept	0.9155	0.05541	239	<.0001
Sex (Female)	-0.02460	0.02322	237	0.2904
Age	-0.00187	0.000910	-0.00187	0.0407
Race (Asian)	0.04640	0.02302	236	0.0450
CNS metastasis at baseline (yes)	-0.02656	0.02352	239	0.2600
CNS Disease Progressed (Yes)	-0.03387	0.009147	-0.03387	0.0002

Utilising the baseline characteristics from the ALEX trial (Table 28), the resulting utility values can be found in Table 29.

Table 28: ALEX baseline characteristics for utility estimates

Covariate	ALEX
Sex (Female)	56%
Age	55 years

Race (Asian)	46%
CNS metastasis at baseline (yes)	40%

Table 29: CPFS (IRC, RECIST + CNS-RECIST) utility estimates

Health state	Utility	St. Error
Progression-free Survival	[redacted]	[redacted]
CNS-progressed Disease	[redacted]	[redacted]

Notably, the CNS-progressed disease utility is higher than the progressed disease utility for any progression location, as previously captured (0.725). This highlights the insufficient evidence available from the ALEX trial to demonstrate the detrimental impact of CNS progressions on patients. This is driven by:

1. The low number of observations in the CNS progressive disease subgroup (73 in alectinib, 432 in crizotinib as opposed to 2341 and 1690 in the non-CNS progression group, respectively)

2. The limited length of follow up post-progression

Thus supporting our approach of utilising literature to appropriately capture quality of life for these patients.

Adapted CPFS (IRC, RECIST)

Table 30: Mixed model 1: adapted-CPFS (IRC, RECIST)

Covariate	Estimate	St. Error	DF	P value
Intercept	0.9027	0.05820	241	<.0001
Treatment (crizotinib)	0.01706	0.02314	237	0.4618
Sex (Female)	-0.02436	0.02321	236	0.2950
Age	-0.00182	0.000915	240	0.0478
Race (Asian)	0.04574	0.02303	235	0.0481
CNS metastasis at baseline (yes)	-0.02616	0.02354	238	0.2675
CNS Disease Progressed (Yes)	-0.04174	0.01222	4436	0.0006

Similarly to above, as treatment was not a statistically significant variable, the mixed model was rerun:

Table 31: Mixed model 2: adapted-CPFS (IRC, RECIST)

Covariate	Estimate	St. Error	DF	P value
Intercept	0.9158	0.05530	239	<.0001
Sex (Female)	-0.02438	0.02317	237	0.2937
Age	-0.00189	0.000908	240	0.0382
Race (Asian)	0.04527	0.02297	236	0.0499
CNS metastasis at baseline (yes)	-0.02693	0.02347	239	0.2523
CNS Disease Progressed (Yes)	-0.04136	0.01221	4447	0.0007

Utilising the baseline characteristics from the ALEX trial (Table 28), the resulting utility values can be found in Table 29.

Table 32: Adapted-CPFS (IRC, RECIST) utility estimates

Health state	Utility	St. Error
Progression-free Survival	[redacted]	[redacted]
Progressed Disease	[redacted]	[redacted]

Similarly to above, the CNS-progressed disease utility is higher than the progressed disease utility for any progression location, as previously captured (0.725)., and highlights the insufficient evidence available from the ALEX trial to demonstrate the detrimental impact of CNS progressions on patients. This is driven by:

1. The low number of observations in the CNS progressive disease subgroup (40 in alectinib, 232 in crizotinib as opposed to 2374 and 1890 in the non-CNS progression group, respectively)
2. The limited length of follow up post-progression

Thus supporting our approach of utilising literature to appropriately capture quality of life for these patients

B20. **Priority question.** Please undertake a subgroup analysis of the EQ-5D data collected in ALEX for the group of patients experiencing CNS progression.

An extension has been requested from NICE to provide this response. Response will be provided by COB 15th December.

B21. Please clarify how sources of utility values for CNS (Roughley *et al.* 2014, Mulvenna *et al.* 2016, Peters *et al.* 2016) were chosen and identified and why a systematic review to identify utility values associated with CNS was not performed.

The HRQoL literature review that was conducted as part of the manufacturer's submission did not adequately capture utility values associated with CNS progression. Consequently, a targeted literature search was carried out and the sources quoted above were captured.

Targeted searches were conducted using 3 sources to pick up any sources reporting quality of life changes for CNS progression in lung cancer:

- Pubmed
- Value in health (to pick up recent abstracts for conferences such as ISPOR)
- Previous NICE submissions in ALK+ve NSCLC

The following search terms were used in pubmed and on the value in health website:

Pubmed	**Value in health**
brain metastases, lung cancer, QALY	non-small-cell-lung cancer in All Content AND brain metastasis in All Content
CNS metastases, lung cancer, QALY	non-small-cell lung cancer in All Content AND brain in All Content AND metastasis in All Content AND impact in All Content
(brain AND non-small-cell-lung cancer) AND metastasis) AND quality) AND life	quality in All Content AND life in All Content AND impact in All Content AND small-cell-lung-cancer in All Content AND brain in All Content

This captured the following studies:

- Mulvenna, P., Nankivell, M., Barton, R., Faivre-Finn, C., Wilson, P., McColl, E., Moore, B., Brisbane, I., Ardron, D., Holt, T., Morgan, S., Lee, C., Waite, K., Bayman, N., Pugh, C., Sydes, B., Stephens, R., Parmar, M. K. & Langley, R. E. 2016. Dexamethasone and supportive care with or without whole brain radiotherapy in treating patients with non-small cell lung cancer with brain metastases unsuitable for resection or stereotactic radiotherapy (QUARTZ): results from a phase 3, non-inferiority, randomised trial. The Lancet, 388, 2004-2014
- Iftekhar Khan, Stephen Morris, Allan Hackshaw, and Siow-Ming Lee. Cost-effectiveness of first-line erlotinib in patients with advanced non-small-cell lung cancer unsuitable for chemotherapy
    - Did not provide utility estimates for patients with CNS or brain metastases
- Zeyad Kanaan, Goetz H Kloecker, Ajit Paintal , and Cesar A Perez. Novel targeted therapies for resistant ALK-rearranged non-small-cell lung cancer: ceritinib and beyond
    - Did not provide quality of life estimates
- Peters, S., Bexelius, C., Munk, V. & Leighl, N. 2016. The impact of brain metastasis on quality of life, resource utilization and survival in patients with non-small-cell lung cancer, available at Elsevier and Pubmed through the Cancer treatment Reviews.

- Skeie BS, Eide GE, Flatebø M, Heggdal JI, Larsen E, Bragstad S, Pedersen PH. Quality of life is maintained using Gamma Knife radiosurgery: a prospective study of a brain metastases patient cohort. [Not available for free]
    - Provided quality of life based on the Functional Assessment of Cancer Therapy-Brain (FACT-BR) questionnaire with the brain cancer subscale (BRCS) questionnaire, with no EQ-5D estimates available.
- Roughley, A., Damonte, E., Taylor-Stokes, G., Rider, A. & Munk, V. C. 2014. Impact of Brain Metastases on Quality of Life and Estimated Life Expectancy in Patients with Advanced Non-Small Cell Lung Cancer. Value in Health, 17, A650.

This targeted review is believed to have captured the best available evidence associated with utility values for CNS.

B22. Please provide the full texts for Solomon 2014 and Felip 2015 included in Table 25 of the CS. The reference for Solomon 2014 provided relates to Solomon 2016. Please ensure the HSUVs provided in Table 25 are those reported in the sources provided.

The full text for Solomon et al. (2014) has been provided as part of this response. Only the abstract is available for Felip et al. (2015), which has also been provided.

Table 25 in the original company submission is erroneous. This table has since been amended; please see the response to question B25 for an updated Table 25.

B23. Please clarify how sources of utility decrements associated with adverse events were chosen and identified (Marti *et al.* 2013, Beusterien *et al.* 2010, Nafees *et al.* 2008, Peters *et al.* 2016, Roughley *et al.* 2014, Mulvenna *et al.* 2016) and why a systematic review to identify utility decrements associated with adverse events and CNS was not performed.

Please note, the response to question B21 captures the approach of how Roche identified Peters et al. 2016, Roughley et al. 2014, Mulvenna et al. 2016. Therefore, this response solely refers to the sources of utility decrements associated with adverse events (Marti et al. 2013, Beusterien et al. 2010, Nafees et al. 2008).

A targeted literature review was conducted to identify literature that reported health utility values for adverse events pneumonitis and neutropenia for patients with advanced or metastatic NSCLC. All searches were conducted on the 29th November 2017 and the following databases were searched:

- National Institute for Health and Clinical Excellence (NICE)
- PubMed

The search strategy consisted of two parts. The first part involved a critical review of previous single technology assessments in NSCLC submitted to NICE. The second involved a targeted search of the literature to find studies where utilities were being addressed to the adverse events experienced with treatment for advanced or metastatic NSCLC.

A critical review of STA company submissions and ERG reports to NICE was completed. A total of 13 reports were identified which reported the relevant adverse event utilities. All STAs reviewed, reported disutilities for neutropenia, none reported a disutility for pneumonitis.

One utility of -0.09/-0.08973 from Nafees et al 2008 (Nafees et al., 2008) was common to all STA's used either in base case or sensitivity analysis.

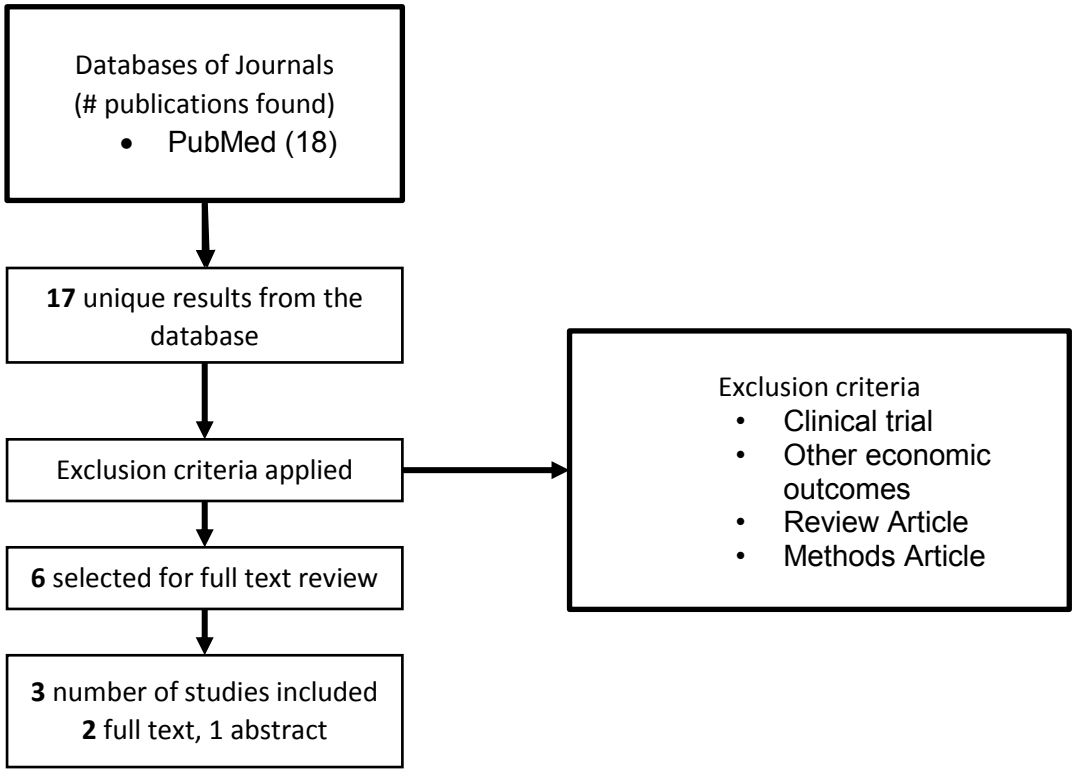
Two other disutility's for Neutropenia were reported, -0.131 from Lewis et al. 2010 (Lewis et al., 2010) and -0.085 from an analysis of the KEYNOTE 010 study (NICE, 2017b).

Second, a targeted review of PubMed was completed to find adverse events disutilities for pneumonitis and neutropenia in advanced or metastatic NSCLC. Titles and abstracts were screened in accordance with pre - defined criteria, outlined in Table 33 below. A PRISMA diagram of included and excluded studies is presented below.

Table 33: Inclusion or Exclusion criteria

Inclusion Criteria	Exclusion criteria
Metastatic or advanced lung cancer	Not metastatic or advanced lung cancer
Health related quality of life	
QALY or quality adjusted life year	Not QOL studies
SF-36 OR SF-12 OR EQ-5D OR EQ-5D-5L OR EUROQOL	No useful HRQoL/ Utility values
Utilities	Reviews of included studies
Time Trade Off or Standard Gamble	
Pneumonitis or Neutropenia	

Figure 36: PRISM diagram for targeted literature review of adverse event disutilities in advanced or metastatic NSCLC



The database search identified 17 studies potentially relevant. Following deduplication and application of the inclusion and exclusion criteria, 6 studies were selected for full text review.

A total of three studies were included. Of these, one study included utility decrements associated with the neutopenia: Nafees et al 2008. However, no utilities could be identified for pneumonitis.

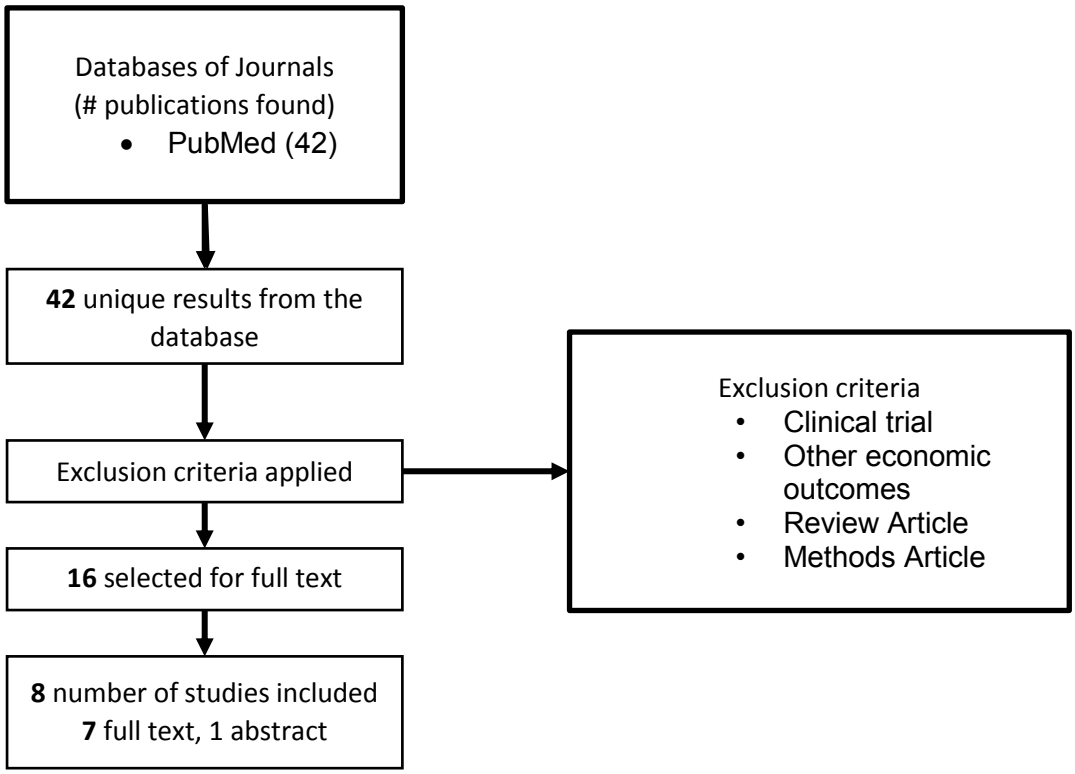
As such, an expanded literature review of PubMed was completed to find adverse events disutility's for pneumonitis. Titles and abstracts were screened in accordance with pre - defined criteria, outlined in Table 34 below. A PRISMA diagram of included and excluded studies is presented below.

Table 34: Inclusion or Exclusion criteria

Inclusion Criteria	Exclusion criteria
Pneumonitis QALY or quality adjusted life year or Health Related Quality or SF-36 or SF-12 or EQ-5D or EQ-5D-5L or EUROQOL or HUI2 or HUI3 Utilities	Not QOL studies No useful HRQoL/ Utility values Reviews of included studies

Time Trade Off or Standard Gamble Pneumonitis Utility or disutility or decrement Published in the last 10 years	

Figure 37: PRISM diagram for targeted literature review of adverse event disunities for pneumonitis



The database search identified 42 studies potentially relevant. Following deduplication and application of the inclusion and exclusion criteria, 16 studies were selected for full text review. A total of eight studies were included following full text review. The 8 studies utility decrements are detailed below in

Table 35. Of these, one study included utility decrements associated with pneumonitis; therefore the inclusion criteria were kept wide to include pneumonia as well.

Table 35: Utility inputs from published literature

Source	Utility
Beausterien et al. 2010(Beusterien et al., 2010)	Grade III/IV pneumonia -0.20 SE 0.02
Swinburn et al. 2012(Swinburn et al., 2012)	Grade III/IV pneumonitis -0.16 SE 0.26
Bakir et al. 2012(Bakır et al., 2012)	Pneumonia (inpatient) -0.008
Marti et al. 2013 (Marti et al., 2013)	Pneumonia (inpatient) -0.008
Kulpeng et al 2015(Kulpeng et al., 2013)	Necrotizing pneumonia after Pnc. Pneumonia -0.18 SE 0.05

Hoshi et al. 2015(Hoshi et al., 2015)	Pneumococcal pneumonia -0.5
Haasis et al. 2015(Haasis et al., 2015)	Necrotizing pneumonia after Pnc. Pneumonia -0.18 SE 0.05
Wang et al. 2017(Wang et al., 2017)	Pneumonia (inpatient) -0.008

It was not deemed appropriate to use a utility associated with necrotizing pneumonia, or pneumonia associated with pneumococcal. Therefore, these were excluded. Second, Swinburn 2012 assessed pneumonitis utility decrements in patients who had stable disease only, thus wasn't considered appropriate to represent a grade 5 utility. Further, it was clear three studies utilised the same utility value: Marti et al, Bakir et al, Wang et al. Thus, one was selected as a representation of all. However, none were conducted in an oncology setting. Therefore, Beusterien 2010 was selected as the most appropriate utility to use.

This targeted review is believed to have captured the best available evidence associated with these parameters, and the values quoted, have been utilised extensively in other NICE appraisals (NICE, 2016, NICE, 2017b, NICE, 2015b, NICE, 2015a)

Further, it should be highlighted, consistent with other related submissions (NICE, 2016) adverse event disutilities are only applied as a scenario analysis.

B24. Please provide the number of patients in ALEX with bone metastases at data cut off as per the IRC endpoint by treatment arm.

This analysis has not yet been processed from the data, thus cannot be provided at this time.

B25. Please extract the Blackhall 2014 paper and add the extraction to Table 25 of the CS as a new row.

The Blackhall 2014 paper had been extracted; however a copying error meant the results were switched. Please see an updated Table 25 below.

Table 36: Update to Table 25 in CS: Study summary and reported utility data of the relevant study identified in the systematic review

Study	Population details	Method of deriving HSUVs	Countries	Mean HSUVs		
				Pre-progression	Post-progression	Other
Solomon 2014 (PROFILE 1014)	Locally advanced, recurrent, or metastatic ALK+ NSCLC (N=343)	Instrument: EQ-5D Valuation: NR Elicitation: NR Scale: NR	Australia, Austria, Belgium, Brazil, Canada, Chile, China, Finland, France, Germany, Hong Kong, India, Ireland Italy, Japan, South Korea, Luxembourg, Mexico, Netherlands, Norway, Peru, Portugal, Russia, Singapore, South Africa, Spain, Switzerland, Taiwan, Ukraine, UK, US	Baseline (SD): • Crizotinib, 0.72 (0.30) • Chemotherapy, 0.71 (0.26) During treatment (SE): • Crizotinib, 0.73 (0.02) • Chemotherapy, NR	NA	NA
Felip, 2015 (PROFILE 1014)	Advanced non-squamous ALK+ NSCLC (N=343)	Instrument: EQ-5D (3L version) Valuation: NR (calculated using a standard algorithm) Elicitation: NR Scale: 0-1	NR	Baseline (SD): • Crizotinib, 0.72 (0.30) • Chemotherapy, 0.71 (0.26) During treatment (SD): • Crizotinib, 0.81 (NR) Chemotherapy, 0.72 (NR)	NA	NA
Blackhall 2014 (PROFILE 1007)	Locally advanced or metastatic ALK+ NSCLC (N=347)	Instrument: EQ-5D (version not clear) Valuation: NR Elicitation: NR Scale: NR	Australia, Brazil, Bulgaria, Canada, China, France, Germany, Greece, Hong Kong, Hungary, Ireland, Italy, Japan, South Korea, Netherlands, Poland, Russia, Spain, Sweden, Taiwan, UK, US	Baseline (SD): • Crizotinib, 0.73 (0.24) • Chemotherapy, 0.70 (0.26) • Pemetrexed, 0.73 (0.24) • Docetaxel, 0.67 (0.29) During treatment (SE):	NA	NA

				• Crizotinib, 0.82 (0.01) • Chemotherapy, 0.73 (0.02) • Pemetrexed, 0.74 (0.02) • Docetaxel, 0.66 (0.04)		

ALK+, anaplastic lymphoma kinase-positive; HSUV, health state utility value; NA, not available; NR, not reported; NSCLC, non-small cell lung cancer; SD, standard deviation; SE, standard error; UK, United Kingdom; US, United States.

Resource use and costs

B26. **Priority question.** Please include a scenario analysis in the model (through a drop-down menu option) that estimates the costs of treating CNS metastasis with steroids (Mulvenna *et al.* 2016), instead of stereotactic radiotherapy.

The following treatment recommendations are outlined in the ESMO guidelines (Novello et al., 2016) regarding ALK+ NSCLC patients that experience CNS progression during the course of their disease. They address the use of corticosteroids and radiotherapy according to patient prognosis and whether the CNS metastases are symptomatic or non-symptomatic.

"In patients with clinically asymptomatic brain metastases, the use of next-generation TKIs may restore control of brain disease, with the possibility to delay cranial radiotherapy." However, corticosteroids are not recommended in this instance.

In patients with symptomatic brain metastases, treatment recommendations match those for NSCLC patients without an ALK rearrangement. Treatment is dependent on each patient's prognosis which is determined by Radiation Therapy Oncology Group recursive partitioning analysis (RPA).

The RPA classification is as follows:

- Class I patients are those < 65 years old, with a good PS (Karnofsky Index (KI) ≥ 70%) and no other extracranial metastases and a controlled primary tumour.
- Class II patients have KI ≥70%, with other extracranial metastases and/or an uncontrolled primary tumour.
- Class III represents all other patients.

ESMO recommends best supportive care for class III patients and advise that these patients should not receive radiotherapy.

In patients with a single metastasis, stereotactic radiosurgery (SRS) or resection is recommended. In patients with two or three metastases SRS is recommended in patients with RPA class I-II. Patients that have more than three brain metastases and are RPA class I-II should be treated with whole brain radiotherapy.

"For most patients with symptomatic brain metastases and/or significant oedema, a dose of dexamethasone of 4 mg/day or an equivalent dose of another corticosteroid is recommended. Tapering of the dose and, if possible, cessation after radiotherapy are recommended. Corticosteroids are not recommended in the case of asymptomatic brain metastases."

In summary, the use of steroids is supportive to the treatment of CNS metastasis, to treat the symptoms associated with metastasis, but not to treat the metastasis itself. Therefore the requested analysis is not an appropriate analysis, hence will not be provided.

B27. **Priority question.** Clinical expert opinion given to the ERG explained that docetaxel is not the only chemotherapy agent used to treat ALK+ NSCLC in the UK. It was reported that pemetrexed or docetaxel are usually given as single therapies or that pemetrexed in combination with carboplatin (or cisplatin) are given as combination therapies. Please consider including a "basket" of chemotherapies as subsequent treatments in the model, and costing this treatment accordingly.

The economic model has been restructured to incorporate the following two options.

The first option (base case) is to use the data from the ALEX trial. To this end, every treatment for which a price is currently available, for every available pack and/or unit size, has been incorporated into the economic model. Prices were not available for the following therapies, which are still developmental products:

- Loratinib
- Brigatinib
- Entrectinib

Patient numbers and dosing schedules are provided in the below table. Please refer to 'Cost Inputs'!$C$12:$M$44 and 'Cost Inputs'!$I$170:$O$189 within the economic model for the individual breakdowns of dose, unit size, pack size, weekly costs and dosing schedules.

Table 37: Subsequent therapies dosing schedule

	Number of patients		Dosing schedule
Drug	Alectinib	Crizotinib	
Ceritinib	4	14	750mg daily
Alectinib	0	10	1200mg daily
Crizotinib	9	2	500 mg daily
Gefitinib	0	2	250mg once daily
Erlotinib	0	1	150mg once daily
Cisplatin	7	5	50-100mg/m2 every 3-4 weeks
Carboplatin	12	1	400 mg/m² every >= 28 days
Pemetrexed	15	5	500 mg/m² every 21 days
Gemcitabine	2	1	1g/m2 3 x per 4 weeks
Paclitaxel	3	0	175mg/m2 every 3 weeks
Docetaxel	0	1	75 mg/m² every 21 days
Nivolumab	2	0	3mg/kg every 2 weeks
Bevacizumab	2	0	7.5 - 15mg/kg every 3 weeks for a maximum of 6 cycles
Cyclophosphamide	1	0	100 - 300mg daily
Doxorubicin	1	0	60-75mg/m2 every 3 to 4 weeks
Vincristine	1	0	1.4 - 1.5mg/m2 weekly

These numbers were used to calculate a weighted average cost associated with subsequent treatments from the ALEX trial data. That is, weekly costs were calculated for each drug, and

the proportion of patients from the above table was used to assign a weighting to each one. The resulting weekly costs were £64.53 for the alectinib arm, and £135.92 for the crizotinib arm. This difference is driven mainly by the large proportion of patients receiving 2L ceritinib in the ALEX trial, which is reflective of the high proportion in the original base-case, and also NICE recommendations. Bevacizumab and nivolumab have a maximum number of cycles defined within the product SPC or NICE recommendations, however are applied for simplicity until progression. Only patients in the alectinib arm received either of these treatments. Consequently, the estimated ICER is somewhat conservative, due to the inflated subsequent treatment cost estimate for the alectinib arm, which is not the case in the crizotinib arm.

Subsequent treatments are applied as single therapies as data could not be linked to provide information on regimens of treatments within the clinical trial.

The second option provides provide patients with docetaxel, pemetrexed , pemetrexed + carboplatin, or pemetrexed + cisplatin, assuming that these are the four possible treatment pathways available to patients, as instructed by the ERG. However, as the respective market shares of these (assumed to be mutually exclusive) pathways are unknown, and have not been provided to us by the ERG, placeholder values are used within the model. These are as below. This option is used in scenario analysis when subsequent therapies are assumed to be the same as clinical practice and not the trial.

Table 38: Subsequent therapies market share

Chemotherapy treatment	Market share, alectinib	Market share, crizotinib
Docetaxel	85%	85%
Pemetrexed	5%	5%
Pemetrexed + carboplatin	5%	5%
Pemetrexed + cisplatin	5%	5%

B28. **Priority question.** Please include a scenario analysis in the model (selectable from a drop-down menu) which estimates the costs of subsequent therapies according to the information given in response to question A2 b (and respective table included).

As noted within the submission (see section B.3.5.1.1) the distribution of subsequent therapies within the trial is unlikely to be reflective of clinical practice (see response to B19 for further details). Therefore, following NICE's preferences (Lee et al.) we provided a base case in the submission in line with clinical practice rather than in line with the trial. Nevertheless, it is acknowledged by doing so, we cannot adequately represent the impact of subsequent therapies on effectiveness.

In order to appropriately inform this analysis, a treatment related weekly cost for each second line therapy is required, an average time on treatment, and list price for each respective treatment. As noted in B27 the table requested by the ERG includes subsequent therapies that are currently being researched in a clinical trial setting, with no available

license. This means no data is available on NHS prices therefore these therapies were excluded from this analysis.

Time on treatment was assumed to be in line with the below table, which also provides sources from which the information was taken. All chemotherapies were assumed to have the same time on treatment as docetaxel, all other TKIs were assumed to have the same time on treatment as crizotinib.

Table 39: Subsequent therapies time on treatment

Treatment	Time on treatment assumed (weeks)	Source(s)
Ceritinib	41.89	ASCEND - 5 (Soria et al., 2017)
Alectinib	60.20	ALUR (Novello, 2017)
Crizotinib & other TKIs	48.14	PROFILE 1007 (Solomon et al., 2016)
Chemotherapies	8.83	ALUR (Novello, 2017)
Nivolumab	9.97	NICE TA 484 (NICE, 2017a)
Bevacizumab	25.13	Heist et al. 2008 (Heist et al., 2008)

B29. Please clarify why the cost of concomitant drugs was not considered in the model.

In total, 89% and 86% patients on crizotinib and alectinib, respectively, received concomitant medications during the study. The most common ATC classes were steroids (38% vs. 31%), analgesics (24% vs. 36%), supplements (25% vs. 28%), antiemetics (27% vs. 21%), laxatives and stool softeners (21% vs. 28%), penicillins (15% vs. 21%), loop diuretics (15% vs. 14%), non-steroidal anti-inflammatories (14% vs. 21%), antihistamines (13% vs. 21%), proton pump inhibitors (21% vs. 13%), opioid analgesics (12% vs. 16%), cough preparations (10% vs. 17%), herbal, homeopathic,& dietary supplements (12% vs. 15%), quinolone antibiotics (13% vs. 15%), antidiarrheals (16% vs. 10%), 5-HT3 Antagonists (15% vs. 5%), anticoagulants (14% vs. 11%), benzodiazepines (11% vs. 11%), antacids (9% vs. 15%), cephalosporin antibiotics (9% vs. 15%), and vitamins & minerals (5% vs. 15%).

These medications are understood to be relatively inexpensive and their inclusion would be expected to have a negligible impact on overall cost-effectiveness results. Furthermore, given that alectinib has a more favourable safety profile, and experienced fewer concomitant medications than crizotinib, this cost omission is thought to be conservative.

B30. It would appear that the cost of docetaxel (which should be given in every 21-day cycle) is being applied weekly in the model ('Cost Inputs'K113). Please correct this in the model.

This has been corrected in the updated model, using a simple adjustment in the dosing sheet within the economic model. The cost was simply divided by 3 to provide an estimate of

the cost per week. The same approach was taken for all of the treatments added to the model in answer to question B27.

B31. Please clarify how sources of subsequent treatment duration (ASCEND-5, ALUR and PROFILE 1007) were identified and chosen. Please provide the full-texts of those papers.

Full texts have been provided alongside our response.

A treatment related weekly cost for each second line therapy was required in order to appropriately inform the cost effectiveness analysis. To do so, a targeted literature search was conducted for the pivotal trials of subsequent TKIs in the second line setting, to best inform anticipated treatment duration. This resulted in the identification of the following clinical trials, which provided average treatment duration for the following regimens:

- ASCEND-5
    - Ceritinib: 42.03 weeks, based on a median PFS by INV of 6.7 months in the crizotinib-failure indication
- ALUR
    - Alectinib: 60.41 weeks, based on a median PFS by INV of 9.6 months in the crizotinib-failure indication
    - Chemotherapy: 8.86 weeks, based on a median PFS by INV of 1.4 months in the crizotinib-failure indication
        - ALUR was identified as opposed to PROFILE 1007 to provide information in a prior TKI setting, as opposed to prior chemotherapy setting.
        - This figure was validated using the ASCEND-5 median PFS of 1.6 months in the chemotherapy arm.
- PROFILE 1007
    - Crizotinib: 48.30 weeks, based on median PFS by INV of 7.7 months in the second line setting

Adverse events

B32. Please clarify why adverse events for patients receiving second line treatments are not considered in the model in terms of impact on quality of life and costs.

The company acknowledges that the inclusion of these parameters would have resulted in a more thorough and complete analysis. However, a conscious decision was made to exclude the costs associated with AEs in second-line treatment. This approach is in-line with the methodology used in TA406.

The inclusion of these parameters is expected to have a negligible impact on overall cost-effectiveness results and biases against alectinib as more subsequent therapies are received in the crizotinib arm.

Scenario analyses are provided around the impact of TKI vs non TKI subsequent therapies on quality of life to explore the impact on quality of life.

Section C: Textual clarifications and additional points

C1. The ERG has found discrepancies between the variables reported in Table 50 of the CS and the model.

a) Please clarify where/how adverse event management costs are varied in PSA as only deterministic values can be identified in the model;

This has now been rectified assuming a normal distribution and that the SD is 0.1 multiplied by the mean cost of resolution. This has very little impact on the model result.

b) Please provide the standard errors of all variables included in PSA (where appropriate), including the respective sources (i.e. if the estimates were assumed or taken from literature);

Provided below

c) Table 50 in the CS states the cost of ALK testing is fixed, but this variable is included in PSA in the model 'Cost Inputs'L72. Please amend Table 50 to reflect this;

Provided below

d) The submission reports a beta distribution for utility values whilst the model is informed by a gamma distribution 'Model Inputs'J38:Q50. Please update Table 50 accordingly.

This has now been fixed within the model using a beta distribution, which is appropriate for varying utility values.

Table 40: Update to Table 50: Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: SE and CI (distribution)	Reference to section in submission	Source for SE
General model parameters				
Time horizon	30 years	Fixed	B.3.2	NA
Discount rate - efficacy	3.5%	Fixed		
Discount rate - costs	3.5%	Fixed		
Population parameters				
Age	55.05 years	Fixed	NR	NA
Body weight	66.60 kg	Fixed		
Height	164.70 cm	Fixed		
Body surface area	1.73 m^2	Fixed		
Clinical inputs				
Assessment of progression	INV	Fixed	B.3.3	NA
Parametric curves				
PFS – alectinib	KM+Exponential	SE: [redacted] Lambda CI: [redacted] Normal	B.3.3	ALEX
PFS – crizotinib	KM+Exponential	SE: [redacted] Lambda CI: [redacted] Normal		
OS – alectinib	Exponential	SE: [redacted] Lambda CI: [redacted] Normal		
OS – crizotinib	Exponential	SE: [redacted] Lambda CI: [redacted] Normal		
Utilities – base case				
Progression-free	[redacted]	SE: [redacted] CI: [redacted] Beta	B.3.4.1	ALEX
Progressed disease (alectinib)	[redacted]	SE: [redacted] CI: [redacted] Beta		Assumption: +/- 10% mean
Progressed disease (crizotinib)	[redacted]	SE: [redacted] CI: [redacted] Beta		
Utilities – Scenario analysis – ALEX data only				
Progression-free	[redacted]	SE: [redacted] CI: [redacted] Beta	B.3.4.1	ALEX
Progressed disease	[redacted]	SE: [redacted]		

		CI: [redacted] Beta		
Utilities – scenario analysis – 2 post progression utilities				
Progression-free state	[redacted]	SE: [redacted] CI: [redacted] Beta	B.3.4.5	ALEX
PPS 2nd line in PPS for TKI	[redacted]	SE: [redacted] CI: [redacted] Beta		
PPS 2nd line in PPS for non TKI	0.66	SE: 0.04 CI: 0.582 – 0.734 Beta		**PROFILE 1014**
PPS 3rd line in BSC	0.47	SE: 0.47 CI: 0.271 – 0.669 Beta		**Nafees et al.**
Adverse event disutilities – scenario analysis				
Neutropenia	-0.09	Fixed (scenario analysis so not included in PSA)	B.3.4.4	NA
Pneumonitis	-0.20	Fixed (scenario analysis so not included in PSA)		
Technology acquisition costs per pack (unit costs at list price)				
Alectinib	£5,032.00	Fixed	B.3.5.1	NA
Crizotinib	£4,689.00	Fixed		
Ceritinib	£4,923.00	Fixed		
Docetaxel – 8ml	£20.44	Fixed		
Administration costs: Intervention and Comparator – per administration				
Alectinib	£9.20	SE: 0.05 CI: 8.28 – 10.12 Lognormal	B.3.5.1	Assumption: +/- 10% mean
Crizotinib	£9.20	SE: 0.05 CI: 8.28 – 10.12 Lognormal		
Administration costs: Subsequent therapies – per week				
Alectinib	£2.30	SE: 0.05 CI: £2.07 – 2.53 Lognormal	B.3.5.1	Assumption: +/- 10% mean
Crizotinib	£2.30	SE: 0.05 CI: £2.07 – 2.53 Lognormal		
Ceritinib	£2.30	SE: 0.05 CI: £2.07 – 2.53 Lognormal		
Docetaxel	£66.31	SE: 0.05 CI: £59.68 - £72.94 Lognormal		
Supportive care costs				
PFS	£74.86	SE: 0.05 CI: £67.37 - £82.35 Normal	B.3.5.2	Assumption: +/- 10% mean
PD (alectinib)	£398.41	SE: 0.05 CI: £358.57 - £438.25 Normal		

PD (crizotinib)	£496.77	SE: 0.05 CI: £447.09 - £546.45 Normal		
Terminal care cost				
Terminal care cost	£3,679.37	SE: 0.05 CI: £1,839.69 - £5,519.06 Lognormal	B.3.5.2	Assumption: +/- 10% mean
Adverse event management costs				
Alectinib	£0.60	SE: 0.05 CI: £0.54 - £0.66 Lognormal	B.3.5.3	Assumption: +/- 10% mean
Crizotinib	£4.13	SE: 0.05 CI: £3.72 - £4.54 Lognormal		
Subsequent treatment				
Treatment distribution: alectinib	Table 35 company submission	Fixed (varied in scenario analysis)	B.3.5.1	NA
Treatment distribution: crizotinib				
Cost of ALK test				
Cost of identifying a person with the ALK mutation	£2,380	SE: 0.05 CI: £2,142 - £2,618 Lognormal	B.3.5.4	Assumption: +/- 10% mean

Note: there are various pack sizes for the additional treatments added to the model. Pack prices can be found within the economic model, cells 'Cost Inputs'!$C$16:$M$42. These costs are not varied instead the final weekly cost of subsequent therapies calculated in cells 'Cost Inputs'!$F$165:$G$165 is varied using a lognormal distribution with SE 0.1.

C2. Please provide a table containing the 21 studies excluded from the original HRQoL search Appendix H.

As highlighted in Appendix H of the company submission (page 128), a list of studies excluded on full text from the original review is not available. This is due to the vendor who conducted the original review, no longer existing.

C3. Are the utility values extracted from Solomon 2014 in Table 25 the utility values reported in Blackhall 2014?

This was a copying error. The updated table can be found in response to B25.

C4. Table 50 of the CS refers to the KM PFS data from ALEX used in the base case analysis being IRC-assessed, whereas Table 55 refers to the base case being INV-assessed. Please confirm whether what is stated in Table 50 is a typo.

Roche can confirm the KM PFS data from ALEX used in the base case analysis was INV-assessed. The text in Table 50 is incorrect. The update can be found in This has now been fixed within the model using a beta distribution, which is appropriate for varying utility values.

Table 40.

C5. Please revise the number of studies in Figure 6 of Appendix G to reflect the 21 unique studies as Figure 6 currently sums to 22.

Of the 21 studies, six considered first-line treatment, and 15 considered previously treated patients. Of the 15 studies which considered previously treated patients, one study considered both patients who had previously received crizotinib and patients who had previously received chemotherapy separately (Zhou et al., 2015). This explains the discrepancy in the figure.

C6. Please provide the text related to* in Figure 5 of Appendix G.

Note: a total of 29 publications were identified, covering 21 unique economic evaluations

C7. Please clarify the number of studies identified from the cost-effectiveness update search and HRQoL update search. Please report the number of studies including and excluding duplicates from the original search and including and excluding additional studies identified from hand searches. Please fill in the table below for both searches.

The requested table has been completed. The number in bold corresponds to the total number of studies included in the analysis. Just to clarify the numbers used are as follows:

- Cost-effectiveness:
    - Total: n=12
    - Hand searching: n=9
    - Identified by previous review and excluded: n=2
- HRQoL:
    - Total: n=3
    - Hand searching: n=0
    - Identified by previous review and excluded: n=0

Copies of the PRISMA flow diagrams for the cost-effectiveness and HRQoL updates have also been included, to re-clarify the study flow for each update.

Cost-effectiveness		
	Additional studies from hand searches included	Additional studies from hand searches excluded
Duplicates from original search included	14 (3 from electronic database + 9 hand searching + 2 references excluded as	5 (3 from electronic database + 2 references excluded as duplicates from the original review)

	duplicates from original review)	
Duplicated from original search excluded	**12** **(3 from electronic database + 9 hand searching)**	3 (3 from electronic database)
HRQoL		
	Additional studies from hand searches included	Additional studies from hand searches excluded
Duplicates from original search included	3 (all from electronic databases)	3 (all from electronic databases)
Duplicated from original search excluded	**3** (all from electronic databases)	3 (all from electronic databases)

Figure 38: PRISMA diagram for the updated economic evaluation review (March 2017)

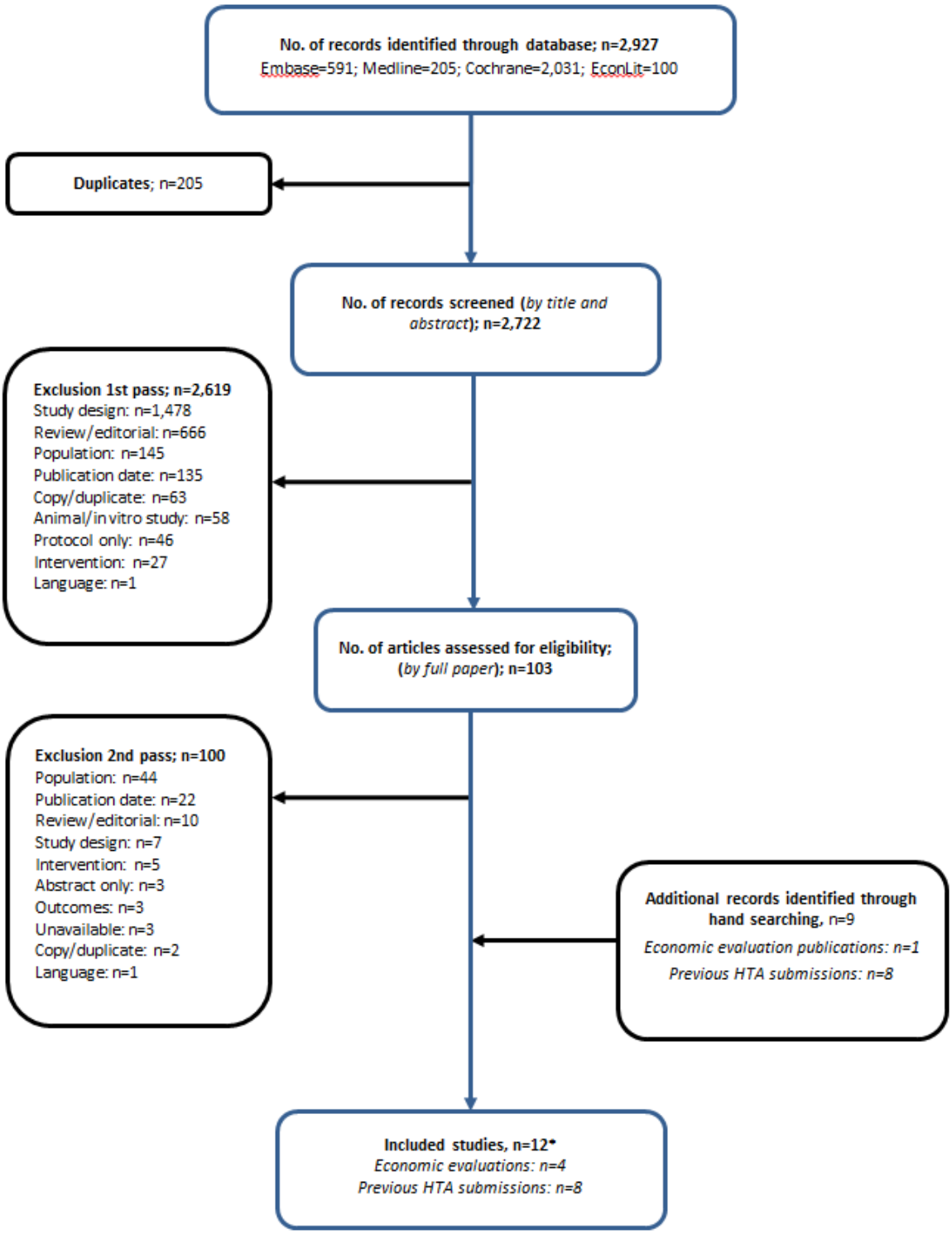
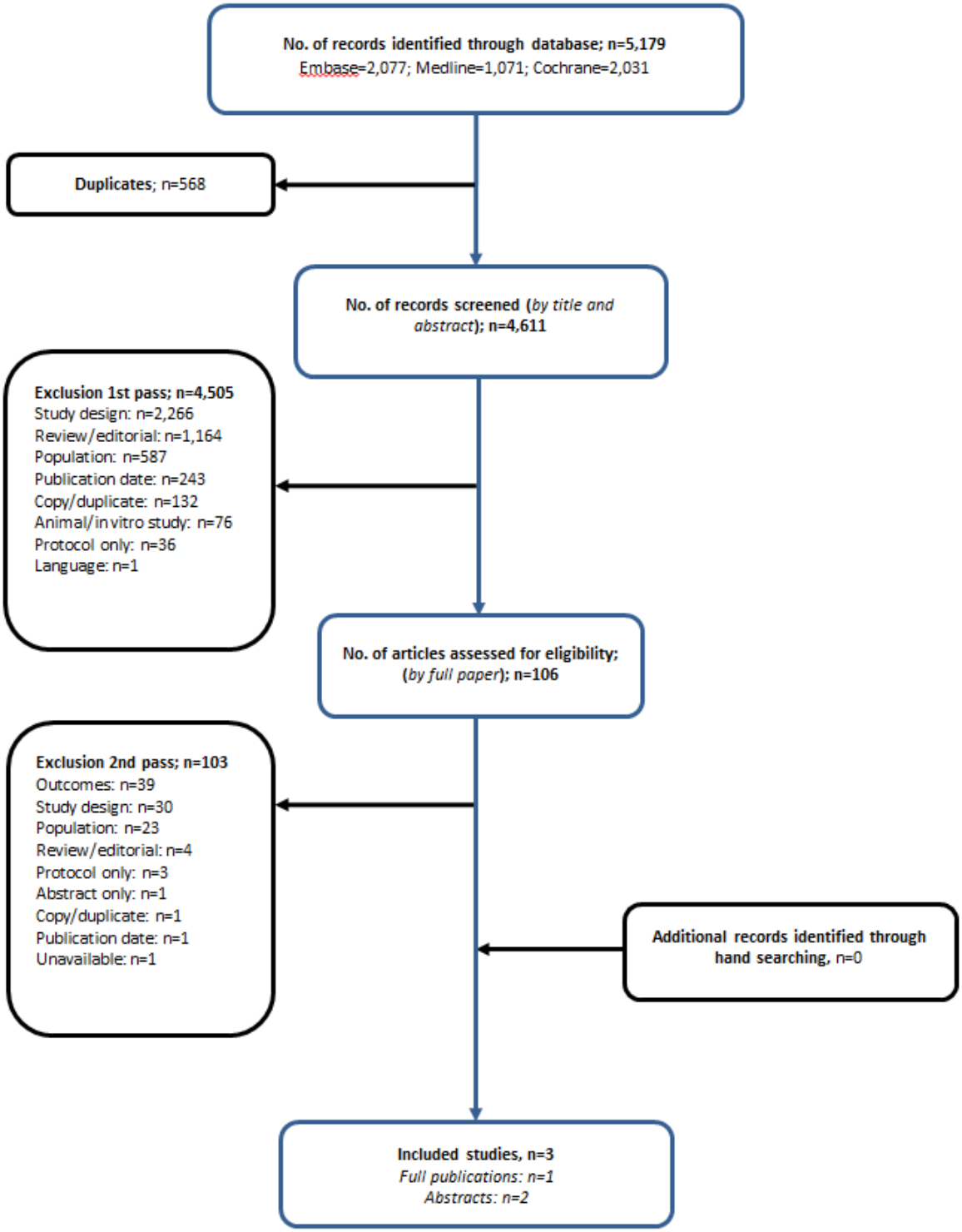


Figure 39: PRISMA diagram for the updated HSUV review (March 2017)



C8. Please clarify why a quality assessment of the included studies such as the Critical Appraisal Skills Programme (CASP) assessment as recommended by the DSU (TSD document 9) was not undertaken on the included HRQoL evidence.

A quality assessment of the utility studies identified in the update was undertaken using the criteria described in the NICE single technology appraisal (STA) evidence submission user guide (April 2017), as adapted from Drummond and Jefferson (1996) (Drummond and Jefferson, 1996). The full quality assessment can be found below. Unfortunately this is not available for the original review, however, as utility data is available within trial, the impact of literature review sourced utilities on this submission is relatively limited.

Table 41: Quality assessment of studies identified by the March 2017 update

	Author	Labbe	Comment	Labbe	Comment	Felip	Comment
	Year	2016		2015		2015	
Utility studies	1. Was the sample size large enough to extrapolate results to the larger population with confidence?	No	Small sample of ALK+ patients	No	Small sample of ALK+ patients	Yes	Large sample size and all patients ALK+
	2. Were the selection criteria yield a population similar to the population of interest?	Yes	Recruited patients with metastatic disease and ALK rearrangements	Yes	Recruited patients with metastatic disease and ALK rearrangements	Yes	Recruited patients with advanced ALK+ NSCLC
	3. Were response rates, loss to follow-up or missing data level likely to threaten the validity of the utility estimates?	No	Good response rate, loss to follow up and missing data unclear	Yes	Information not reported	Yes	Information not reported
	4. Were missing data handled properly?	Not clear	Not reported	Not clear	Details not reported	Not clear	Details not reported
	5. Was a suitable and valid interview process use for valuation?	Yes	Suitable methods employed	Yes	Not clear; details not reported	Yes	Not clear; details not reported
	6. Were health states described by the patients?	Yes	Patients described health states using EQ-5D-3L	Yes	Patients described health states using EQ-5D-3L	Yes	Patients described health states using EQ-5D-3L
	7. Were the health states valued according to societal preferences ?	Yes	Canadian, UK, and US tariffs applied	No	Not clear; details not reported	No	Not clear; details not reported

	Author	Labbe	Comment	Labbe	Comment	Felip	Comment
	Year	2016		2015		2015	
	8. Were the analysis technics deemed appropriate?	Yes	Appropriate methods used	No	Not clear; details not reported	No	Not clear; details not reported
	9. Did utility (-ies) incorporate decrement for quality of life loss from adverse events ?	Yes	Only for some sub-groups of the population (not ALK+ patients as sample size too small)	No	Reported only overall utility for patient sub-groups	No	Reported only baseline and on treatment utilities
	10. Is there any sign of bias in the analysis?	Yes	Single-centre study	Yes	Single-centre study	No	No additional signs of bias

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Alectinib for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer [ID925]

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	Consultant Medical Oncologist
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ✓ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The British Thoracic Oncology Group (BTOG) is the multi-disciplinary group for health care professionals involved with thoracic malignancies in the UK and Ireland. BTOG represents all the disciplines involved in thoracic malignancies throughout the UK and Ireland – medical and clinical oncologists, respiratory physicians, surgeons, radiotherapists, radiologists, pathologists, nurses, pharmacists, primary care community smoking cessation, public health and scientists. The basis of BTOG's activities to date has always been to support health care professionals and represent patients with the overall aim to improve outcomes for this range of cancers. BTOG is hosted by University Hospitals of Leicester NHS Trust based at Glenfield Hospital. BTOG does not receive any funding from the NHS but is supported through sponsorship and educational grants from industry and registration fees. BTOG registered as an independent charity in March 2016 recognising the importance of appropriate governance, effective planning to deliver organisational aims and objectives thus acting with integrity and being open and accountable.
5b. 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.)	1. Control cancer 2. Improvement of symptoms 3. Improvement of quality of life 4. Prolongation of survival
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.)	1. Reduction in size of the tumour by a clinically significant degree (traditionally 30% reduction or more) 2. Prolongation of survival by at least 3 months over current standard of care
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. An ALK targeting agent with good blood-brain barrier penetration. This is needed for effective treatment of established brain metastases at the start of treatment, as well as prevention of development of brain metastases for those without brain involvement at the start of treatment.
What is the expected place of the technology in current practice?	

9. How is the condition currently treated in the NHS?	Crizotinib is standard of care for the 1st line treatment of advanced stage ALK translocated lung cancer.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	National Institute for Health and Care Excellence (NICE, 2016): Crizotinib for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer (TA406) European Society of Medical Oncology (2016): Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up (Annals of Oncology 27 (Supplement 5): v1–v27, 2016) American Society of Clinical Oncology (ASCO, 2017): Systemic Therapy for Stage IV Non-Small Cell Lung Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update (J Clin Oncol 35(30) 3484-3515) NB. All these guidelines pre-date the full release of the first-line Alectinib data, and licensing of the drug in this setting, and so do not include Alectinib as a recommended treatment.
• 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.)	It is widely accepted that patients with advanced stage ALK-translocation positive lung cancer should receive an ALK inhibitor as first-line therapy. Since its approval by NICE in September 2016, Crizotinib is regarded as standard practice in England and there is a broad consensus about this.

• What impact would the technology have on the current pathway of care?	The pathway of care would not change, in that there is already an oral ALK tyrosine kinase inhibitor (TKI), Crizotinib, available for use on the NHS. The current technology would replace Crizotinib, and because the two drugs are given in the same way (orally) and at the same frequency (monthly cycles) there would be no changes. Given the impressive effect on brain metastases, both treatment of established metastases and prevention of new metastases, there is likely to be less need for neurosurgical or neuro-radiotherapy intervention, and associated neurological investigations.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes: both first line, oral, ALK TKIs used until disease progression.
• How does healthcare resource use differ between the technology and current care?	No difference in administration, routine tests or assessment of response. Potential for fewer neurological investigations and treatments, as detailed above.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care, oncology unit and centres. Outpatient based.
• What investment is needed to introduce the technology? (For	Nil. All facilities in place. Minor education of medical and nursing teams about common side effect profile.

example, for facilities, equipment, or training.)	
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. The ALEX clinical trial has shown a clinically and statistically significant improvement for patients treated with alectinib compared with crizotinib for progression free survival, time to progression of brain metastases, and objective response rate. There is no worsening of adverse events. Consequiently on the basis of greater clinical efficacy and a favourable side effect profile, alectinib provides clinically meaningful benefits.
• Do you expect the technology to increase length of life more than current care?	Yes, although at present the data to support this comes from progression free survival, not overall survival. Although cross-over was not allowed in the clinical trial (ALEX), the availability of Alectinib as a second line therapy, and the use of subsequent lines of chemotherapy in this patient group with a comparatively good prognsosis, may result in no clear overall survival benefit being evident.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes, especially on the basis of prevention of brain metastases and better control of existing brain metastases, but also on the basis of a longer duration of disease control (ALEX). There is also a more favourable side effect profile for alectinib although, because the adverse of events for standard of care (crizotinib) are usually manageable, this may have a comparatively minor effect on quality of life.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Only effective for patients with ALK-translocated, advanced, non-small cell lung cancer. No other groups identified at present.

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.)	No meaningful differences. No additional clinics, monitoring or testing. No additional concomitant treatments.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Treatment would be stopped when there is clinical and/or radiological evidence of disease progression, as is the case for the current stand of care (crizotinib). This would be established by routine re-staging investigations (likely CT of chest and abdomen +/- pelvis), every 2-3 months, which is standard practice for existing therapy.

15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No.
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. The impact on prevention and treatment of brain metastases is absolutely critical. Development and/or progression of brain metastases is a physically and psychologically devastating event which grossly affects quality of life. Any treatment that reduces the incidence of brain metastases is welcome, as is any agent that can treat existing brain metastases without the need for neurosurgery or cranial radiotherapy. On the basis of the evidence available Alectinib achieves both of these (ALEX study).
• Is the technology a 'step-change' in the management of the condition?	Yes – the huge difference in progression free survival for patients with brain metastases treated with Alectinib compared to Crizotinib (ALEX study), is indicative of the step-change.

• Does the use of the technology address any particular unmet need of the patient population?	Yes – control and prevention of brain metastases.
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?	Alectinib, on the whole, has a more favourable side effect profile than current standard of care (Crizotinib), with less need for dose reductions and dose interruptions (ALEX study). In particular, these is less frequent and less severe nausea, diarrhoea, vomiting, peripheral oedema, taste change and abnormal liver function tests. There is a greater incidence of elevated bilirubin, muscle pain and anaemia with alcetinib, but this is on the whole outweighed by the benefits. Formal quality of life assessment is not yet available from the phase 3 clinical trial of 1st line alectinib (ALEX).
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	The comparator arm reflects UK standard of care, as does the clinical setting and line of therapy. The inclusion of ECOG performance status 0-2 patients means that the trial patient population is more representative of the real clinical practice than most clinical trials in this situation. The patient demographics are generally representative of UK clinical practice (including younger age, as ALK translocated lung cancer is usually a disease of younger patients), with the exception of race: in the

	clinical trials approximately 45% of patients were of Asian origin. UK clinical practice would typically have a lower percentage of Asian patients.
• If not, how could the results be extrapolated to the UK setting?	I believe that the results can be extrapolated to the UK setting.
• What, in your view, are the most important outcomes, and were they measured in the trials?	1. Overall survival: measured, but data immature so current results cannot yet be interpreted (ALEX). 2. Progression free survival: large clinically and statistically significant difference between two treatment groups (ALEX). 3. Progression free survival in patients with brain metastases: large clinically and statistically significant difference between two treatment groups (ALEX). 4. Time to brain (CNS) disease progression: large clinically and statistically significant difference between two treatment groups (ALEX). 5. CNS objective response rate and duration of response: large clinically significant difference between two treatment groups (ALEX).
• If surrogate outcome measures were used, do they adequately predict	Progression free survival is a recognised and agreed marker for assessing survival in lung cancer. It is particularly useful in situations where an overall survival benefit may be 'drowned out' by use of subsequent

long-term clinical outcomes?	lines of therapy. This is especially pertinent to the ALK-translocated lung cancer population for whom several lines of therapy are expected and a generally better overall survival would be expected.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not to my knowledge.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Not to my knowledge.
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA406]?	Not to my knowledge.
21. How do data on real-world experience compare with the trial data?	There is little prospective real-world data, reflecting the novelty of the data.

Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	N/A

Key messages
24. In up to 5 bullet points, please summarise the key messages of your submission. • Alectinib would replacs existing treatment (crizotinib) with no need for change in treatment pathways or additional infrastructure • Alectinib shows clear clinically and statistically significant improvement in progression free survival compared to standard of care • Alectinib demonstrates impressive control of existing brain metastases, and prevention of development of new brain metastases • Alectinib is associated with a more favourable side-effect profile than the current stand of care • No conclusive overall survival data is available due to immature data

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Professional organisation submission

Alectinib for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer [ID925]

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 Society**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The British Thoracic Society (BTS) is the professional society for respiratory medicine and related health care professions. The Society exists to improve standards of care for people who have respiratory diseases and to support and develop those who provide that care. It is a registered charity and a company limited by guarantee.
5b. 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.)	
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.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	The British Thoracic Society supports the proposed appraisal. There is an urgent need more treatment options for patients with advanced lung cancer given the very poor prognosis.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	
• Are any clinical guidelines used in the treatment of the	

condition, and if so, which?	
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	
• In what clinical setting should the technology be	

used? (For example, primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	
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.)	

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
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?	
• Is the technology a 'step-change' in the management of the condition?	
• Does the use of the technology address any particular unmet need of the patient population?	
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?	
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	

• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
20. Are you aware of any new evidence for the comparator	

treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]? [delete if there is no NICE guidance for the comparator(s) and renumber subsequent sections]	
21. How do data on real-world experience compare with the trial data?	
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	
22b. Consider whether these issues are different from issues with current care and why.	

Topic-specific questions	
23 [To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.] **if there are none delete highlighted rows and renumber below**	
Key messages	

24. In up to 5 bullet points, please summarise the key messages of your submission.

-
-
-
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NHS England submission on the NICE appraisal of 1st line alectinib in the treatment of locally advanced/metastatic ALK mutation positive non small cell lung cancer

1. The correct comparator for alectinib was crizotinib as 1st line treatment of ALK positive NSCLC at the time the trial was initiated. NICE has since recommended ceritinib as a 1st line treatment option. Although NICE has recommended 2nd line ceritinib post 1st line crizotinib, 1st line ceritinib is clearly superior to 1st line crizotinib both systemically and in the treatment of brain metastases and thus it has become the main treatment option used in routine commissioning. NHS England does not commission the use of crizotinib post ceritinib as there is no evidence to support the benefit of such an approach and there is strong biological plausibility to indicate the lack of efficacy of crizotinib post ceritinib in the treatment of ALK pos NSCLC.
2. The current correct 1st line comparator would be ceritinib although NICE recognises that this was not the case at the time of the scoping of the 1st line alectinib appraisal.
3. Roche chose to not make an evidence submission to NICE for the use of alectinib post crizotinib when this (in effect) 2nd line indication was licensed. NICE therefore terminated the appraisal and NHS England accordingly does not commission the use of alectinib post crizotinib. The standard systemic therapy for patients progressing on alectinib would be platinum-based chemotherapy (not docetaxel-based).
4. NHS England recognises that sometimes patients have to start on chemotherapy for symptomatic reasons and before the ALK mutation result is known. In this situation, NHS England commissions either ceritinib 2nd line or (less commonly now) crizotinib followed by ceritinib.
5. NHS England observes that the median duration of follow-up in the 1st line alectinib phase III trial is only 18 months and that the median PFS in the alectinib arm has not yet been met. Follow-up is therefore still short and results immature from the point of assessing key longer term outcomes, especially overall survival. NHS England knows from the NEJM publication of this trial that further analyses are planned.
6. NHS England notes that in the alectinib phase III trial CT scans of both the body and the brain were done every 8 weeks. Such a practice will not occur in the NHS. Whilst scans would be done relatively early to check on disease response and also done at any time if there is a suspicion as to disease progression, patients who are symptomatically well and stable will have occasional scans but not at 8 weekly intervals. Brain metastases that are not seen at diagnosis but subsequently develop are thus most likely to be diagnosed when symptomatic.
7. NHS England observes that the trial primary end point was progression free survival (PFS) as assessed by the investigator. This is what will happen in practice if NICE recommends alectinib and thus is what NHS England would wish cost effectiveness analyses to be based on. An additional reason for this is given below in paragraph 8.

8. NHS England also knows that treatment with alectinib will continue after RECIST-defined disease progression in two main scenarios. The first is when there is a dimensionally small increase in an already small marker lesion: this would trigger definition of disease progression but is clinically irrelevant as the patient remains well; alectinib would thus continue until there is clinically significant progression ie the development of symptoms. The second is when there is continued systemic response to alectinib but disease progression in the brain which is then amenable to active treatment with radiotherapy of various types. Treatment would continue until systemic progression or loss of control of the intra-cerebral disease. The same outcomes of these two scenarios may not apply to crizotinib as a proven option is there which is also NICE recommended and thus commissioned (ceritinib): clinicians are likely to stop crizotinib and switch to ceritinib earlier, particularly for those with brain metastases
9. NHS England notes that there was no protocol-defined cross over in the alectinib phase III trial. There are many trials of new agents in ALK positive NSCLC eg brigatinib, lorlatinib, entrectinib. The follow up data in the alectinib phase III trial thus needs to show what agents were used in which arm after alectinib as these could easily affect survival and any imbalance between arms could impact on survival and thus cost effectiveness.
10. In the cost effectiveness analyses and in any inclusion of PFS and CNS-RECIST data, NHS England would wish there to be no double counting of events. The time to treatment discontinuation is therefore very important although in the patients who relapse in the brain but not elsewhere, there will be the additional costs of treating the brain metastases as well as the continued drug cost.
11. NHS England notes that Roche does not regard NICE's End of Life criteria as being met.
12. NHS England notes that the drug administration cost per cycle assumed for alectinib/crizotinib by Roche is £9-20. These drugs are high cost chemotherapy drugs and thus the oral chemotherapy administration tariff should be used. This in 2017/18 is £120.
13. NHS England notes too that Roche assumes CT scans every 8 weeks. This will not happen for a drug with a response rate of about 80% and as outlined above.
14. NHS England observes that in the model Roches assumes crizotinib use post alectinib. This will not occur in view of NHS England's current commissioning position of crizotinib post ceritinib (as described above).
15. NHS England notes that the first chemotherapy given post alectinib or crizotinib is docetaxel-based. This is incorrect: NHS England commissions platinum-based combination chemotherapy first in this situation with docetaxel potentially coming next. The costs of platinum-based chemotherapy with pemetrexed thus need to be incorporated into the cost effectiveness analysis: use of such chemotherapy will be

higher post alectinib than post the crizotinib-ceritinib sequence as there is always loss of actively treated patient numbers from one line of therapy to the next.

[redacted]

NHS England [redacted]

March 2018

Submission from Roy Castle Lung Cancer Foundation, for consideration by NICE, in their review of Alectinib for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer [ID925]

Submitting Organisation

Roy Castle Lung Cancer Foundation is a UK wide lung cancer charity. We fund lung cancer research, tobacco control initiatives and work in lung cancer patient care (information, support and advocacy activity).

The Foundation has contact with patients/carers through its UK wide network of over 50 monthly Lung Cancer Patient Support Groups, online Forums and its Lung Cancer Information Helpline.

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 10%, 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 non small cell lung cancer (nsclc).

General Points

1. For patients with advanced or metastatic nsclc, cure is not a treatment option. In this scenario, improving quality of life, symptom management and even small extensions in duration of life are of considerable significance to the individual and their family.

2. The relatively recent addition of targeted therapies and immunotherapy, in the treatment of nsclc, has ensured new active therapy options for many with nsclc. However, overall outcomes for many of this patient population remains poor. The availability of new targets and therapy choices, being of key future importance.

3. The importance of 'end of life' therapies. When considering the cost of treatment, it is not appropriate, for example, to give the same weighting to the final six months of life, as to all other six months of life. It is important for this to be part of any numeric equation, which is looking at cost and quality of life. This point is of crucial importance to patients and relatives in this situation

4. Improvement in symptoms. Patients with advanced or metastatic non small cell lung cancer are often debilitated with multiple and distressing symptoms. Symptoms such as breathlessness are very difficult to manage clinically. Therapies with anti-tumour activity often provide the best option for symptom relief.

This Product

1. Well tolerated
   Oral therapy - therefore, ease of administration.

   Other therapies in ALK positive nsclc are available. Crizotinib is approved through NICE appraisal, for use in untreated ALK positive nsclc. Ceritinib is currently undergoing Single Technology Appraisal in this indication and has positive NICE appraisal in second line, after failure of Crizotinib therapy. As such, experience in the use and side effect management of this class of therapies is now commonplace.
   We understand that side effects associated with Alectinib include constipation, oedema (swelling of the ankles and feet and of the eyelids), muscle pain, diarrhea and nausea. Alectinib may also cause more serious side effects, such as hepatotoxicity, lung toxicity and cardiac problems (bradycardia). In the anecdotal patient experience available to us, it appears to be generally well tolerated – in particular, when compared with current standard cytotoxic therapy for nsclc.

2. Very targeted population.

   The ALK gene rearrangement is found in about 2% to 7% of patients with nsclc. As other therapies in this target population are already available, as above, diagnostic testing is available. Although we do note issues with turnaround time, available tissue etc...

3. Outcome of treatment

   We do not have any additional data, beyond that publically available.

   We note, however, the results of the Phase 111 Trial, published in August 2017 in The New England Journal of Medicine. This study compared Alectinib with Crizotinib. All patients in the study were untreated and all had advanced ALK positive nsclc, including with asymptomatic CNS disease. During a median follow up of 17.6 months (Crizotinib) and 18.6 months (Alectinib), an event of disease progression or death occurred in 62 of the 152 patients (41%) in the Alectinib group and 103 of 151 patients (68%) in the Crizotinib group.
   Also, we note with interest, a total of 18 patients (12%) in the Alectinib group had an event of CNS progression, as compared with 68 patients 45%) in the Crizotinib group.
   A response occurred in 126 patients (82.9%) in the Alectinib arm and in 114 patients (75,5%) in the Crizotinib arm.
   Toxicity of more than Grade 3 was less frequent in the Alectinib group – (41% versus 50% with Crizotinib).

   Our observations come from a combination of one-to-one discussion with lung cancer patients, published research, on line patient contact and our patient information helpline.

In summary

Patients with advanced and metastatic lung cancer are in a particularly devastating situation. ALK gene rearrangement is found in a very small number of lung cancer patients but, new

target therapies offer much better therapy options in this small segmented patient group. Alectinib offers a further therapy option for these patients. As compared with Crizotinib, research has shown Alectinib to have superior efficacy and lower toxicity in first line treatment of ALK positive nsclc.

[redacted], [redacted] **RCLCF.**

November 2017.

NICE National Institute for Health and Care Excellence

Clinical expert statement

Alectinib for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer [ID925]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

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 expert statement

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Alastair Greystoke**
2. Name of organisation	**Newcastle University**

3. Job title or position	**Senior Lecturer**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Palliate symptoms and prevent progression as long as possible.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	An improvement in Progression free survival of more than 3 months, an improvement in radiological response rates by 10 % or a reduction in the development of central nervous metastases by 5%.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes.
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	Crizotinib (ceritinib is presently under evaluation by NICE)
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Nice appraisal TA406
• 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 the pathway is well defined. I do not believe there are major differences across the NHS.
• What impact would the technology have on the current pathway of care?	Alectinib would be an alternative option to crizotinib
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes

• How does healthcare resource use differ between the technology and current care?	No major differences
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist oncology clinics
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No major investment required
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
• Do you expect the technology to increase length of life more than current care?	Yes. Overall survival data for the ALEX study has not yet been reported, and will be confounded by extensive crossover from the crizotinib arm. However given the differences in control of disease, particularly in the brain, I would be very surprised if access to this treatment did not lead to significantly increased survival compared to if there was only access to crizotinib in the 1st line setting.

• Do you expect the technology to increase health-related quality of life more than current care?	Yes
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients with central nervous system metastases are more likely to derive additional benefit from the use of alectinib as opposed to the present NICE approved technology crizotinib.
The use of the technology	
14. 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	No major differences

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	ALK testing is already recommended within the NHS to help identify patients who should be offered these therapies. Patients will be monitored by serial CT scans as with any palliative lung cancer treatment. Treatment will stop when there is radiological and clinical progression on treatment. There is no additional monitoring required.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Delay in central nervous system metastases results in significant improvement in health and may not be accurately captured by quality of life data within the study
17. Do you consider the technology to be innovative in its potential to make a significant and substantial	No. whilst it is probably an improved strategy to use alectinib up front compared to crizotinib followed by a 2nd generation ALK inhibitor such as alectinib or ceritinib this has not formally been answered within a clinical trial as yet.

impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	The progression free survival and brain disease control seen with agent in the ALEX study suggest that it is a significant "step-up" from the present standard of care.
• Does the use of the technology address any particular unmet need of the patient population?	Yes. These patients have high rates of central nervous system metastases. Alectinib delays the onset of these metastases which can be difficult to treat.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Side-effects similar to other ALK inhibitors, and may be less than with the present NICE approved technology of crizotinib .
Sources of evidence	

19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	Response rates , Overall Survival, Progression free Survival, Control of brain disease and health related quality of life
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	No. Progression free survival does not tend to predict for subsequent overall survival in ALK lung cancer studies due to extensive cross over and confounding from subsequent treaments.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
20. Are you aware of any relevant evidence that might	No

not be found by a systematic review of the trial evidence?	
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance 406 in September 2016?	No
22. How do data on real-world experience compare with the trial data?	Due to the selection of patients for clinical trials the data may over-estimate progression free and overall survival when compared to the real world population.
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	No

23b. Consider whether these issues are different from issues with current care and why.	No difference from current issues

Key messages

24. In up to 5 bullet points, please summarise the key messages of your statement.

- Alectinib leads to significantly improved progression free survival and delay in brain metastases over crizotinib
- An overall survival benefit is unlikely to be seen in clinical studies
- There are no major clinical barriers to the implementation of alectinib into NHS practice
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NICE National Institute for Health and Care Excellence

Clinical expert statement

Alectinib for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer [ID925]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

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 expert statement

- 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	Dr Riyaz Shah
2. Name of organisation	Maidstone and Tunbridge Wells NHS Trust

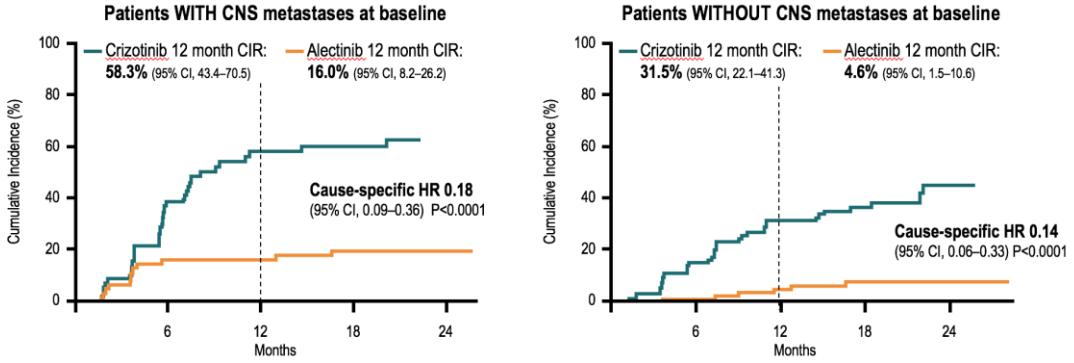
3. Job title or position	Consultant Medical Oncologist
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. 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 arrest the growth and thereby prolong the life of patients with ALK translocated lung cancer.
8. 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 response rate above 75% and the progression free survival of more than 20 months (based on the PFS of Crizotinib of 10.9m (PROFILE 1014; Solomon et al NEJM 2014) and Ceritinib of 16.6m (Soria et al Lancet 2017)
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There is a great unmet need with these patients. They have a very high incidence of brain metastases. These are often symptomatic and carry a significant morbidity and mortality burden. We desperately need treatments that penetrate the CNS and reduce the intracranial disease burden
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	Crizotinib is the NHS first line standard of care at the moment based on PROFILE 1014
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE guidelines approve Crizotinib as 1st line therapy currently
• 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.)	The pathway of care is very well defined in that Crizotinib is the only 1st line ALK inhibitor with both EMA and NICE approval. There will not be any differences of opinion on this issue
• What impact would the technology have on the current pathway of care?	Alectinib will completely replace Crizotinib as the 1st line standard of care for this disease
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Currently Alectinib is licenced post Crizotinib failure. The ALUR trial confirms its activity in this setting compared to chemotherapy. It is not currently NICE approved as so in England/Wales there is no NHS access to Alectinib. At the time if writing this review, Alectinib has CHMP approval in EMA and by the time of the NICE committee meeting it is likely to be licenced 1st line.

• How does healthcare resource use differ between the technology and current care?	The use of OPD appointments, doctor visits and nurse visits are not likely to differ much between Crizotinib and Alectinib. The scanning frequency is likely to be the same. Alectinib is significantly better tolerated and there may be a lower healthcare resource burden with fewer OPD appointments to see doctors/nurses. Alectinib is neuroprotective and has much greater rates of CNS disease control. The cost of managing brain metastases is significant as many of these patients are younger and fitter. There will be a higher rate of stereotactic radiotherapy/surgery use in the Crizotinib arm.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	This technology should be the first line standard of care for advanced ALK translocated lung cancer.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	ALK testing is already widely available in the UK. I do not foresee any investment requirement to introduce this technology other than the drug procurement costs
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, dramatically so. The ALEX trial shows highly statistically significant and clinically meaningful benefits in terms of duration of response, progression free survival, time to CNS progression. It also has a significantly reduced cumulative rate of brain metastases compared to Crizotinib.
• Do you expect the technology to increase length of life more than current care?	Yes. I strongly suspect this agent will prolong life. The difference in PFS difference between Crizotinib and Alectinib is very large. However, it's another thing to prove it. Overall survival in randomised trials of ALK translocated lung cancer do not show significant differences due to the very high rate of ALK inhibitor (ALKi) therapy in the post progression setting. This cancer is exquisitely sensitive to ALKi therapy. In PROFILE 1014 84% of the chemotherapy arm patients switched over to receive Crizotinib. With such a

	ALKi sensitive cancer and very high rates of crossover, demonstrating an OS benefit is unlikely to be possible. The IFCT-1302 CLINALK retrospective dataset (Duruisseaux et al Oncotarget 2017) suggests a mOS of 30 months with Crizotinib but significantly shorter in patients who do not go on to receive further ALKi. However, this case series does show a large increase in mOS in those patients who then went on to receive next generation ALKi such as Alectinib. Of patients in the ALEX trial who did not have baseline brain mets at baseline, at 12 months, 4.6% of the Alectinib group had developed brain mets. However, by the same 12 month mark 31.5% of patients in the Crizotinib arm had developed brain mets. Progressive brain mets is associated with lower survival. An important case series from the UK (Yip et al Lung Cancer 2017 Vol 103, Supp 1 , S28-29) looked at outcomes in 120 patients with advanced ALK lung cancer from 21 centres. The median overall survival from starting Crizotinib was 14.8 months and median PFS of 9.76 m. The latter compares favourably with the 10.9m median PFS from PROFILE 1014. Only 25 patients received a second generation ALKi and the median OS in this subgroup was 29 months. The Yip data clearly shows that UK practice is substandard and associated with unnecessary early death. The most likely reason for low usage of next generation ALKi is that many patients “drop off” with rapid deterioration most likely due to progressive brain mets. Moving next generation ALKi into the first line setting is likely to result in a significant change in the survival of this group of patients.
• Do you expect the technology to increase	Yes

health-related quality of life more than current care?	
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The evidence suggests it has higher rates of intracranial disease control over Crizotinib, however it also shows that there is a neuroprotective effect in those without CNS disease. The neuroprotection is superior to Crizotinib. This was shown in the ALEX presentation at ESMO 2017 (Gadgeel et al). The graphs from this presentation clearly demonstrate the effect **CUMULATIVE INCIDENCE RATE OF CNS PROGRESSION (IRC, ITT)** • A competing risk analysis with CNS progression, non-CNS progression and death as competing events was conducted* 
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current	It will be very easy to deliver with no significant practical implications. Alectinib would simply replace Crizotinib as 1st line standard of care

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.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	CT scans of the chest/abdomen/pelvis are primarily used to monitor benefit. In addition, cranial MRI would be used to monitor CNS disease. Start rules would be the presence of ALK translocation with advanced lung cancer and adequate performance status. Stop rules would be evidence of clinically significant cancer progression.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the	Yes. The neuroprotective effects and the rate of CNS control needs to be considered as a special and unique aspect to ALK translocated lung cancer. At presentation 25-30% of patients will have brain mets. Many will go on to relapse with brain mets. Brain metastases are uniquely difficult to treat and palliate. Patients and care givers are often totally devastated by being told the cancer has spread to the brain.

quality-adjusted life year (QALY) calculation?	Alectinib clearly reduces the chance of CNS metastases developing in ALEX when compared to Crizotinib (see Q13) Alectinib seems to be associated with a sustained and durable duration of CNS control. There is a significant life adjustment if brain metastases develop or even if detected at baseline. These patients are disallowed from driving for at least 1 year. This can have disastrous effects on the patient and their care givers. These patients tend to be a bit younger than the lung cancer averages and many are in employment
17. 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. The main innovation relates to CNS penetration and excellent control of intracranial disease. Additionally, it seems to have a favourable toxicity profile. The efficacy data is a paradigm shift in the 1st line treatment of this disease and it is likely to make a substantial and significant impact on QoL. Predominantly by being less toxic, preventing the development of brain mets and delaying the progression of existing brain mets.
• Is the technology a 'step-change' in the management of the condition?	Yes. This is widely considered a paradigm shift in the ALK positive field.

• Does the use of the technology address any particular unmet need of the patient population?	Yes. As stated, it is less toxic and more effective with longer duration of disease control (both intra and extra cranially) and neuroprotective effects.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	This agent is generally very well tolerated.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	The standard arm of the ALEX trial mimics UK practice only in as much as Crizotinib is the NICE 1st line standard of care. However, it is likely that this this is as far as things go. Within the trial, it is very likely that large numbers patients in the Crizotinib arm will go on to receive next generation ALKi's. However, in the UK, contemporaneous data shows low levels of next generation ALKi use with concomitantly poorer survival (Yip et al BTOG annual meeting 2017). See Q12 Thus, it is v likely that UK practice will deliver poorer outcomes in the context of 1st line Crizotinib
• If not, how could the results be extrapolated to the UK setting?	The trail gives some indication of where UK practice could go if there was access to first line next generation ALKi in the form of Alectinib.

• What, in your view, are the most important outcomes, and were they measured in the trials?	Progression free survival and overall survival were the most important. All these were measured in the trial. In addition the PFS in patients with brain mets and the cumulative incidence of brain mets in those with no baseline CNS disease.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	The endpoints used in the ALEX trial constitute a conventional paradigm for assessing efficacy in oncology trials.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not that I am aware of.
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No. To my knowledge ALEX is the only trial testing Alectinib vs Crizotinib in the 1st line setting within the context of a head to head randomised controlled trial.
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology	The final overall survival curves for the PROFILE 1014 trial were presented at the ESMO annual meeting Madrid 2017. This showed that at a median of 46 months of follow up the median overall survival in the chemotherapy group was 47.5 months and in the Crizotinib arm the median had not been reached. There

appraisal guidance 406 in September 2016?	was a non-statistically significant trend for better overall survival in the Crizotinib arm with a hazard ratio of 0.76 however the confidence interval was just outside significance by conventional statistical methodology
22. How do data on real-world experience compare with the trial data?	An important case series from the UK (Yip et al Lung Cancer 2017 Vol 103, Supp 1 , S28-29) looked at outcomes in 120 patients with advanced ALK lung cancer from 21 centres. The median overall survival from starting Crizotinib was 14.8 months and median PFS of 9.76 m. The latter compares favourably with the 10.9m median PFS from PROFILE 1014. Only 25 patients received a second generation ALKi and the median OS in this subgroup was 29 months. The Yip data clearly shows that UK practice is substandard and associated with unnecessary early death. The most likely reason for low usage of next generation ALKi is that many patients “drop off” with rapid deterioration most likely due to progressive brain mets.
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	no
23b. Consider whether these issues are different from issues with current care and why.	

Key messages
24. In up to 5 bullet points, please summarise the key messages of your statement. • There is very strong data supporting Alectinib as 1st line standard of care • The PFS in Crizotinib arm of 11.1 months confirms the standard arm was behaving as expected • The PFS in Alectinib is superior (hazard ratio 0.47) with a median that has not been reached • Alectinib prevents brain metastases and also is better at controlling existing brain metastases • Current UK outcomes in ALK lung cancer is woeful and needs to improve to the level of similar economies (eg France)

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NICE National Institute for Health and Care Excellence

Patient expert statement

Alectinib for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer [ID925]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Lesley Holland**

2. Are you (please tick all that apply):	☐ a patient with the condition? ☐ a carer of a patient with the condition? ✓ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation	National Lung Cancer Forum for Nurses
4. Did your nominating organisation submit a submission?	☐ yes, they did ✓ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ✓ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☐ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ✓ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	As a lung cancer specialist nurse I care for patients who have lung cancer. It is a disease often with no cure that can lead to complex symptoms causing considerable physical and psychological distress

Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	I believe patients and carers feel there are new treatments becoming available for patients with lung cancer, as long as they are eligible for the treatments.
10. Is there an unmet need for patients with this condition?	No. Currently there is a drug available for patients with untreated Anablastic Lyymphoma Kinase- positive advanced Non small cell lung cancer
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	Benefits of this treatment might include • Alectinib is given to patients with the ALK positive receptors. It is given in tablet form which much easier for the patients to take. And the side effects for patients appear to be minimal. • Because the treatment is in tablet form at home, the patients only have to attend an appointment with the oncologist once a month, this is vastly reduced from the alternative treatments. • Family members are better able to support patients to administer a tablet at home. • Patients will have less travelling to hospital appointments • Alternative treatments have more side effects and patients are often hospitalised to manage the side effects. • Psychologically patients taking this treatment seem to accept it as a therapy much easier as it is included in their daily routine of medicines management at home. • Patients also have the benefit of knowing they have a treatment that is completely targeted to their disease. • Overall the quality of life for patients who are able to receive the treatment appears to be improved

	• There are only a few patients in the total population of NSCLC patients who will have the ALK receptor to target so the treatment will not by the nature of numbers be a common treatment given, however the outcomes could be significant in terms of disease free progression, but more over the quality of life of palliative patients. • I cannot comment on its efficacy over and above the drug currently being used
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	The side effects of this therapy can be complex to treat as generally the medical teams do not have so much experience of using. The more this type of drug is used the easier this will become
Patient population	
13. 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.	Not known
Equality	
14. Are there any potential equality issues that should be taken into account when	

considering this condition and the technology?	
Other issues	
15. Are there any other issues that you would like the committee to consider?	
Key messages	
16. In up to 5 bullet points, please summarise the key messages of your statement: • Tablet Form • Less side effects to conventional chemotherapy • Improved quality of life • Improved life psychologically and for the family • Less hospital appointments and less inpatient stays for patients and their family	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

Alectinib for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer [ID925]

STA REPORT

This report was commissioned by the NIHR HTA Programme as project number 17/56/01

BMJ Technology Assessment Group

Title: Alectinib for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer

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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.

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Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows: Edwards SJ, Kew KM, Bacelar M, Wakefield V, Marceniuk G. Alectinib for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer: A Single Technology Appraisal. BMJ Technology Assessment Group, 2017.

Contributions 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
Kayleigh M Kew	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 and clinical results sections
Victoria Wakefield	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and assisted with drafting the clinical results sections
Mariana Bacelar	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
Gemma Marceniuk	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 ERG report.

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Abbreviation	In full
1L	First line
2L	Second line
AE	Adverse event
AIC	Akaike information criterion
ALK	Anaplastic lymphoma kinase
ALK-TKI	Tyrosine kinase inhibitor of anaplastic lymphoma kinases
ALT	Alanine transaminase
ACP	American College of Physicians
AST	Aspartate transaminase
AUC	Area under the curve
BIC	Bayesian information criterion
BID	Twice-daily
BL	Baseline
BNF	British National Formulary
CDF	Cancer Drugs Fund
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CENTRAL	Cochrane Central Register of Controlled Trials
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CNS	Central nervous system
CNS PD	Progressive disease involving the CNS
CNS RECIST	Modified Response Evaluation Criteria in Solid Tumours for intracranial lesions
CNS PFS	Central nervous system progression free survival
CPK	Creatine phosphokinase
CQ	Clarification question
CR	Complete response
CS	Company submission
CSR	Clinical study report
DARE	Database of Abstracts of Reviews of Effects
DOR	Duration of response
ECOG PS	Eastern Cooperative Oncology Group performance status
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
eMIT	Electronic market information tool
EORTC	European Organisation for Research and Treatment of Cancer
EPAR	European public assessment report
EQ-5D(-3L)	EuroQol 5 dimensions (3 levels)
ERG	Evidence review group
FAD	Final Appraisal Determination
FDA	United States Food and Drug Administration
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUV	Health-state utility value

HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
INV	Investigator-assessed
IRC	Independent Review Committee-assessed
ITT	Intention-to-treat population
KM	Kaplan-Meier
LYG	Life years gained
MA	Marketing authorisation
NA	Not applicable
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	Not evaluable
NHS	National Health Service
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NLCA	National Lung Cancer Audit
NR	Not reported
NSCLC	Non-small cell lung cancer
ONS	Office for National Statistics
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
OWSA	One-way sensitivity analysis
PAS	Patient access scheme
PASLU	Patient Access Schemes Liaison Unit
PD	Progressive disease
PFS	Progression-free survival
PH	Proportional hazards
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient-reported outcome
PSA	Probabilistic sensitivity analysis
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life years
RCT	Randomised clinical trials
RECIST	Response Evaluation Criteria in Solid Tumours
RET	Rearranged during Transfection
RR	Relative risk
SAE	Serious adverse event
SD	Stable disease
SD	Standard deviation
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
STA	Single technology appraisal
TA	Technology appraisal
TKI	Tyrosine-kinase inhibitor

TRAE	Treatment-related adverse event
TSD	Technical support document
TTD	Time to treatment discontinuation
UK	United Kingdom
ULN	Upper limit of normal
WBRT	Whole brain radiotherapy
WHO	World Health Organization
WTP	Willingness to pay

1 SUMMARY

1.1 Critique of the decision problem in the company's submission

The company submitted clinical and economic evidence in support of the effectiveness of alectinib (Alecensa®; Roche) for adults with untreated anaplastic lymphoma kinase positive (ALK+) advanced non-small-cell lung cancer (NSCLC).

The company provided an overview of the population with ALK+ advanced NSCLC, in relation to the wider lung cancer population, including common symptoms, prognosis, and the effects on patients' and their carers' health-related quality of life (HRQoL). Approximately 5% lung cancers test positive for rearrangement on the ALK gene, which activates pathways that can be targeted with tyrosine kinase inhibitors (TKIs) to inhibit tumour growth and spread. Patients with ALK+ NSCLC are generally younger, more often female, and the cancer is less commonly associated with smoking history than the wider lung cancer population, so ALK+ NSCLC tends not to be picked up in screening programmes.

Alectinib as monotherapy is a second-generation ALK-TKI that first received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) in December 2016 for adult patients with ALK+ advanced NSCLC previously treated with crizotinib (a first-generation ALK-TKI). In October 2017, the CHMP issued a positive opinion to extend the marketing authorisation for alectinib to first-line (1L) use in the same population, which was granted in December 2017.

The company provided an overview of the current treatment pathway in England for patients with ALK+ advanced NSCLC. The Evidence Review Group's (ERG's) clinical experts confirmed that crizotinib is currently the preferred 1L treatment for adults confirmed as having ALK+ advanced NSCLC (TA406), and the only appropriate comparator for alectinib. The ERG notes that ceritinib, a second-generation ALK-TKI first approved by NICE for 2L use after crizotinib, has since been recommended for 1L treatment and, "may replace crizotinib as the standard of care internationally" (Final Appraisal Determination [FAD], TA500). The ERG's clinical experts agreed that second-generation ALK-TKIs (alectinib and ceritinib) would be preferred over crizotinib as 1L treatment, but expressed concern about a lack of available 2L treatment options should they be used at 1L.

The clinical evidence presented in the company's submission (CS) is based solely on the multicentre phase III randomised controlled trial (RCT), ALEX. The study randomised 303 people with untreated, histologically confirmed ALK+ advanced NSCLC to receive alectinib or crizotinib until disease progression or unacceptable toxicity. The ERG considers the population, intervention and comparator of ALEX to be relevant to the decision problem outlined in the final scope issued by the National Institute for Health and Care Excellence (NICE), and analogous to UK clinical practice. All clinically

relevant outcomes were reported in the CS and no subgroups of interest were defined in the NICE final scope.

1.2 Summary of clinical effectiveness evidence submitted by the company

Clinical effectiveness evidence is derived solely from the multicentre phase III randomised trial, ALEX. The company did not pool results of ALEX with any indirect evidence (i.e. via one or more common comparators in related RCTs of alectinib and crizotinib), and the ERG considered the potential for increased precision by doing so would likely to be outweighed by the clinical heterogeneity introduced. The ERG considered ALEX to provide high quality comparative clinical effectiveness evidence which closely matches the decision problem outlined in the final scope issued by NICE.

The population of ALEX comprised 303 adults with untreated, histologically confirmed ALK+ advanced NSCLC. The population of ALEX reflects that ALK+ NSCLC affects a younger population who are more often female, and with less smoking history than the wider NSCLC population. Characteristics were generally well balanced between groups. The population of ALEX may represent a relatively healthy subset of all patients with ALK+ advanced NSCLC, but generally reflect patients in England despite the small proportion recruited from UK centres (1%). Patients with CNS metastases at baseline were eligible if they were asymptomatic or had completed radiotherapy at least 14 days before study entry. The proportion of patients with CNS metastases at baseline (42% and 38% for alectinib and crizotinib, respectively) reflects that brain metastases are common and often present early in ALK+ NSCLC, but is higher than seen in UK clinical practice because asymptomatic patients are not scanned routinely.

Patients randomised to alectinib in ALEX (n = 152) received 600 mg orally, twice daily and patients randomised to crizotinib in ALEX (n = 151) received 250 mg orally, twice daily, in line with their respective marketing authorisations. In both groups, treatment continued until progressive disease (PD) according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1) or unacceptable toxicity Randomised treatment could be continued beyond isolated asymptomatic progression in the CNS at the investigator's discretion, which the company highlight is not indicated in the marketing authorisation for alectinib. The ERG considers that this asymptomatic CNS progression may not be detected in clinical practice, but notes from clinical experts that treatment with ALK-TKIs often continues in UK practice until patients show progression in multiple sites, because subsequent treatment options are limited.

The primary outcome was investigator-assessed (INV) progression-free survival (PFS). Secondary outcomes were PFS assessed by independent review committee (IRC PFS), OS, overall response rate (ORR), duration of response (DOR), health-related quality of life (HRQoL), and adverse events (AEs),

in line with the NICE final scope. HRQoL in ALEX was measured by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ30) and lung cancer module (EORTC-LC13), and the EuroQol 5 dimensions (EQ-5D-3L). AEs were captured by study physicians who were aware of treatment assignment, according to Common Terminology Criteria for Adverse Events (CTCAE version 4).

The CS included additional outcomes relating to CNS progression that were not listed in the NICE final scope to capture the proposed activity of alectinib in the CNS, which is likely to differentiate it from crizotinib. On the advice of clinical experts, the ERG considered it important to capture this proposed benefit, given the important effects of CNS progression on prognosis and patients' quality of life. Outcomes included time to CNS progression (CNS PFS) for all patients regardless of baseline CNS metastases, and CNS ORR and DOR in the subset of patients with CNS metastases at baseline (64 and 58 patients in the alectinib and crizotinib groups, respectively).

The company outlined that CNS progression could be picked up via two separate IRC assessments in ALEX: the main RECIST v1.1 to identify systemic PD, and a second modified RECIST assessment defined specifically for the trial to identify intracranial lesions (hereafter referred to as CNS RECIST). The company submitted an adapted PFS outcome at the clarification stage which became their preferred analysis, which counted time to the first event from the main IRC RECIST assessment or the IRC assessment using CNS RECIST. The company's preferred analysis of CNS PFS also counted events from RECIST or CNS RECIST. The ERG considered results from PFS and CNS PFS based on standard RECIST the most clinically relevant, and more comparable to related trials and NICE technology appraisals.

Randomisation in ALEX was carried out centrally and was stratified by Eastern Cooperative Oncology Group performance status (ECOG PS), race and presence of CNS metastases at baseline. Where available, the ERG considers PFS, CNS PFS and ORR assessed by independent review committee (IRC) likely to be less biased than the investigator assessments (INV) because ALEX was an open-label study. HRQoL and safety assessments may also be subject to bias because patients and investigators were aware of treatment assignment.

Median PFS and CNS PFS and associated confidence intervals (CIs) were not reported by the company for analyses based on RECIST+CNS RECIST, but there was a clear benefit of alectinib over crizotinib. The ERG's preferred measure of PFS (IRC RECIST) showed a statistically significant and clinically meaningful benefit of alectinib compared with crizotinib; median PFS 25.7 months for alectinib (95% CI: 19.9 months to not estimable) and 10.4 months for crizotinib (95% CI: 7.7 to 14.6 months). The alectinib benefit was statistically significant across all predefined subgroups (age group, sex, race

category, smoking status, ECOG PS, CNS mets at baseline and prior brain radiation), except those based on very small numbers (active smokers and ECOG PS 2).

ALEX was not powered to detect a statistically significant difference in OS between groups. At the February 2017 data cut-off, median follow-up was 18.6 months in the alectinib group and 17.6 months in the crizotinib group; a similar number of patient in each group had died (35 in the alectinib group and 40 in the crizotinib group; HR 0.76; 95% CI: 0.48 to 1.20; p-value 0.24) and median OS had not been reached in either group. One-year survival rates were similar at 84.3% for alectinib (95% CI: 78.4 to 90.2%) and 82.5% for crizotinib (95% CI: 76.1 to 88.9%). [redacted].

The ORR benefit of alectinib compared with crizotinib was not statistically significant by INV (82.9% vs 75.5%, respectively) and IRC assessments (78.9% vs 72.2%); median DOR was immature but favoured alectinib (not estimable) over crizotinib (11.1 months; HR for alectinib versus crizotinib: 0.36, 95% CI: 0.24 to 0.53).

There was a significant CNS ORR benefit of alectinib compared with crizotinib in patients with measurable CNS lesions at baseline (81.0% vs 50.0, respectively), and in the combined subgroup of patients with measurable or nonmeasurable CNS lesions at baseline (59.4% vs 25.9%, respectively); CNS DOR was longer in the combined subgroup only (HR 0.23; 95% CI 0.10 to 0.53).

Within the HRQoL and patient reported outcomes (PROs), there was no statistically significant difference between groups in the time to confirmed clinically meaningful deterioration on a composite symptom endpoint on the EORTC LC13 or Global Health Status on the EORTC QLQ-C30. Both treatment arms demonstrated clinically meaningful improvement of at least 10 points for multiple lung cancer symptoms (cough, chest pain, pain in other parts, fatigue, and dyspnoea).

Statistically significant differences in PROs favouring alectinib were longer lasting improvement for various symptoms (cough, chest pain, other pain, fatigue), better tolerability for some AEs (diarrhoea, constipation, peripheral neuropathy, nausea/vomiting, appetite loss, and dysphagia), and longer lasting clinically meaningful improvement in HRQoL. In general, numerical or graphical data were not provided to substantiate the differences.

Most patients in both groups reported at least one AE of any cause or grade and the number of patients reporting at least one serious AE, Grade 3–5 AE, fatal AE, or AE leading to treatment discontinuation, were similar. AEs leading to dose reduction and dose interruption were somewhat less frequent in the alectinib group despite longer median treatment duration for alectinib than crizotinib (17.9 vs 10.7, respectively). The rate of treatment-related AEs was higher in the crizotinib group (89%) than the alectinib group (77%), but may be subject to attribution bias because safety assessments were conducted

by study physicians. The CS did not present information about whether AEs were more likely to occur at the beginning of treatment for either drug.

The safety profile of alectinib observed in ALEX is broadly in line with the Summary of Product Characteristics (SmPC). All-cause AEs that occurred more frequently at any Grade with alectinib than crizotinib were anaemia, myalgia, increased blood bilirubin, increased weight (noted as a new adverse drug reaction), musculoskeletal pain, and photosensitivity reaction. All-cause AEs that were more common at any Grade with crizotinib than alectinib were nausea, diarrhoea, vomiting, peripheral oedema, dysgeusia, dizziness, alopecia, elevated liver enzymes, eye disorders, and interstitial lung.

Grade 3–5 events were mostly infrequent in both groups, but some differences were noted in favour of crizotinib for anaemia and abnormal kidney function, and in favour of alectinib for elevated liver enzymes. SAEs of lung and acute kidney infections were recorded with alectinib, and instances of pneumonitis, pulmonary embolism and pyrexia were recorded in both groups.

1.3 Summary of cost effectiveness evidence submitted by the company

The modelled population was based on the ALEX population data, for both alectinib and crizotinib. While the company's original model was an appropriate reflection of the NICE final scope, it did not explicitly differentiate between systemic progression with CNS involvement (hereafter referred to as CNS progression), from systemic progression without CNS involvement (hereafter referred to as non-CNS progression), other than to account for the costs and benefits associated with the overall percentage of CNS progressions as a one-off estimation. In response to a clarification request from the ERG, the company used the ALEX data to explicitly model CNS progression in the model. The CNS data have some issues due to the study design of ALEX; thus the company's updated analysis of this population has some limitations.

The company developed a *de novo* model in Microsoft Excel® to assess the cost-effectiveness of alectinib in comparison with crizotinib in patients with ALK+ NSCLC. The model is a cohort-based partitioned survival model, which includes four health states: progression-free survival (PFS), non-CNS progressed disease (PD), CNS progressed disease (CNS PD), and death. Patients receive treatment with alectinib or crizotinib until disease progression or unacceptable toxicity. All progressed patients are assumed to receive subsequent treatments in the economic analysis. The partitioned survival (or area under the curve [AUC]) approach means that the proportion of patients modelled in each health state is based on parametric survival curves for each clinical outcome.

A time horizon of 30 years (lifetime) is adopted in the model and time is discretised into weekly cycles. A half-cycle correction was applied in the model. The analysis was carried out from an NHS and

Personal Social Services (PSS) perspective. Costs and health effects are discounted at an annual rate of 3.5%, in line with the NICE Reference Case.

In order to extrapolate OS, PFS and CNS PFS data into the model time horizon, the company fitted a variety of parametric curves to ALEX Kaplan-Meier (KM) data. The company reports fitting clinical data with exponential, Weibull, Gompertz, log-logistic, lognormal and generalised gamma models in accordance with guidance from NICE Technical Support Document (TSD) 14. The fit of each parametric model was compared with the observed KM data and statistical fit was assessed using the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC). The company also explored the option of including KM curves with different parametric tails used for extrapolation.

Once the best-fitting model was selected, survival curves for alectinib and crizotinib were derived through the use of survival functions and were then used to estimate the proportion of patients in each health state for every cycle of the economic model. The proportion of patients in each health state of the model were derived through the following equations:

- PFS = P(PFS);
- Non-CNS PD = P(CNS PFS) – P(PFS);
- CNS PD = P(OS) – P(CNS PFS);
- Death = 1 – P(OS).

Where P(PFS) is the proportion of progression-free patients taken from the PFS curve, P(CNS PFS) is the proportion of CNS-progression-free patients taken from the CNS PFS curve and P(OS) is proportion of patients alive taken from the OS curve.

Given the RCT design of ALEX, the company used the trial data to obtain OS, CNS PFS and PFS data for alectinib and crizotinib. The CS states that given that head-to-head evidence was available, it was not necessary to rely upon the proportional hazards (PH) assumption and thus treatment curves were fitted independently in the model.

In order to incorporate CNS progression in the updated model, the company has included two options for analysis in the economic model:

1. Add CNS RECIST outcomes to the PFS KM data (company's base case in the updated model);
2. Separate RECIST and CNS RECIST-assessed CNS outcomes and only use RECIST-assessed CNS outcomes, so that the original PFS KM data could be used in the model.

The company chose option 1, and used a Gamma distribution to extrapolate CNS data in the model.

The company selected the exponential distribution to fit PFS data in the model, given it produced the most clinically plausible survival outcomes. Given the poor fit of the exponential curve to the KM data, the company used the KM curves up to 18 months (where the company reports that censoring increases), and then replaced the tail of the KM curve by a fitted/extrapolated exponential curve. The company used the exponential distribution to model the OS curves for alectinib and crizotinib.

The company estimated utility values associated with the PFS and the non-CNS PD health states in the economic model, through the use of ALEX data. The company also incorporated CNS PD utility data in the analysis, however these were estimated from different literature sources. In the model, utility values were assumed to be constant over time, although age-related utility decrements published in Ara and Brazier 2010 were incorporated in the analysis. The company also accounted for the impact of adverse events and post-progression treatments on patients' quality of life in a scenario analysis.

The costs included in the economic model fall within include: acquisition and administration costs associated with the intervention and comparator and with subsequent treatments; disease management costs; costs of managing adverse events and the costs of managing CNS metastases.

According to the company's updated base case analysis, the incremental cost-effectiveness ratio (ICER) for alectinib compared with crizotinib is £72,544 per QALY gained. When the patient access scheme (PAS) for alectinib is applied to the economic results, the final ICER decreases to [redacted] per QALY gained. The probabilistic sensitivity analysis ICERs are £72,651 for the list price analysis and [redacted] when the PAS for alectinib is used.

1.4 ERG commentary on the robustness of evidence submitted by the company

1.4.1 Strengths

Clinical

Direct clinical effectiveness evidence for alectinib versus crizotinib, the only relevant comparator at the time evidence was submitted, was available multicentre phase III randomised trial that was largely low risk of biases. While there was scope for bias associated with the study's open label design, results for PFS and ORR were also available by blinded independent review committee (IRC). Options for analysing PFS and CNS progression were provided to assess the robustness of results to the criteria used for assessment (i.e. RECIST or RECIST+CNS RECIST).

The population, intervention, comparator, and outcomes in ALEX reflect the decision problem outlined in the final scope issued by NICE; the population generally reflects patients in England with ALK+

advanced NSCLC despite the small proportion recruited from UK centres (1%). Baseline characteristics were mostly well balanced between groups, and the treatments were given in line with their marketing authorisations.

Subgroup results were available, or provided at the clarification stage, to assess the impact of key effect moderators outlined by the ERG's clinical experts (ECOG PS, CNS metastases at baseline, and CNS progression during the study, and subsequent therapies).

Economic

The formulae within the economic model are generally sound and the economic model is well constructed. The economic model is based on RCT data, and therefore does not need to rely on indirect comparisons of treatment effectiveness data.

1.4.2 Weaknesses and areas of uncertainty

Clinical

ALEX has not demonstrated that the statistically significant benefits of alectinib over crizotinib for PFS and CNS PFS translate into a difference in OS. Six- and 12-month landmark analyses suggest [redacted], but the number of patients with CNS progression and the immaturity of OS in ALEX mean the between-group difference cannot be assessed reliably.

The company's preferred analyses of PFS and CNS PFS include events from the modified CNS RECIST, which may not reflect how PD would be assessed or managed in UK clinical practice. The company stated that the PFS and CNS PFS analyses based on IRC RECIST+IRC CNS RECIST are, "the most complete and robust analysis of the impact of CNS metastases", but accepted that events captured by CNS RECIST, "may be earlier than would be in clinical practice as CNS RECIST is not routinely used in the NHS" (company clarification response to question A10).

The ERG could not verify the methods of analysis for CNS PFS fully. PD not involving the CNS was not censored for CNS PFS and so the analysis includes patients experiencing secondary CNS progression. Variation in the extent of benefit could not be quantified because summary statistics were not available for all analyses. The company did not provide sufficient detail about events that could occur in a sequence, and how often this happened – e.g. CNS progression by CNS RECIST preceding PD with CNS involvement by RECIST – for the ERG to confirm that events had been counted or censored appropriately in each analysis to avoid double counting.

Randomised treatment could be continued beyond isolated asymptomatic CNS progression in ALEX at the investigator's discretion, which the company highlight is not indicated in the marketing

authorisation for alectinib. The ERG considers that this asymptomatic CNS progression may not be detected in clinical practice, but notes from clinical experts that treatment with ALK-TKIs often continues in UK practice until patients show progression in multiple sites, because subsequent treatment options are limited. Comparison of ALEX time to treatment discontinuation (TTD) and PFS curves suggest treatment beyond PD was uncommon in both groups, which may not reflect UK clinical practice. There was no consensus between the ERG's clinical experts regarding how often this occurs in UK clinical practice, under what circumstances (e.g. patient factors and availability of an alternative treatment), and the potential impact on OS.

Subsequent therapies were not recorded systematically in ALEX, which limits the conclusions that can be drawn about comparability of OS from ALEX to the UK treatment pathway. Subgroup analyses [redacted].

HRQoL was difficult to assess systematically because numerical or graphical summary data were not provided, and data have not yet been published from ALEX. The results submitted may be subject to reporting bias because, in general, only statistically significant benefits of alectinib were reported.

Economic

The ERG's main concerns are focused on the subsequent treatments received in ALEX and consequently, in the model; and in the CNS data and its respective modelling. It also remains unclear to the ERG if clinicians will use alectinib beyond disease progression in the UK, or what further treatments will be considered for patients who progress on alectinib. Even though the marketing authorisation for alectinib does not permit treatment beyond progression, treating patients with (the same) ALK inhibitor beyond disease progression seems established practice in the UK. This also relates to the availability of subsequent therapies, although if alectinib is recommended by NICE, there will be no available guidance to support alectinib as a second-line treatment, or to treat with other ALK inhibitors after alectinib.

The key issues with of the CS are summarised below, in more detail:

1. Treatment beyond progression/subsequent therapy regimen: Similar to alectinib, patients could receive treatment with crizotinib beyond progression at the investigator's discretion in ALEX, although TTD and PFS curves were very close, in both treatment arms. The ERG is concerned with the implications of the latter for crizotinib in clinical practice. If crizotinib was given for a shorter period of time in ALEX than it would in clinical practice, there might be a negative

bias in the observed outcomes from ALEX against crizotinib. Without knowing how alectinib would be prescribed in clinical practice, it is difficult to anticipate the extent, direction, or even existence of a bias in terms of relative effectiveness. However, if alectinib is given according to the marketing authorisation, then it could be argued that ALEX is a fair representation of time on treatment for alectinib but potentially underestimates the time on treatment with crizotinib, compared with clinical practice

Treatment beyond progression has been raised as an issue in the related appraisals of first-line crizotinib (TA406) and ceritinib (TA500). In both associated pivotal trials (PROFILE 1014 for crizotinib and ASCEND-4 for ceritinib, respectively), approximately 75% of patients continued treatment beyond progression with crizotinib and ceritinib. Clinical experts in TA406 reported that they would wait until the disease has progressed at multiple sites before changing treatment, because there are limited alternative options for these patients in the UK. The experts suggested that in the future, as more treatment options become available, people might switch to an alternative therapy more quickly. The Committee concluded that in current practice, treatment with ceritinib, and to a lesser extent crizotinib, continues beyond disease progression.

The ERG considers it important to emphasize that any analysis of subsequent therapies in ALEX and its impact on trial outcomes is very incomplete and so flawed, as subsequent therapies were not systematically captured in ALEX. Of all patients who discontinued study treatment, only 41% of these have data regarding subsequent treatment. The type, or in fact existence, of subsequent treatments for the remaining 59% of the ALEX population is unknown; however, it is likely that 100% of patients received subsequent therapies. This, of course, means that the data available for the 41% of patients in ALEX might (or might not) present a very skewed picture of the actual subsequent treatments regimens received in the trial population. Crossover to the alternative treatment was not part of the study protocol but patients could receive the alternative treatment as subsequent therapy if it was available, and clinically indicated at their local centre. At least nine patients in the alectinib group received crizotinib as a subsequent TKI, and 10 patients in the crizotinib received subsequent alectinib. As only 41% of the data are known, it is not possible to assess if more patients “crossed over”. Therefore, while the ERG agrees with matching the clinical effectiveness data to its respective costs and benefits (i.e. modelling the clinical trial subsequent therapies with its respective costs and QALYs), this analysis is not possible with the limited data available from ALEX, and any attempt will introduce a high degree of uncertainty to the analysis. Given that modelling the trial therapies relies heavily on assumptions, the ERG finds it more valuable to link these assumptions to the anticipated use of the drugs in UK clinical practice, rather than on the anticipated use of drugs in the ALEX trial.

The ERG finds the company's estimates of subsequent therapies in ALEX unlikely to be reflective of clinical practice in the UK as they are based on assumptions rather than on the actual trial data. Furthermore, the ERG disagrees with the company's assumptions made with regards to the proportion of patients receiving subsequent treatments in the UK, included in the company's scenario analysis for costs. The company base case analysis assumed that 29% of alectinib patients receive a subsequent TKI, while 72% of crizotinib patients move on to a subsequent TKI. The company's scenario analysis assumed a subsequent TKI treatment for 60% of alectinib patients, and for 90% of crizotinib patients.

With regards to crizotinib, the England audit data (Yip *et al*, 2017) available suggests that 18% of patients who received crizotinib, received a second-line TKI. Nonetheless, the audit results could be an underestimation, because the audit was not limited to first line crizotinib, and as the clinical experts advising the ERG have explained, clinical practice has been rapidly evolving in this setting, with more patients getting access to more treatment options. Nonetheless, this estimate differs greatly from the 72% assumed by the company in their base case analysis. Furthermore, clinical expert opinion provided to the ERG indicates that (although there is no clinical consensus on how to treat progressed patients after alectinib), it would appear plausible that alectinib patients would be fitter than crizotinib patients, and therefore more likely to tolerate subsequent treatment with a TKI. The clinical experts added that, the reason why a relatively low percentage of patients receive a TKI treatment after crizotinib in the UK is related to the development of CNS metastases, which leave the patients too ill to receive a further TKI, and so chemotherapy is the only viable option. As clinical experts anticipate that alectinib will have a protective effect on the CNS compared with crizotinib, it is likely that a higher percentage of alectinib patients receive a subsequent TKI. Again, this is contradictory to the data used by the company, where a considerably higher proportion of patients receives a TKI after crizotinib than after alectinib.

2. Progression with CNS involvement: The ERG has some reservations with regards to CNS data and its incorporation in the economic model. The details of the updated model including the CNS data analysis were described in a short document provided by the company after clarification; therefore, the ERG based its critique on the latter and on inspection of the economic model. The limited information available in the document shed some light on CNS data collection in the trial but is not entirely transparent and so the ERG is still unclear on a few aspects of the company's analysis. The ERG had to make assumptions with regards to the data, which are discussed throughout this report, however, it is important to caveat the ERG's assumptions. If the latter are not correct, then the company's model is flawed as the manipulation of the data in the economic analysis is likely to be incorrect. The ERG remains

unclear on the validity of the incorporation of clinical data into the economic model. It is vital that the company clarifies the following issues:

a) All RECIST-assessed primary CNS events were simultaneously systemic progressions;

b) How were secondary CNS events captured in the CNS PFS KM curves (i.e. systematically or not systematically)?

c) How can OS and CNS PFS curves (and whether these are KM or extrapolated curves) cross when primary non-CNS events were censored from the CNS PFS curves?

The ERG disagrees with the method used by the company to cap the CNS PFS data. Given that the company took the minimum risk each cycle to determine the proportion of patients in the CNS PFS curve, the risk of death (taken from the OS curve) was used from month 20 (approximately) to estimate the CNS PFS curve in the model for alectinib, and from month 50 (approximately) to estimate the CNS PFS curve for crizotinib. Nonetheless, the OS and CNS PFS curves for alectinib do not cross until 42 months. A similar situation is observed for the crizotinib model, where the OS and CNS PFS curves do not cross until 163 months. The ERG does not see a reason why the risk of events in the CNS PFS curve should not be higher than the risk of events in the OS curve. In fact, the CNS PFS curve includes death and progression events, and therefore the of events in the curve should, on average, be higher than the risk of events in the OS curve. Alternatively, the company should have capped the CNS PFS curve by the OS curve when these cross, as the OS curve cannot be below the CNS PFS curve (yielding a negative proportion of patients in the model). The ERG replaced the company's approach by capping the CNS PFS curve by the OS curve.

The ERG disagrees with the method used for the estimation of newly progressed patients in the model as it uses a fixed proportion of CNS events (captured by the RECIST+CNS RECIST measure) throughout the analysis. A more robust approach would have been to estimate the number of newly progressed patients every cycle, instead of relying on a fixed proportion.

3. Progression-free survival: The ERG generally agrees with the company's approach of selecting the exponential tail to fit the PFS KM data as it provided the most conservative scenario, from a clinical point of view, for alectinib. While for crizotinib, the exponential curve is the second most conservative (with the Weibull curve predicting the lower survival), the ERG considers that choosing different distributions to model PFS across treatment arms is not justified in this case. Furthermore, the combination of using the exponential curve for alectinib and crizotinib, is in itself a conservative approach, as the Weibull curve would have predicted a lower survival for crizotinib. Given that the exponential curve was the worst fitting distribution to the KM PFS

data, the ERG sees the benefit of using the KM PFS curves for the initial period of the model. However, the exponential tail of the curve was still derived from fitting an exponential distribution to the KM curve, which proved to be a bad fit. Hence, the portion of the curve used after 18 months is still based on a badly fitting curve. The ERG undertook some initial exploratory analysis to assess the impact of using more flexible modelling options (for example, using spline models). Nonetheless, because the shape of the KM curves exhibits a plateau from about 15 months for alectinib, where the number of patients at risk in the KM curve is still generally robust (83 patients; 55% for alectinib), all exploratory analysis conducted by the ERG produced curves with very long (and clinically implausible) tails.

Another consequence of using an exponential curve is the fact that at 18 months (where the exponential tails are used in the model), the hazard ratio between the alectinib and crizotinib PFS curves becomes proportional. This is because the underlying hazard in each curve will remain constant throughout the rest of the model. There is no clinical justification for this and, in fact, the company's assessment of PH indicated that the PH assumption is unlikely to hold for PFS data.

Finally, the ERG considers that the choice of the cut-off point (18 months) for the KM data used by the company is quite arbitrary. This should have been better substantiated, and some sensitivity analysis should have been undertaken by the company to reflect the impact of changing this parameter in the analysis. At 18 months, there are 22% and 45% of patients at risk in the crizotinib and alectinib curves, respectively. The company reports that censoring increases after this point. However, the same could be argued for other cut-off points, and more importantly, the alectinib and crizotinib curves do not necessarily have the same "appropriate" cut-off points.

4. Overall survival: The ERG's clinical experts suggested most people with ALK+ NSCLC are expected to live between 1 to 3 years from initiation of treatment with crizotinib. The experts' experience is substantiated by a recent audit of crizotinib for ALK+ advanced NSCLC at 20 UK centres since it was added to the Cancer Drugs Fund in 2012. Median OS for the 99 patients in the audit was 13.5 months, which compares to approximately 80% of crizotinib patients being alive at 12 months in ALEX and in PROFILE 1014. The more mature PROFILE 1014 data shows a 4-year survival of 56.6%, which again is a very different estimate to the clinical experts' predictions.

   The company considered that a naïve comparison of the ALEX and the PROFILE 1014 studies is inappropriate as patients in PROFILE 1014 are considered to be healthier and therefore, perform better. However, the ERG finds these populations comparable, to some degree.

Comparing the crizotinib groups in ALEX and PROFILE 1014, the ERG notes the difference in the proportion of patients with brain metastases at baseline, and prior treatment for brain metastases, which may support the company's assertion, but considers other characteristics (age, ECOG performance status, stage of disease and smoking history) comparable between the two trials. The analysis performed in TA406 to adjust PROFILE 1014 data to real-life data, resulted in a median OS for crizotinib of 21.7 months and a mean adjusted OS of 29 months. This compares to the approximately 68% of patients still alive in the unadjusted OS curve for PROFILE 1014 at 22 months (note that median OS was not reached in the unadjusted OS curve). Although it is not possible to draw final conclusions from this naïve comparison, it could be argued that if ALEX data were to be adjusted to real-life data, the survival predictions for crizotinib would be more conservative.

The ERG considers that ALEX does not provide robust evidence to substantiate a long-term OS benefit of alectinib compared with crizotinib. Furthermore, comparative OS data from ALEX may not be a reasonable reflection of what would be seen in UK clinical practice because treatment beyond PD may differ for alectinib and crizotinib in practice, and subsequent therapies available to patients in ALEX do not reflect the UK pathway for ALK+ advanced NSCLC.

The ERG disagrees with the company's approach of using an exponential model to estimate OS in the model. The exponential distribution was the second-worst fitting distribution to the KM OS data for crizotinib. Additionally, using the exponential distribution to fit both treatment arms implicitly assumes PHs, which the company demonstrated is not a valid assumption for OS data. Therefore, in the interest of consistency with the approach taken for the PFS data, the ERG requested that the company used the KM OS curve for the initial period of the model, where the fit of the exponential curve to the KM data was not very good. The ERG emphasises that the same caveats noted for the PFS approach apply to using the KM+exponential curves in the OS data, but recognises that this approach yields the most conservative survival outcomes.

5. Quality of life analysis: The ERG has two main concerns regarding the company's modelling approach including the utility value applied to patients with CNS metastases, and the quality of life of patients on subsequent therapies. The HSUV associated with CNS progression was taken from Roughly *et al.* 2014, which is a conference abstract, providing a limited description of methods and results. Consequently, the ERG could not investigate in detail the data used, and it was not possible to compare patient demographics with the population in ALEX, as advised by the NICE Technical Support Uunit (DSU document 12). Given the company's conclusion that the PD state-related utilities identified in the literature are generally lower than the PD state utilities derived from the ALEX trial (which the company attributed to the availability of TKIs

as subsequent therapies in the trial), it is not possible to assess if the utility values related with general disease progression (without CNS metastases) are comparable in ALEX, and in the paper. It is possible the utility values for overall progressed patients in Roughley *et al.* 2014 are lower than in ALEX, which would mean that using an unadjusted CNS utility value from Roughley *et al.* 2014 potentially overestimates the impact of CNS metastases on patients' quality of life. This would, in its turn, lead to an overestimation of the benefit of alectinib, considering its advantageous profile in preventing CNS progression.

The ERG considers that the impact of subsequent therapies on patients' quality of life is a key model driver. As the ERG does not consider the company's estimates of subsequent therapies to be reflective of clinical practice, the ERG ran three scenario analyses to reflect the uncertainty around the changes in clinical practice if alectinib is recommended. These scenarios include the possibility of alectinib patients being more, less, and equally likely than crizotinib patients to receive subsequent treatment with a TKI. All patients not receiving a TKI as subsequent treatment were assumed to receive a non-TKI (i.e. 100% of patients receive subsequent treatment in the ERG's analysis). As clinical experts could not find a consensus on the likely proportion of patients to allocate to these scenarios, the ERG used the ALEX trial data and the England audit data as a form of validation. Given the ERG's concerns that the proportions used by the company (i.e. approximately 70% of crizotinib patients receive a subsequent TKI and 30% of alectinib patients receive a subsequent TKI) are not reflective of clinical practice, the ERG had to make some assumptions with regards to the missing data on the 59% of patients and their subsequent treatments in ALEX. Given the England audit data suggests 18% of patients receive a second-line TKI after crizotinib, the ERG assumed that the 31.4% (Table A) known to receive a TKI after crizotinib in ALEX could be a reasonable approximation to the UK clinical practice. In order to estimate the proportion of patients receiving a TKI after alectinib, the ERG assumed the following:

a) 64% of patients receive a TKI after alectinib. This estimate assumes that all the 97 alectinib patients with missing data on subsequent treatments in ALEX received a TKI. To these 97 patients add the 13 patients for whom there are data, and are known to have received a subsequent TKI (Table A);

b) 31.4% of patients get a TKI after alectinib;

c) Taking the minimum known value from ALEX, which is based on the 13 alectinib patients receiving a second-line TKI (Table A). This amounts to 19.1% (13 divided by 152) of patients receiving a post-alectinib TKI.

These analyses are caveated by the fact that CNS impact on patients' quality of life has not been included, and by the fact that the sources for utility values and treatment duration related with subsequent therapies are taken from various literature sources.

Table A. Subsequent therapies captured in ALEX for 41%* of patients who have permanently discontinued study treatment (adapted from clarification response, Table 3)

	Alectinib		Crizotinib	
Treatment	**2nd line (n = 68)**	**3rd line + (n = 68)**	**2nd line (n = 105)**	**3rd line + (n = 105)**
Any subsequent anti-cancer therapy	31 (45.6%)	9 (13.2%)	40 (38.1%)	4 (3.8%)
Any TKI	13 (19.1%)	5 (7.4%)	33 (31.4%)	3 (2.9%)
Ceritinib	2 (2.9%)	2 (2.9%)	13 (12.4%)	1 (1.0%)
Alectinib	0 (0.0%)	0 (0.0%)	8 (7.6%)	2 (1.9%)
Crizotinib	6 (8.8%)	3 (4.4%)	2 (1.9%)	0 (0.0%)
Other (lorlatinib, brigatinib, gefitinib, entrectinib, erolotinib)	5 (7.4%)	1 (1.5%)	10 (9.5%)	0 (0.0%)
Platinum compound (carboplatin, cisplatin)	16 (23.5%)	3 (4.4%)	6 (5.7%)	0 (0.0%)
Antimetabolite (pemetrexed, gemicitabine)	14 (20.6%)	3 (4.4%)	6 (5.7%)	0 (0.0%)
Taxane (paclitaxel, docetaxel)	3 (4.4%)	0 (0.0%)	0 (0.0%)	1 (1.0%)
Immunostimulant (nivolumab)	0 (0.0%)	2 (2.9%)	0 (0.0%)	0 (0.0%)
Angiogenesis inhibitor (bevacizumab)	2 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other (cyclophosphamide, antineoplastic agent NOS, anti PD-L1, doxorubicin, vincristine)	3 (4.4%)	1 (1.5%)	1 (1%)	0

Abbreviations: NOS, not otherwise specified; PD-L1, programmed death-ligand; TKI, tyrosine kinase inhibitor
*Subsequent therapies are not known for the remaining 59% of patients who have permanently discontinued study treatment.

6. Cost analysis: The ERG considers that the cost estimations in the model are generally sound, but disagrees with the estimation of the cost of crizotinib in the model. A full pack of crizotinib provides patients with 30 days of treatments, whereas a pack of alectinib provides 28 days of treatment. As the full-pack cost and administration cost are applied up-front, every 4 cycles (i.e. every 4 weeks or 28 days), two days of crizotinib treatment are wasted in each 4-weekly administration cycle. Therefore, to address this issue, the ERG amended the cost of crizotinib in the model so one full-pack is purchased every 30 days as opposed to every 28 days.

The company carried out a scenario analysis assuming a distribution of subsequent therapies in line with current UK practice. The ERG does not consider the estimates used to be reflective of clinical practice in the UK as 90% of crizotinib patients are assumed to receive a subsequent TKI (compared with the 18% reported in the England audit). Therefore, the ERG ran the three scenarios analyses described in the QALY discussion, to explore the uncertainty around subsequent treatments' costs. To further reflect UK clinical practice, the ERG assumed that the treatments available for subsequent treatment lines consisted on crizotinib and ceritinib (post-alectinib) and ceritinib (post-crizotinib). In order to estimate the distribution of patients allocated to crizotinib or ceritinib post alectinib, the ERG used the data available from ALEX, which shows that 2.9% of alectinib patients received ceritinib and 8.8% of patients received

crizotinib. The ERG reweighted these values, to account for the entire subgroup of patients receiving a TKI post-alectinib. The final proportions used in the ERG's analysis are 25% for ceritinib and 75% for crizotinib.

Clinical expert opinion sought by the ERG revealed that there seems to be a consensus on the use of stereotactic radiosurgery (SRS), to treat CNS metastases whenever patients' clinical condition allows it. The issue remains, that only few patients are eligible for SRS as candidates cannot have more than a maximum of two metastatic sites. Therefore, how ineligible patients are managed in UK clinical practice remains unclear.

Although it seems that there is not a consensus among the clinical community, clinical expert opinion provided to the ERG explained that clinical practice seems to be moving away from WBRT and increasingly using steroids, as supported in the Mulvenna *et al.* 2016 paper. While the company suggests that 23% of patients receive SRS and 77% of patients receive WBRT, the ERG's clinical expert agreed on the proportion of patients receiving SRS but considered that the remaining 77% would receive steroids, as opposed to WBRT, given its lack of proven advantage over steroids and its side effects on patients.

1.5 Summary of exploratory and sensitivity analyses undertaken by the ERG

Economic

The exploratory analyses undertaken by the ERG uses RECIST-based outcomes for PFS and CNS PFS. The analyses consist on the following:

1. The ERG capped the CNS PFS curve by the OS curve. The ERG disagrees with the method used by the company to cap the CNS PFS curve by taking the minimum risk each model cycle for OS, CNS PFS and background survival, to determine the proportion of patients in the CNS PFS curve.

2. The ERG estimates the number of newly progressed patients every cycle, instead of relying on a fixed proportion. Therefore, the ERG replaced the company's method (Equation 2) with the following formula: $(CNS\ PD_{t+1} - CNS\ PD_t) + (1 - OS_{t+1}/OS_t) * (CNS\ PD_t)$. The ERG disagrees with the method used for the estimation of newly progressed patients in the model as it uses a fixed proportion of CNS events (captured by the CNS RECIST+RECIST measure) throughout the analysis.

3. The ERG replaced the exponential curves used to estimate OS for alectinib and crizotinib by the KM+exponential tail curves;

4. The ERG's clinical experts advised that the frequency of oncologist visits should be every 4 weeks as opposed to every 5 to 6 weeks. The ERG replaced this in the economic model.

5. The ERG ran three scenario analyses to reflect the uncertainty around the changes in clinical practice if alectinib is recommended. Furthermore, the ERG removed the third line of treatment from the company's analysis as this line of treatment was not incorporated as an option for the cost analysis in the company's model (only second line treatment was included). These scenarios consist on the following:

    a) Assuming 64% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib;

    b) Assuming patients on alectinib are equally likely to receive a subsequent TKI as crizotinib patients (31.4% of patients assumed for both);

    c) Assuming 19.1% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib;

6. The ERG ran the three scenarios analyses described in 5, to estimate the costs of each alternative scenario. To further reflect UK clinical practice, the ERG assumed that the TKI treatments available for subsequent treatment lines consisted on crizotinib (75% of total TKI treatments) and ceritinib (25% of total TKI treatments) (post-alectinib) and ceritinib (post-crizotinib);

7. The ERG conducted exploratory analysis to reflect a scenario where 77% of patients receive steroids rather than WBRT to manage their CNS metastases;

8. Given that CNS-related utility value is one of the key drivers of the economic results, the ERG ran a scenario where the utility associated with CNS progression was varied by a range of values. The base case utility value (0.52) was increased by 1%, 2%, 3%, 4% and 5%.

Results from the ERG analysis are reported in Table B. From a methodological point of view, changing the OS modelling approach from an exponential to a KM+exponential curve has a considerable impact on the company's corrected ICER (£75,079 to £80,146).

The other key model drivers are related to the clinical assumptions incorporated in the economic analysis. The two main drivers are the assumptions related with subsequent therapies in the model, namely the proportion of patients receiving a TKI and a non-TKI after treatment with alectinib or crizotinib. This has implications for the incremental costs, and to a greater extent, for QALY gain related with alectinib. The other key driver of the analysis is the modelling of CNS metastases, in terms of its impact on patients' quality of life (Figure A) and treatment costs.

The ERG reports three exploratory ICERs, reflecting three different scenarios in terms of subsequent therapies received after alectinib (Table C and Table D). The ERG caveats the analyses presented due to the high degree of uncertainty embedded in the ALEX's data regarding patients' subsequent therapies. Related to this, is the estimated survival from ALEX, which as evidence suggests, can be highly dependent on the availability of subsequent treatment with ALK-TKIs.

The assumptions incorporated in the ICERs presented in Table C and Table D include the scenario analyses numbered and described in Table B. The exception is the company's scenario analysis, which assumes that only 23% of patients receive SRS while 77% of patients receive WBRT.

The ERG produced three different ICERs, ranging from £129,195 to £140,467, per QALY gained. The lowest ICER corresponds to the scenario where a lower proportion of alectinib patients (19%) compared with crizotinib patients (31%) receive subsequent TKIs. Conversely, the highest ICER corresponds to the scenario where more alectinib patients (64%) receive subsequent TKIs, compared to crizotinib patients. When the same proportion of patients is assumed to receive subsequent TKIs, ICER amounts to £132,510, per QALY gained. The three ERG's exploratory ICERs amount to [redacted], [redacted] and [redacted] when the alectinib PAS is applied (Table D).

Table B. Results of the ERG's scenario analysis

Analysis from list	Results per patient	Alectinib (1)	Crizotinib (2)	Incremental value (1-2)
0	**Company's corrected base using RECIST outcomes**			
	Total costs (£)	£225,992	£149,354	£76,638
	QALYs	3.82	2.80	1.02
	ICER		**£75,079**	
1	**Capping the CNS PFS curve by the OS curve**			
	Total costs (£)	£225,805	£149,110	£76,695
	QALYs	3.86	2.84	1.02
	ICER		**£75,219**	
2	**Using different method to estimate newly progressed patients**			
	Total costs (£)	£216,959	£140,949	£76,010
	QALYs	3.82	2.80	1.02
	ICER		**£74,463**	
3	**Replacing the exponential curves used to estimate OS for alectinib and crizotinib by the KM+exponential tail curves**			
	Total costs (£)	£225,841	£149,912	£75,929
	QALYs	3.79	2.84	0.95
	ICER		**£80,146**	
4	**Changing the frequency of oncologist visits to every 4 weeks as opposed to every 5 to 6 weeks**			

	Total costs (£)	£227,309	£150,048	£77,261
	QALYs	3.82	2.80	1.02
	ICER		**£75,689**	
5 a)	**Assuming 64% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib**			
	Total costs (£)	£225,992	£149,354	£76,638
	QALYs	3.83	3.01	0.82
	ICER		**£93,856**	
5 b)	**Assuming 31.4% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib**			
	Total costs (£)	£225,992	£149,354	£76,638
	QALYs	3.78	3.01	0.76
	ICER		**£100,220**	
5 c)	**Assuming 19.1% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib**			
	Total costs (£)	£225,992	£149,354	£76,638
	QALYs	3.76	3.01	0.75
	ICER		**£102,851**	
6 a)	**Assuming 64% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib**			
	Total costs (£)	£241,685	£139,839	£101,846
	QALYs	3.82	2.80	1.02
	ICER		**£99,774**	
6 b)	**Assuming 31.4% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib**			
	Total costs (£)	£228,927	£139,839	£89,088
	QALYs	3.82	2.80	1.02
	ICER		**£87,275**	
6 c)	**Assuming 19.1% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib**			
	Total costs (£)	£224,113	£139,839	£84,274
	QALYs	3.82	2.80	1.02
	ICER		**£82,560**	
7	**Assuming patients receive steroids rather than WBRT to manage their CNS metastases**			
	Total costs (£)	£218,134	£137,108	£81,026
	QALYs	3.82	2.80	1.02
	ICER		**£79,378**	

Abbreviations used in the table: CSR, clinical study report; ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; QALY, quality-adjusted life year; RDI, relative dose intensity; TRAE, treatment-related adverse event.

Figure A. Scenario analysis 8

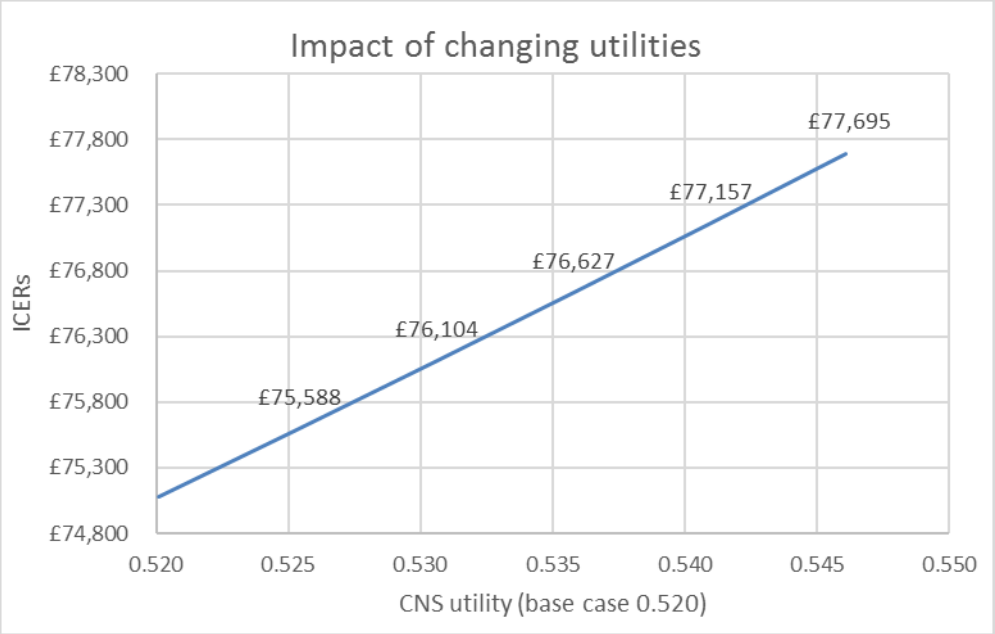


Table C. ERG's alternative base case ICERs

	Results per patient	Alectinib (1)	Crizotinib (2)	Incremental value (1-2)
0	**Company's corrected base using RECIST outcomes**			
	Total costs (£)	£225,992	£149,354	£76,638
	QALYs	3.82	2.80	1.02
	ICER			**£75,079**
1	**Capping the CNS PFS curve by the OS curve**			
	Total costs (£)	£225,805	£149,110	£76,695
	QALYs	3.86	2.84	1.02
	ICER (compared with base case)			£75,219
	ICER with all changes incorporated			**£75,219**
2	**Using different method to estimate newly progressed patients**			
	Total costs (£)	£216,959	£140,949	£76,010
	QALYs	3.82	2.80	1.02
	ICER (compared with base case)			£74,463
	ICER with all changes incorporated			**£74,858**
3	**Replacing the exponential curves used to estimate OS for alectinib and crizotinib by the KM+exponential tail curves**			
	Total costs (£)	£225,841	£149,912	£75,929
	QALYs	3.79	2.84	0.95
	ICER (compared with base case)			£80,146
	ICER with all changes incorporated			**£77,948**
4	**Changing the frequency of oncologist visits to every 4 weeks as opposed to every 5 to 6 weeks**			
	Total costs (£)	£227,309	£150,048	£77,261

	QALYs	3.82	2.80	1.02
	ICER (compared with base case)			£75,689
	ICER with all changes incorporated			**£78,593**
Company's SA	**Company's scenario analysis assuming that 23% of patients receive SRS and 77% of patients receive WBRT**			
	Total costs (£)	£219,830	£139,751	£80,079
	QALYs	3.82	2.80	1.02
	ICER (compared with base case)			£78,450
	ICER with all changes incorporated			**£82,839**
5a+6a	**Assuming 64% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib**			
	Total costs (£)	£241,685	£139,839	£101,846
	QALYs	3.83	3.01	0.82
	ICER (compared with base case)			£124,727
	ICER with all changes incorporated			**£140,467**
5b+6b	**Assuming 31.4% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib**			
	Total costs (£)	£228,927	£139,839	£89,088
	QALYs	3.78	3.01	0.76
	ICER (compared with base case)			£116,501
	ICER with all changes incorporated			**£132,510**
5c+6c	**Assuming 19.1% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib**			
	Total costs (£)	£224,113	£139,839	£84,274
	QALYs	3.76	3.01	0.75
	ICER (compared with base case)			£113,099
	ICER with all changes incorporated			**£129,195**
	Abbreviation used in table: ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; QALYs, quality-adjusted life years; RDI, relative dose intensity.			

Table D. ERG's alternative base case ICERs with alectinib PAS

	Results per patient	**Alectinib (1)**	**Crizotinib (2)**	**Incremental value (1-2)**
0	**Company's corrected base using RECIST outcomes**			
	Total costs (£)	[redacted]	£145,064	[redacted]
	QALYs	3.82	2.80	1.02
	ICER			[redacted]
1	**Capping the CNS PFS curve by the OS curve**			
	Total costs (£)	[redacted]	£144,821	[redacted]
	QALYs	3.86	2.84	1.02
	ICER (compared with base case)			[redacted]
	ICER with all changes incorporated			[redacted]
2	**Using different method to estimate newly progressed patients**			

	Total costs (£)	[redacted]	£136,660	[redacted]
	QALYs	3.82	2.80	1.02
	ICER (compared with base case)			[redacted]
	ICER with all changes incorporated			[redacted]
3	**Replacing the exponential curves used to estimate OS for alectinib and crizotinib by the KM+exponential tail curves**			
	Total costs (£)	[redacted]	£145,618	[redacted]
	QALYs	3.79	2.84	0.95
	ICER (compared with base case)			[redacted]
	ICER with all changes incorporated			[redacted]
4	**Changing the frequency of oncologist visits to every 4 weeks as opposed to every 5 to 6 weeks**			
	Total costs (£)	[redacted]	£145,758	[redacted]
	QALYs	3.82	2.80	1.02
	ICER (compared with base case)			[redacted]
	ICER with all changes incorporated			[redacted]
Company's SA	**Company's scenario analysis assuming that 23% of patients receive SRS and 77% of patients receive WBRT**			
	Total costs (£)	[redacted]	£135,461	[redacted]
	QALYs	3.82	2.80	1.02
	ICER (compared with base case)			[redacted]
	ICER with all changes incorporated			[redacted]
5a+6a	**Assuming 64% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib**			
	Total costs (£)	[redacted]	£139,839	[redacted]
	QALYs	3.83	3.01	0.82
	ICER (compared with base case)			[redacted]
	ICER with all changes incorporated			[redacted]
5b+6b	**Assuming 31.4% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib**			
	Total costs (£)	[redacted]	£139,839	[redacted]
	QALYs	3.78	3.01	0.76
	ICER (compared with base case)			[redacted]
	ICER with all changes incorporated			[redacted]
5c+6c	**Assuming 19.1% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib**			
	Total costs (£)	[redacted]	£139,839	[redacted]
	QALYs	3.76	3.01	0.75
	ICER (compared with base case)			[redacted]
	ICER with all changes incorporated			[redacted]
	Abbreviation used in table: ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; QALYs, quality-adjusted life years; RDI, relative dose intensity.			

2 BACKGROUND

2.1 Critique of company's description of underlying health problems

The ERG considers Section B.1.3 of the company submission (CS) to provide a reasonable overview of the key aspects of anaplastic lymphoma kinase-positive (ALK+) advanced non-small-cell lung cancer (NSCLC), and to be relevant to the NICE final scope.[1] The CS provides an overview of ALK+ NSCLC in relation to lung cancer including common symptoms, prognosis, and the effects of lung cancer on patients' and their carers' health-related quality of life (HRQoL). The ERG's clinical experts agree with the background information on lung cancer and ALK+ NSCLC provided by the company, but the ERG considered it necessary to add some detail on the aetiology of lung cancer and ALK+ NSCLC.

The ERG notes that 89% of lung cancer cases a year in the UK are linked to major lifestyle (e.g. tobacco smoking) and other risk factors such as family history and genetic risk factors.[2] Lung cancer comprises two main histological types: small cell lung cancer (SCLC) which accounts for 10–15% of lung cancers and NSCLC which accounts for the remaining 85–90% of lung cancers.[3, 4] Within these types, tumours can be further classified into histological subtypes, including adenocarcinoma and squamous cell carcinoma.[4] The ERG's clinical experts outlined that, in addition to diagnosing histology, tumour tissue is now routinely tested for a range of known genetic mutations to tailor treatment options. Across types and subtypes, NSCLC is commonly advanced at the point of diagnosis (~90%).[4]

Approximately five percent of NSCLC tumours test positive for mutation or 'rearrangement' in the ALK gene.[5] The ALK rearrangement leads to coding of abnormal enzymes called tyrosine kinases that support cancer growth. The ERG's clinical experts outlined that the genetic driver of ALK+ NSCLC means patients with the variant are generally younger, less often male, and the cancer is less commonly associated with smoking history than the wider NSCLC population. As a result, ALK+ NSCLC tends not to be picked up in screening programs of populations at high risk for lung cancer, and the impact of the disease and treatment differs from the wider lung cancer population, e.g. due to employment and family commitments. Historically, ALK+ NSCLC was associated with poor prognosis,[6] but this has greatly improved since the emergence of tyrosine kinase inhibitors (TKIs), such as alectinib, crizotinib and ceritinib,[7] that target and inhibit the faulty ALK-driven pathways by which the tumours grow and spread.

2.2 Critique of company's overview of current service provision

The ERG's clinical experts confirmed that crizotinib is now the preferred first-line (1L) treatment for adults confirmed as having ALK+ advanced or metastatic NSCLC in England, based on the NICE STA TA406 published in 2016.[8] The ERG notes that the updated NICE clinical guideline for the diagnosis and management of lung cancer (CG121)[9] was published in 2011, which preceded the NICE

recommendation of the ALK tyrosine kinase inhibitors (ALK-TKIs) crizotinib and ceritinib for ALK-positive NSCLC. CG121 recommends chemotherapy for patients with stage III or IV NSCLC and good performance status (WHO 0, 1 or a Karnofsky score of 80–100) to improve survival, disease control and quality of life.[9] The ERG's clinical experts agreed that the development of ALK-TKIs such as crizotinib for patients with ALK rearrangement means these treatments have largely replaced the older chemotherapy regimens recommended at 1L for NSCLC in CG121.[9] However, the older chemotherapy regimens remain the recommended treatment for patients without ALK+ rearrangement (Figure 1).

The ERG notes that ceritinib was approved by NICE for the 1L treatment of ALK+ advanced NSCLC during the preparation of the ERG's report for this STA (TA500[10]). The Final Appraisal Determination (FAD) for TA500 states that, "The clinical experts considered that second-generation ALK inhibitors [which includes ceritinib and alectinib] are an innovative class of drugs. They have a broader spectrum of activity than first-generation ALK inhibitors [i.e. crizotinib] and may replace crizotinib as the standard of care internationally".[10] As such, the ERG considers crizotinib standard first-line therapy for the purposes of the current STA, but highlights that clinical practice may change once ceritinib becomes available for the untreated population.

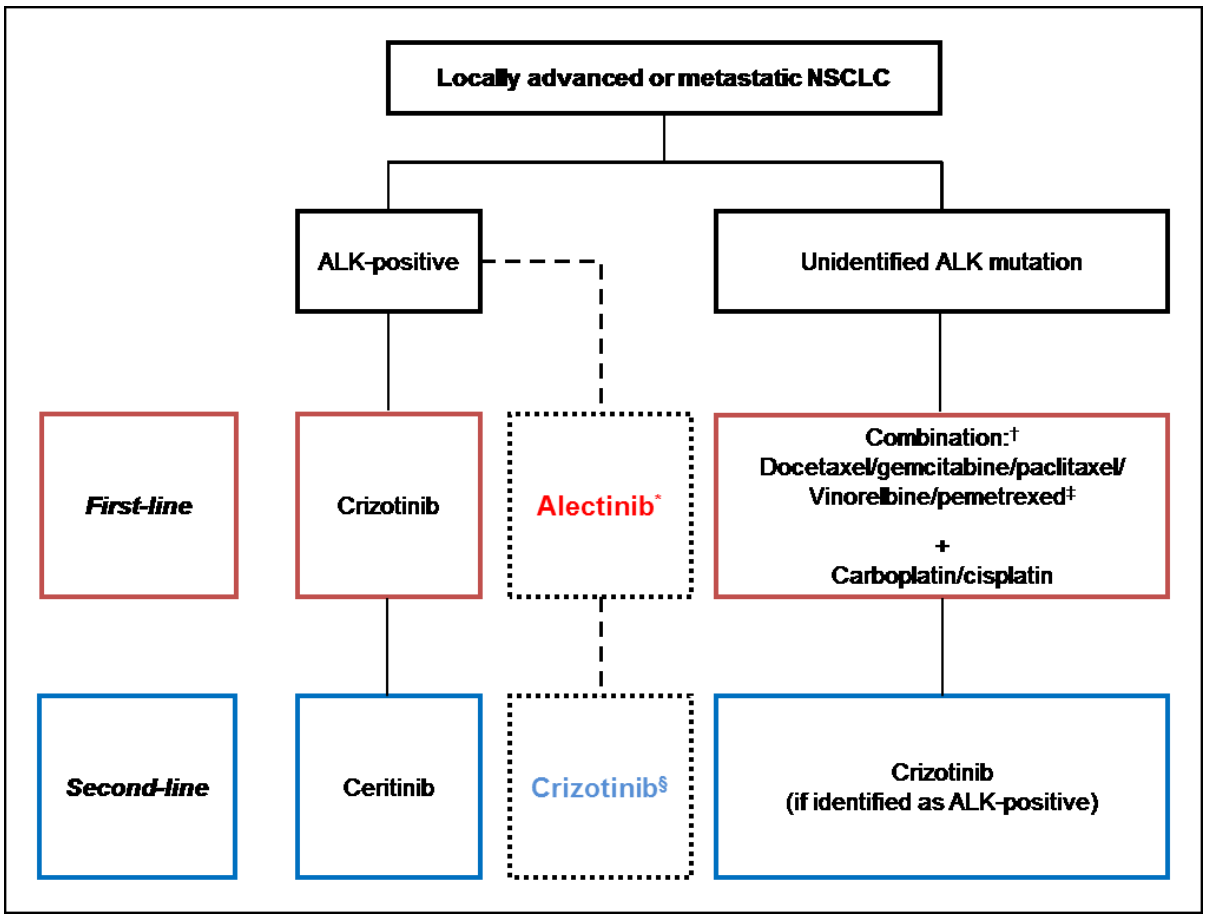
At second line (2L), the ERG's clinical experts agreed that ceritinib is the currently preferred treatment following first-line crizotinib, which was recommended by NICE TA395 in 2016.[11] However, the ERG's clinical experts outlined that single-agent or combination third generation and platinum chemotherapies are still used for some patients at 2L or later, which is not reflected in Figure 1. Crizotinib is also recommended by NICE at 2L for previously treated ALK-positive advanced NSCLC in adults (TA422)[12] and the ERG's clinical experts agreed that it may be used at 2L for patients who received chemotherapy before confirmation of positive ALK status (Figure 1).[10]

The company propose alectinib for advanced or metastatic ALK-positive NSCLC as an alternative to crizotinib at 1L (Figure 1). There was uncertainty within the ERG's clinical experts and experts consulted for TA500 (ceritinib),[10] about whether crizotinib, a first-generation ALK-TKI, would be used as a 2L treatment after a second-generation ALK-TKI such as alectinib or ceritinib, as depicted in Figure 1. Given the acknowledged differences between first- and second-generation ALK-TKIs, some clinical experts considered it counterintuitive that crizotinib would be given after failure on a superior class of therapy. However, the recommendation associated with ceritinib, the only second-generation ALK-TKI available for use at 2L (TA395) specifies prior crizotinib use, so it is not a NICE-recommended option after 1L alectinib.

The ERG considers the treatment pathway depicted by the company in Figure 1 is in line with the most recent NICE Pathway guidance for treating NSCLC, and the description of standard practice in the UK outlined by the ERG's clinical experts. However, ceritinib will soon be available for 1L use and there

is uncertainty how this will affect the treatment pathway.[13] The proposed positioning of alectinib is in line with how it would be likely to be used in England, but there is similar uncertainty within clinical experts about whether crizotinib will be the preferred treatment after alectinib

Figure 1. Treatment pathway for advanced or metastatic NSCLC and the company's proposed positioning of alectinib (Reproduced from CS pg. 16, Figure 1)



*Dotted box indicates proposed position of alectinib based on anticipated indication, i.e. first-line ALK-positive patients and patients identified as ALK-positive during first-line chemotherapy †If patients cannot tolerate a platinum combination, offer single-agent chemotherapy with a third-generation drug; ‡Pemetrexed in combination with cisplatin is recommended as an option for the first-line treatment of patients with locally advanced or metastatic NSCLC only if the histology of the tumour has been confirmed as adenocarcinoma or large-cell carcinoma; §Dotted box indicates potential treatment pathway subsequent to alectinib.

Cost of alectinib

Table 1 provides an overview of the key features and drug acquisition costs associated with alectinib use at 1L for patients with ALK+ NSCLC. The ERG notes that crizotinib and alectinib are both given orally and are likely to be associated with similar administration costs. Alectinib and crizotinib need to be preceded by a diagnostic test to confirm a patient's ALK status. Full details on the anticipated resource use and costs associated with alectinib are discussed in Section 5.

Table 1. Overview of key features and drug costs associated with alectinib (adapted from the CS Table 2, pgs 10–11)

Feature	Description
UK approved name and brand name	UK approved name: alectinib Brand name: Alecensa®
Mechanism of action	Alectinib is a small molecule, CNS active, highly selective, and potent oral next generation inhibitor of ALK and RET tyrosine kinase receptors. While binding to the tyrosine kinase domain of ALK, alectinib prevents the binding of ATP and thus autophosphorylation of the ALK receptor, restoring apoptosis and inhibiting tumour cell growth and proliferation. In nonclinical studies, inhibition of ALK tyrosine kinase activity led to blockage of downstream signalling pathways including STAT3 and phosphoinositide 3-kinase/AKT and therefore induction of apoptosis.[14] Alectinib induced tumour regression in nonclinical mouse xenograft models, including anti-tumour activity in the brain, and prolonged survival in intracranial tumour animal models.[15]
Marketing authorisation/CE mark status	The EC granted a marketing authorisation for alectinib as a monotherapy, *"for the treatment of adult patients with ALK-positive advanced NSCLC previously treated with crizotinib."* on 16/02/2017. A further full submission has been made to the EMA for the indication considered in this appraisal, with a positive CHMP opinion adopted on 12/10/2017. Marketing authorisation granted in December 2017.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Current marketing authorisation: "*Alecensa as monotherapy is indicated for the treatment of adult patients with ALK-positive advanced NSCLC previously treated with crizotinib.*" Anticipated marketing authorisation relevant to this appraisal: "*Alectinib as a monotherapy is indicated for the first line treatment of adult patients with ALK-positive advanced NSCLC.*"
Method of administration and dosage	Oral, 600 mg BID (four 150 mg capsules)
Additional tests or investigations	None. Testing for ALK rearrangement and hence sensitivity to ALK inhibitors is a standard part of the diagnostic work up of lung-cancer specimens.
List price and average cost of a course of treatment	List price per pack: £5,032.00 Based on the economic model, the median treatment duration is 22.5 months, mean is 30.8 months.
Patient access scheme (if applicable)	A simple discount has been submitted to the Department of Health, but has not yet been approved.

Abbreviations: ALK, anaplastic lymphoma kinase; ATP, adenosine triphosphate; BID, twice-daily; CHMP, Committee for Medicinal Products for Human Use; CNS, central nervous system; EMA, European Medicines agency; mg, milligram; NSCLC, non-small cell lung cancer; STAT3, signal transducer and activator of transcription 3,

Number of eligible patients

The company presented their estimate of the number of patients eligible for 1L treatment with alectinib over the next 5 years (2018–2022) in their budget impact analysis (Table 2). The company estimated that 18,600 patients in the UK will be diagnosed with NSCLC in 2018, however the ERG was unable to ascertain the origin of this figure from the sources cited by the company. The ERG notes that the company have also included an assumption for the year-on-year growth of lung cancer incidence to arrive at their estimate that 18,600 patients with NSCLC (1L) in the UK in 2018. However, the company did not provide details of their assumption of the rate of year-on-year growth in the CS or budget impact analysis.

The company applied a 72% rate of tissue availability followed by an [redacted] biomarker testing rate to the 18,600 patients and then assumed 4% of the resulting patients would be ALK+. This resulted in an estimate of [redacted] patients with untreated ALK+ NSCLC in 2018. In the CS (page 12), the ERG notes that the company reported that, "approximately 3-5% of people with advanced NSCLC have ALK fusion genes 6, 8, 9, equating to approximately 365 people in England". The ERG is unsure how this value of 365 was reached and how it relates to the [redacted] reported in the company's budget impact analysis submission.

The company applied a 95% drug treatment rate and a [redacted] non-clinical trial rate in their calculation of the number of patients eligible for 1L treatment with alectinib. In addition, it was assumed only [redacted] of the UK patients would be from England. In summary, the company estimated that in 2018 there will be [redacted] ALK+ NSCLC patients eligible for 1L alectinib in England with ALK+ advanced NSCLC (Table 2).

The ERG considers that the number of patients eligible for alectinib at 1L may be somewhat higher than the company estimate. Using data from the Office for National Statistics (ONS) for new lung cancer cases in England in 2015 (37,637; which is likely to underestimate 2018 incidence), and applying the rates used by the company of 88% for NSCLC, 53% for Stage IV disease at diagnosis and 4% for ALK fusion genes, results in an estimate of 702 patients potentially eligible for treatment with alectinib.[16] The ERG acknowledges that the actual figure is likely to be slightly lower based on biomarker testing, tissue availability and actual drug treatment rates and applying the company's rates for these results in an estimate of approximately [redacted] patients. The ERG is unsure why a non-clinical trial rate was included in the company's calculation and has omitted it from the ERG estimation.

Table 2. Company's estimate of the proportion of patients potentially eligible for treatment with alectinib (adapted from Company budget impact analysis Table 2, pg. 7)

		2018	2019	2020	2021	2022	Source used by company
Estimated 5-year prevalence – diagnosed 1L NSCLC		18,600	18,758	18,931	19,100	19,279	European Network of Cancer Registries, International Agency for Research on Cancer[17] Cancer Research UK[18] UK National Lung Cancer Audit (NLCA; 2012–2015)[19]
Tissue availability rate	72%	13,392	13,506	13,630	13,752	13,881	UK National Lung Cancer Audit (NLCA; 2012–2015)[19]
Biomarker testing rate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Kantar Health Lung Market Research
Biomarker positivity rate	4%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Prevalence ~3–5%, thus average utilised[5, 20-23]
Drug treatment rate	95%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Assumption: proportion of patients will progress rapidly, and not receive treatment
Non-clinical trial rate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Market research: Based on a sample of N=80 Consultant UK Oncologists
England as a % of UK	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Office for National Statistics [24]
1L ALK eligible population (UK)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: 1L, first-line; ALK, anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer; UK, United Kingdom.

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

The company provided a summary of the final decision problem issued by the National Institute for Health and Care Excellence (NICE), together with the rationale for any deviation from the scope[1] (Table 3).

Table 3. Summary of decision problem as outlined in the company's submission (adapted from CS Table 2, pgs 7–8)

	Final scope issued by NICE	**Decision problem addressed in the submission**	**Rationale if different from the scope**
Population	Adults with untreated ALK+ advanced NSCLC	Adults with untreated ALK+ advanced NSCLC	NA
Intervention	Alectinib	Alectinib	NA
Comparator(s)	Crizotinib	Crizotinib	NA
Outcomes	•Overall survival •Progression-free survival •Response rates •Adverse effects of treatment •Health-related quality of life	As in scope plus: •Duration of response •Time to CNS progression	NA
Economic analysis	•Cost per life year gained (LYG) •Costs per QALY gained	•Cost per life year gained (LYG) •Costs per QALY gained	NA
Subgroups to be considered	NA	NA	NA
Perspective for outcomes	All direct health effects, whether for patients or, when relevant, carers	Direct health effects for patients, excluding QoL associated with brain mets	Full benefits of alectinib not captured by the QALY
Perspective for costs	NHS or social services perspective	NHS or social services perspective	NA
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	30 years	Long enough to reflect all important differences in costs or outcomes between the technologies
Synthesis of evidence on health effects	Based on systematic review	Based on systematic review	NA
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.	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	NA
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Reported by patients	NA
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	EQ-5D values derived using the UK tariff	NA

Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	No equity issues identified	NA
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	Published literature, and previous health technology appraisals.	NA
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	3.5% across costs and health effects	NA
Abbreviations used in table: ALK+, anaplastic lymphoma kinase positive; CNS, central nervous system; LYG, life years gained; NA, not applicable; NHS, National Health Service; NSCLC, non-small-cell lung cancer; PSS, Personal Social Services; QALY, quality-adjusted life year			

3.1 Population

The company submitted clinical effectiveness evidence from the multinational ALEX[25] phase III randomised controlled trial (RCT), and supporting evidence from a second phase III RCT conducted in Japan (J-ALEX).[26] Data from J-ALEX was not included in the review of cost-effectiveness because it included patients who were pretreated with chemotherapy, and used half the expected licensed dose of alectinib (300 mg twice daily instead of 600 mg twice daily). As such, the evidence review group (ERG) focuses its critique on ALEX.

ALEX recruited adults with untreated anaplastic lymphoma kinase positive (ALK+) advanced or recurrent non-small-cell lung cancer (NSCLC). The population matches the population defined in the NICE final scope,[1] where 'untreated' refers to no prior systemic therapies for ALK+ advanced NSCLC. Th ERG's clinical experts did not consider the inclusion of patients with recurrent or locally advanced disease (IIIb) outside the NICE final scope,[1] and only 3% and 4% of the alectinib and crizotinib groups, respectively were stage IIIb (the rest being stage IV). The ERG's clinical experts considered the ALEX population reflective of UK patients with ALK+ advanced or metastatic NSCLC.

As outlined in Section 2, the ERG's clinical experts indicated that ALK+ NSCLC occurs more commonly in a younger population with lighter smoking history and a more equal split between the sexes than the wider NSCLC population; this is reflected in the baseline characteristics of ALEX. The ERG's clinical experts also highlighted that the high proportion of patients with central nervous system (CNS) metastases in ALEX reflects that CNS metastases are more common and generally occur earlier in ALK+ NSCLC than in other lung cancers. However, the ERG notes that only patients with asymptomatic CNS metastases, or those who had completed radiotherapy 14 days prior to the trial, were eligible for ALEX, which would not generally be picked up in clinical practice because asymptomatic patients are not routinely scanned.

The ERG's clinical experts highlighted that, as is often the case due to clinical trial inclusion criteria, the ALEX population may be somewhat healthier than would be seen in clinical practice, reflected by

the high proportion of patients with Eastern Cooperative Oncology Group performance score (ECOG PS) of 0 or 1.

Only three patients (1%) were recruited from UK centres, 97 (32%) from other Western European countries (Italy, Spain, Portugal, France and Switzerland), 42 from North America (14%), and 124 (41%) from Asia (South Korea, Hong Kong, Thailand, Singapore, Taiwan and China); other recruitment regions included Australasia, Eastern Europe and South America. The ERG's clinical experts advised that the baseline characteristics and prior non-systemic therapies are nonetheless reflective of patients in England, but highlighted that the provision of subsequent therapies after discontinuation of the randomised treatment is unlikely to be similar. The ERG requested various data about subsequent therapies from the company at the clarification stage because type of therapy received has been shown to have an important effect on overall survival (OS) in this population[27, 28] (discussed in more detail in Section 4.3).

The ERG considers the data presented within the submission to be representative of patients with ALK+ advanced NSCLC in England and to be relevant to the decision problem that is the focus of this single technology appraisal (STA).

3.2 Intervention

Alectinib (Alecensa®, Roche Registration Ltd) is a small molecule tyrosine kinase inhibitor (TKI) which targets both ALK and RET (rearranged during transfection) tyrosine kinase receptors to inhibit tumour cell growth and proliferation.[14] Animal models showed alectinib to induce tumour regression and prolong survival, with activity in the CNS.[15]

The European Medicines Agency (EMA) issued a marketing authorisation (MA) for alectinib in February 2017 for patients with ALK+ advanced NSCLC previously treated with crizotinib,[29] based on evidence from two single-arm studies.[30, 31] A NICE STA was scheduled for the pretreated indication (TA438), but the company failed to submit evidence so alectinib is currently not available on the NHS for ALK+ advanced NSCLC. The Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion in October 2017 recommending an extension to the MA to include adults with untreated ALK+ advanced NSCLC based on evidence from ALEX, and the updated MA and EPAR was released in January 2018. The United States Food and Drug Administration (FDA) approved alectinib for patients with crizotinib-pretreated ALK+ metastatic NSCLC in December 2015, which was extended to all ALK+ metastatic NSCLC in November 2017.[32]

The intervention in the ALEX study was alectinib for adults with untreated ALK+ advanced NSCLC, in line with the extended MA and the NICE final scope.[1] Patients assigned to alectinib were given 600

mg (as four 150 mg capsules) orally twice daily in line with the EPAR [29] A lower dose (300 mg twice daily) was used in J-ALEX which is used as supportive evidence only.

In their response to clarification, the company outlined a discrepancy between the design of ALEX and the MA for alectinib with regards to treatment with alectinib beyond progressive disease (PD), stating that:

"whilst a patient with asymptomatic isolated CNS progressive disease could, at the discretion of the investigator, remain on treatment in the ALEX trial, there are no such criteria in the anticipated license of alectinib. As such, in UK clinical practice, all patients will discontinue treatment at progressive disease, irrespective of symptoms."

The company did not discuss how frequently this occurred or whether it was more common in one group than the other. The EPAR for alectinib states that treatment with alectinib should be continued until PD or unacceptable toxicity[29] The ERG considers that this asymptomatic CNS progression may not be detected in clinical practice, but notes from clinical experts and related STAs (TA500 and TA422) that treatment with ALK-TKIs in UK clinical practice may be guided by symptoms rather than radiographic evidence of PD, particularly if it is at a single site and subsequent treatment options are limited. Comparison of ALEX time to treatment discontinuation (TTD) and PFS curves suggest treatment beyond PD was uncommon in both groups. There was no consensus between the ERG's clinical experts regarding how often this occurs in UK clinical practice, under what circumstances (e.g. patient factors and availability of an alternative treatment), and the potential impact on OS.

3.3 Comparators

The NICE final scope[1] lists the first-generation ALK-TKI, crizotinib (Xalkori®, Pfizer Ltd), as the only relevant comparator for alectinib in the population of interest, which was the comparator used in the ALEX study. The ERG's clinical experts confirmed that, at the time the scope was finalised, crizotinib was the only relevant comparator as it has become standard 1L therapy for patients in England with ALK+ advanced NSCLC. As outlined in Section 2, ceritinib, a second-generation ALK-TKI, has since received NICE approval for the same indication (November 2017), and its final appraisal determination (FAD) states that its benefits over crizotinib mean it may replace crizotinib as the preferred 1L option. While ceritinib is now a relevant comparator for this STA, it was not at the time the NICE scope was finalised, or indeed by the time the company submitted evidence for alectinib. The ERG thus considers that evidence submitted by the company covers the comparators that were relevant at the time of submission.

Patients assigned to received crizotinib in ALEX were given 250 mg orally, twice daily (500 mg daily dose) in line with its European MA for use in ALK+ NSCLC.[33] Reasons for interruption and

discontinuation were in line with the SmPC. As with alectinib, patients could receive treatment beyond asymptomatic CNS progression in ALEX at the investigator's discretion.

3.4 Outcomes

All outcomes listed in the NICE final scope[1] were included in the company submission (CS), namely:

- OS;
- PFS;
- Response;
- Adverse effects (AEs) of treatment;
- Health-related quality of life (HRQoL).

Outcomes not specified in the final scope for which evidence was presented in the submission are:

- Duration of response (DOR);
- Time to CNS progression (also referred to as CNS PFS) – including the growth or spread of existing CNS metastases or the development of CNS metastases during the study;
- CNS response, and DOR, for patients with CNS metastases at baseline.

The primary outcome in ALEX was investigator-assessed (INV) PFS, defined as the time from randomisation to progression by Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST v1.1)[34] or death from any cause. INV PFS in the ITT population was initially presented as the company's preferred PFS analysis in the CS and results for PFS assigned by an independent review committee (IRC), a secondary outcome in ALEX, were presented to substantiate the results.

Time to CNS progression (CNS PFS) was a secondary outcome in the ALEX trial that was not listed in the NICE final scope.[1] After consultation with clinical experts, the ERG considered that it was important to reflect CNS activity in the review of cost effectiveness. CNS progressions are a common site of progression in ALK+ NSCLC with distinct clinical and cost implications, and the company propose the activity of alectinib in the CNS is an important benefit that is not reflected fully by PFS.

The ERG noted inconsistencies between the analysis of time to CNS progression and PFS in the submitted evidence, and asked the company to clarify how events were counted in each analysis. The company confirmed that time to CNS progression had been represented erroneously as a function of PFS in the CS because CNS progression could be captured by either one of two separate IRC procedures

in ALEX: one for systemic progression for the main IRC PFS outcome (based on RECIST v 1.1), and a second specifically to identify intracranial CNS lesions using a modified version of RECIST (hereafter referred to as "CNS RECIST").

For PFS and CNS PFS to be internally consistent, both had to include events from the IRC RECIST assessment, or from both the IRC RECIST and IRC CNS RECIST assessment. The ERG's preferred PFS and CNS PFS are based only on validated RECIST v1.1 because it is likely to be the least biased and most clinically relevant representation of PD, and the most comparable to how PFS is represented in other NICE technology appraisals. The company chose PFS and CNS PFS based on RECIST+CNS RECIST as their preferred analyses because they were the, "the most complete and robust analysis of the impact of CNS metastases", but accepted that events captured by CNS RECIST, "may be earlier than would be in clinical practice as CNS RECIST is not routinely used in the NHS" (company clarification response to question A10).

OS was defined as expected as time from randomisation to death from any cause in the ITT population. ALEX was not powered to detect a significant difference in OS and the median had not been reached in either group at the time of the primary analysis; the immaturity of OS is noted as a key limitation of the ALEX data and is discussed in Section 4.3.

The NICE final scope[1] did not list any subgroups of interest but the CS included INV PFS results by age (<65 vs ≥65 years old), sex, race (Asian vs non-Asian), smoking status, ECOG PS (0 or 1 vs 2), presence of CNS metastases at baseline and patients with pre-treatment radiation therapy for CNS lesions. At the clarification stage, the ERG asked for the same subgroups for IRC PFS (detailed in the clinical study report [CSR]), and *post-hoc* subgroup analyses for OS by type of subsequent therapy and presence of CNS metastases at baseline. The subgroup analyses were not run on the company's preferred PFS based on RECIST+CNS RECIST events.

Response outcomes in the CS, all according to RECIST v1.1[34] criteria, were objective response rate (ORR; total patients with either complete or partial response), complete response (CR), partial response (PR), rates of stable disease (SD) and PD, and duration of response (DOR). Results in the CS were by INV-assessment and the clinical study report (CSR)[35] included results by IRC. The CS also reported CNS response and duration of CNS response for the subset of patients with CNS lesions at baseline, based on a separate modified CNS RECIST process undertaken by the IRC.

Adverse effects (AEs) were recorded for all patients who received at least one dose of the study drug, which was all patients in the intention to treat (ITT) population (n = 303). AEs were recorded by investigators at each patient visit, either reported by the patient or noted by study personnel, until 4 weeks after the last dose of study drug (CSR,[35] pg 2033); severity was graded according to the National

Cancer Institute Common Terminology Criteria for Adverse Events version 4 (NCI CTCAE v4).[36] The CS included a range of AE data, including all-cause and treatment-related AEs of all grades, AEs of Grade 3 and above, those requiring treatment discontinuation, dose reduction or interruption, and specific events reported by at least 10% of either arm or with a difference of at least 5% between groups.

HRQoL was measured with the EuroQol 5-Dimensions 3-Levels tool (EQ-5D-3L) for overall health status, the European Organisation for Research and Treatment of Cancer Quality of Life Core 30 questionnaire (EORTC QLQ-C30), and the EORTC lung cancer module (EORTC LC13). Results from the EORTC scales included time-to-deterioration of lung cancer symptoms, patient functioning, treatment burden and tolerability.

Based on advice from clinical experts, the ERG considers the outcomes presented in the submission clinically relevant to the decision problem outlined in the NICE final scope.[1] The submission and CSR[35] provided comprehensive results for all analyses, and included results for sensitivity and secondary outcomes that allowed the ERG to assess the robustness of the evidence by comparing results for outcomes measured in more than one way (e.g. INV vs IRC-assessed PFS). Additional data were also provided by the company on the ERG's request at the clarification stage. The CNS-specific endpoints were outside the NICE scope but the ERG consider it appropriate to reflect CNS progression in the review of cost-effectiveness. The ERG considers PFS and CNS PFS based on the main RECIST IRC assessment to be more clinically relevant and comparable to other STAs than those incorporating events from a separate IRC process using CNS RECIST.

3.5 Other relevant factors

At the time of writing, the company have submitted a proposed discount to the Patient Access Scheme Liaison Unit, which was unconfirmed at the time of writing. The company did not highlight any equality issues related to the submission.

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review

The company conducted a systematic literature review (SLR) with broad inclusion criteria to, "identify and select the clinical evidence relevant to the technology being appraised", for patients with anaplastic lymphoma kinase positive (ALK+) advanced non-small-cell lung cancer (NSCLC). The company describe the inclusion of 34 studies (15 randomised controlled trials [RCTs], 1 non-RCT, 16 single-arm trials and two case series), and focused on four RCTs,[37-39] including ALEX,[25] that are relevant to the first-line (1L) ALK+ advanced NSCLC population. However, ultimately, no additional clinical effectiveness evidence from the SLR needed to be incorporated because the ALEX regulatory trial closely matches the decision problem outlined in the NICE final scope.[1]

Studies identified in the SLR, detailed in Appendix D1.1 of the CS, therefore only serve to confirm that no additional alectinib evidence should have been included, and to provide comparable populations to validate the observed data from ALEX and the long-term survival extrapolation for the review of cost-effectiveness. The evidence review group (ERG) has provided a brief overview of the company's SLR process, focussing on the four RCTs of untreated ALK+ populations identified by the company (ALEX, PROFILE 1014,[37] ASCEND-4[38] and PROFILE 1029[39]).

4.1.1 Searches

Search strategies for EMBASE and MEDLINE, MEDLINE In-Process and the Cochrane Library were provided in Tables 1, 2 and 3 of Appendix D1.1 of the CS, respectively (EMBASE and MEDLINE strategy reproduced in Appendix 10.1). The ERG considers the combination of condition, treatment and study design search terms used by the company to be appropriate and comprehensive, except for the terms relating to prior treatment (MEDLINE and EMBASE #3, MEDLINE In-Process #3, Cochrane Library #6). The ERG considers that terms such as 'untreated' or 'first NEAR line' would have been more appropriate, or the string could have been omitted entirely to capture all evidence relevant to the natural history of ALK+ advanced NSCLC, regardless of line of treatment.

Electronic databases were searched from inception to 2 February 2017 and Appendix D1.1 also details tracking of e-alerts until 20 March 2017. The company also conducted searches of trial registries (clinicaltrials.gov, the World Health Organisation International Clinical Trials Registry Platform [WHO ICTRP] and the European Union Clinical Trials Register [EU-CTR] on 15 January 2017) and conference proceedings (Table 5, CS Appendix D1.1).

Due to time constraints, the ERG was unable to replicate the company's search and appraisal of identified abstracts for all databases and additional searches. The ERG considers the company's search

process mostly appropriate but, in addition to the critique regarding prior therapy terms above, noted that the searches supporting the SLR predated most relevant 2017 conferences.

4.1.2 Inclusion criteria

The ERG considers the study eligibility criteria outlined in Table 6, CS Appendix D1.1 (reproduced in Appendix 10.1) appropriate to identify evidence relevant to the decision problem. Intervention, line of therapy, study design, date and language criteria were broad and population criteria were specific to ALK+ advanced and metastatic NSCLC); the ERG considers this approach appropriate to identify complete and relevant contextual evidence for the technology being appraised.

Population criteria were adults with metastatic NSCLC confirmed as ALK+ by any method. Specific populations with brain metastases were eligible. The company defines four relevant subpopulations based on prior treatment received for ALK+ NSCLC: neither crizotinib nor chemotherapy (Population A), chemotherapy but no crizotinib (Population B), crizotinib but not chemotherapy (Population C), and both crizotinib and chemotherapy (Population D). Population A reflects the decision problem and matches the population of ALEX, but the ERG considers that studies of other populations could provide information to inform the economic model that is not available from ALEX, such as type and duration of second-line (2L) therapies after crizotinib. Mixed populations were only included if data for ALK+ NSCLC were reported separately or if at least 80% of the population were ALK+, which the ERG considers appropriate.

Intervention and comparator inclusion criteria were very broad and included ALK tyrosine kinase inhibitors (ALK-TKIs; e.g. brigatinib, lorlatinib), platinum and other chemotherapies (e.g. cisplatin, paclitaxel, gemcitabine) and other drug classes (e.g. immunotherapies, checkpoint inhibitors and epidermal growth factor receptor [EGFR] inhibitors). Given that only ceritinib, crizotinib and docetaxel were included by the company as relevant subsequent therapies for the review of cost-effectiveness, it is unclear why it was necessary to include such a large range of treatments; this is reflected in the large number of studies listed as 'included' that do not feature in the submission (see 4.1.3).

The categorisation of study design eligibility into 'for inclusion in the NMA' and 'for inclusion in the qualitative review' was not necessary given that no network meta-analysis (NMA) or other indirect comparison was undertaken for this single technology appraisal (STA), but the ERG considers the inclusion of randomised and non-randomised evidence appropriate. Retrospective chart reviews were not eligible, which the ERG considers may have been an important source of information to inform subsequent therapy profiles and clinical plausibility of overall survival (OS) extrapolations.

The ERG considers all other eligibility criteria reasonable (i.e. date limits, publication type, and language) and in line with the decision problem for this STA.

4.1.3 Critique of data extraction

The company presented a Preferred Reporting Items for Systematic Reviews (PRISMA) flow diagram to illustrate the study selection process (Figure 37, Appendix 10.1). The PRISMA diagram shows the number of citations identified from the three electronic databases and the hand searches, and gives reasons for exclusion at the abstract review and full-text appraisal stages (Figure 37, Appendix 10.1). Full details of the abstracts identified in handsearching (Table 9, CS Appendix D1.1), exclusion criteria, lists of excluded studies (Tables 7 and 8, Appendix D1.1), unpublished studies identified from trial registries (Table 11, 12 and 13, CS Appendix D1.1), and ongoing studies with trial protocols only (Table 14, CS Appendix D1.1) were all provided in Appendix D1.1.

The PRISMA flow diagram shows that 34 studies were included in the company's SLR process, but the ERG counted 28 studies across several tables presented in CS Appendix D1.1 (Tables 10, 15, 16 and 17). The ERG collated a summary of the 28 included studies from these tables for information (Table 60, Appendix 10.1) to illustrate the large degree of variation between study treatments and prior therapies resulting from the broad inclusion criteria. The ERG could not identify the six remaining studies not listed in any of the tables listing included studies.

Within the 28 included studies for which information as available, the ERG notes that 21 did not assess alectinib (Table 60, Appendix 10.1). Of the seven studies of alectinib, the ERG considers that J-ALEX,[26] submitted as supportive evidence only and not included in the review of cost-effectiveness, does not provide relevant evidence because it included patients who were pretreated with chemotherapy, and used half the dose of alectinib compared with that used in ALEX (300 mg twice daily instead of 600 mg twice daily). Also within the seven alectinib studies was an RCT of alectinib (600 mg twice daily) versus crizotinib (250 mg twice daily), which the ERG considers outside the NICE final scope[1] because it recruited a population who had received prior treatment with crizotinib and platinum-based chemotherapy (ALUR).[40] The four remaining alectinib studies identified in the company's SLR either assessed the lower 300 mg twice daily dose or recruited mixed pretreated populations (Hida 2016,[41] Iwama 2017,[42] Metro 2016,[43] and Tamura 2017[44]; see Table 60).

The ERG thus considers ALEX to provide the only relevant comparative evidence for alectinib versus the comparator of interest in the population defined in the NICE final scope.[1] The ERG agrees with the company that J-ALEX provides supportive evidence only. The ERG also agrees that three other phase III open-label RCTs of patients with untreated ALK+ NSCLC (Population A; PROFILE 1014,[37] ASCEND-4[38] and PROFILE 1029[39]) and three phase III open-label RCTs in pretreated ALK+ NSCLC populations (Populations B and D) provide relevant contextual evidence to support the review of cost-effectiveness and inform subsequent therapy post-progression survival in the economic model. The

eight studies used in the CS are shown in Table 4, and a comparison of baseline characteristics for the four Population A studies has been reproduced in Appendix 10.210.1 (Table 61).

Table 4. Summary of the ALEX study and seven related Phase III RCTs identified in the company's SLR

Study ID/Ref ID	Registration	Location	N	Intervention	Comparator	Population	Role in submission
ALEX/Peters 2017[25]	NCT02075840	International	303	ALEC 600x2	CRIZ 250x2	A	Primary study for clinical effectiveness data.
J-ALEX/Kim 2016c[26]	JapicCTI-132316	Japan	207	ALEC 300x2	CRIZ 250x2	A/B (64%/36%)	Supplementary evidence for alectinib; not included in economic model.
PROFILE 1014/Solomon 2014[37]	NCT01154140	International	343	CRIZ 250x2	PEM + CIS or CARB	A	Validation of crizotinib PFS/OS. Comparison of % with brain metastases at baseline.
PROFILE 1029/Lu 2016[39]	NCT01639001	International	207	CRIZ 250x2	PEM + CIS or CARB	A	Comparison of crizotinib PFS.
ASCEND-4/Soria 2017[38]	NCT01828099	International	376	CER 750	PEM +/- CIS or CARB	A	Comparison of % with brain metastases at baseline.
ALUR/Roche 2016[40]	NCT02604342	International	107	ALEC 600x2	PEM or DOC	D	2nd line alectinib duration post-crizotinib in the economic model.
ASCEND-5/Scagliotti 2016[45]	NCT01828112	International	231	CER 750	PEM or DOC	D	2nd line ceritinib duration post-crizotinib in the economic model.
PROFILE 1007/Shaw 2013a[46]	NCT00932893	International	347	CRIZ 250x2	PEM or DOC	B	2nd line crizotinib and chemo durations post-chemotherapy.

Abbreviations: ALEC, alectinib; CARB, carboplatin; CER, ceritinib; CIS, cisplatin; CRIZ, crizotinib; DOC, docetaxel ID, identifier; N ALK+, number with anaplastic lymphoma kinase mutation; NR, not reported; OL, open-label; P I, phase one study; P II, phase two study; PEM, pemetrexed; RCT, randomised controlled trial; SLR, systematic literature review; USA, United States of America. Population A: naïve to crizotinib and chemotherapy; Population B: naïve to crizotinib but not chemotherapy; Population C: naïve to chemotherapy but not to crizotinib; Population D: prior crizotinib and chemotherapy.
Note: Where specified for clarity, doses are in mg

In summary, the company's SLR was broad and identified multiple studies, most of which were not used to support the submission. Nonetheless, the company's SLR process described in Appendix D1.1 of the CS was comprehensive and transparent, and the ERG considers that ALEX, and the seven additional studies supporting the review of cost-effectiveness, were chosen appropriately from the full list of identified studies. However, the exclusion of retrospective chart reviews may have overlooked important evidence to validate OS observed in ALEX, and to assess the plausibility of extrapolations used for the review of cost-effectiveness.

4.1.4 Quality assessment

The company assessed the four Population A RCTs using the Cochrane Risk of Bias Tool.[47] A summary of the company's risk of bias judgements is shown in Table 5. The full risk of bias assessments for ALEX, PROFILE 1014,[37] PROFILE 1029[39] and ASCEND-4[38] were provided during the clarification process and can be found in Appendix 10.2 (Table 62, Table 63, Table 64 and Table 65). The ERG conducted an independent validation of the company's assessment of ALEX, given that this was the only study from which clinical effectiveness data were derived (Table 6).

Table 5. Summary of company's Cochrane risk of bias assessments of Population A randomised controlled trials (RCTs), including ALEX (adapted from CS Appendix D1.3, Table 19)

Risk of bias domain	ALEX[2]	PROFILE 1014[37]	PROFILE 1029[39]	ASCEND-4[38]
Random sequence generation	●	●	●	●
Allocation concealment	●	●	●	●
Participant + personnel blinding	●	●	●	●
Outcome assessor blinding	●	●	●	●
Incomplete outcome data	●	●	●	●
Selective reporting	●	●	●	●
Other bias	●	●	●	●

Abbreviations: CS, company submission; ERG, evidence review group.
● low risk of bias, ● unclear risk of bias, ● high risk of bias.

Table 6. ERG's validation of the company's Cochrane risk of bias assessment of ALEX (company ratings and justifications from Table 7, clarification response)

Risk of bias domain	Rating	Company justification	ERG comments
Random sequence generation	●	Randomisation was stratified using a block-stratified randomisation procedure, suggesting randomisation sequence generated adequately	The ERG agrees with the company's rating.
Allocation concealment	●	Randomisation was performed centrally via interactive voice or web-based response system	The ERG agrees with the company's rating.

Participant + personnel blinding	●/●	Study was open-label. IRC corroborated INV assessments, and IRC assessments of secondary endpoints PFS and TTP outcomes were made blind, so these are unlikely to have been affected. IDMC meetings were conducted blind to the sponsor. The primary outcome was PFS assessed by INV, and this could have been affected potentially by the lack of blinding, however. Discontinuation from treatment (any reason) was higher in the CRZ control arm (105/151, 69.5%) than in the ALEC arm (68/152, 44.7%), as was withdrawal by subjects (11/151, 7.3% with CRZ vs. 3/152, 2% with ALEC)	The ERG agrees with the company's rating. Risk of bias is dependent on blinding for that outcome. PROs and INV outcomes at high risk of bias.
Outcome assessor blinding	●/●	The primary outcome was PFS assessed by INV, and this could have been affected by the lack of blinding, as could ORR (also assessed by INV), hence high risk of bias. Secondary endpoints (PFS, Time to CNS progression) were assessed by blinded IRC so these are associated with a low risk of bias. OS would also be associated with a low risk of bias.	As above. The ERG agrees with the company's rating.
Incomplete outcome data	●	No missing outcome data for primary and key secondary outcomes	Time to event outcomes were censored appropriately. The ERG considers this domain high risk for PROs.
Selective reporting	●	All primary and key secondary outcomes reported (data in confidence). Of the secondary outcomes listed in clinicaltrials.gov data regarding pharmacokinetic endpoints and HRQoL (time to deterioration in QLQ-C30 or in QLQ-LC13, QLQ-C30 scores, QLQ-LC13 scores) have not yet been reported.	The ERG considers this domain low risk of bias. Full data were available or provided during clarification to cover the NICE scope.
Other bias	●	Baseline characteristics well balanced and there were no protocol violations. All patients randomised were treated as planned. Mean dose intensity was 92.4% with CRZ and 95.6% with ALEC. 38% and 42% had BM at BL (IRC assessed), and 38% and 40% (INV assessed) for CRZ and ALEC, respectively. These %s, although balanced within the study, are higher than in PROFILE 1014, PROFILE 1029 and ASCEND-4, which could influence inter-study comparisons. Whether it could affect the comparison of relative effects is not known.	The ERG did not identify any other risks of bias.

Abbreviations: AEs, adverse events; ALEC, alectinib; BL, baseline; BMs, brain metastases; CHEMO, chemotherapy; CRZ, crizotinib; HRQoL, health-related quality of life; IDMC, independent data monitoring committee; INV, investigator-assessed; IRR, independent radiology review; ORR, objective response rate; OS, overall survival; PEM, pemetrexed; PFS, progression-free survival; PROs, patient reported outcomes; QLQ-C30, quality of life questionnaire core 30; QLQ-LC13, quality of life questionnaire lung cancer module; TTP, time to progression.

The ERG considers ALEX to be a well-conducted study that provides high quality evidence to support the decision problem. The open-label design has implications on the reliability of some outcomes and, where both are available, the ERG considers those captured by IRC to be more reliable than those assigned by INV.

4.1.5 Evidence Synthesis

No evidence synthesis was necessary because ALEX was the only study that provided evidence relevant to the decision problem.

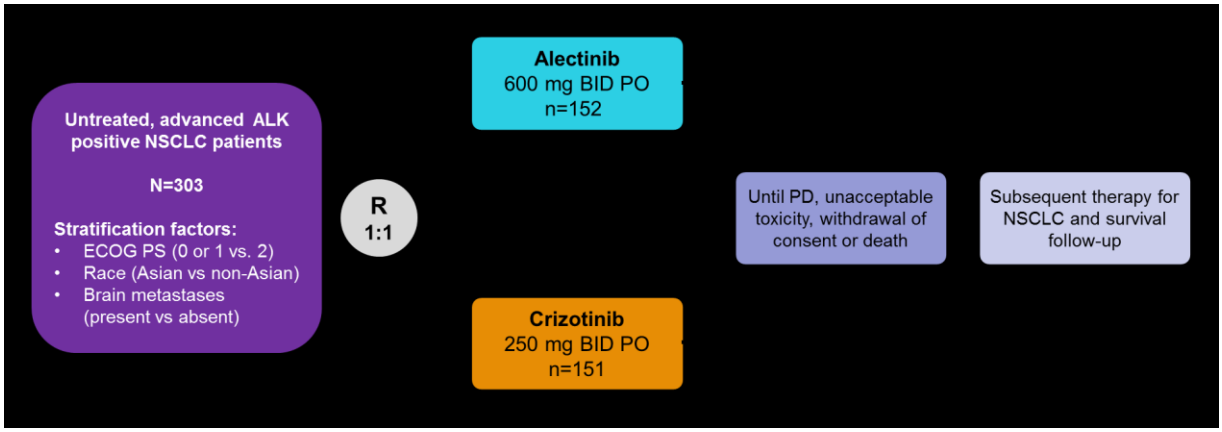
4.2 *Critique of trials of the technology of interest, their analysis and interpretation*

4.2.1 Trial conduct

Clinical effectiveness evidence presented in the CS for alectinib was from ALEX, a phase III open-label randomised controlled trial (RCT). ALEX recruited 303 patients with previously untreated ALK+ advanced or recurrent NSCLC across 98 study sites in 29 countries; around 40% of the population were from Asian countries and only three patients were recruited from UK centres (1%).

The design of ALEX is represented in Figure 2. Patients were allocated to alectinib 600 mg twice daily (n = 152) or crizotinib 250 mg twice daily (n = 151) in a 1:1 ratio by block-stratified randomisation via an interactive voice or web-based response system. Stratification factors were Eastern Cooperative Oncology Group performance score (ECOG PS, 0 or 1 vs 2), race (Asian vs non-Asian), and central nervous system (CNS) metastases at baseline (present vs absent).

Figure 2. ALEX study design (reproduced from CS, Figure 2, pg 18)



Abbreviations: ALK, anaplastic lymphoma kinase; BID, *bis in die* (twice daily); ECOG PS, Eastern Cooperative Oncology Group Performance Score; NSCLC, non-small-cell lung cancer; PD, progressive disease; PO, *per os* (orally); R, randomised.

Study treatments were administered orally twice daily, and patients, investigators and study personnel were aware of treatment assignment. At the clarification stage, the company explained that a double-blind, double-dummy design was not chosen because differences in capsule size and standard dose reductions between alectinib and crizotinib capsules would have resulted in patients taking multiple matched capsules, potentially affecting compliance and complicating dose management. Rules for concomitant medications, dose interruption and dose reduction were prespecified in the protocol.

A PRISMA diagram of participant flow was provided by the company in Appendix D1.2 of the CS (reproduced in Appendix 10.3). The diagram indicates that 84 (55%) and 46 (30%) patients in the alectinib and crizotinib groups, respectively, were still on the study treatment at the February 2017 data cut-off. Of the remaining patients, a similar proportion of each group had died (23% of the alectinib group and 26% of the crizotinib group), a larger proportion of patients in the crizotinib group (18%)

than the alectinib group (11%) had been lost to follow-up or declined to participate, and most others were being followed for OS after discontinuation of the study drug (10% of the alectinib group and 24% of the crizotinib group).

The primary outcome of ALEX was INV PFS, defined as the time from randomisation to disease progression according to Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST v1.1), or death from any cause. The company clarified that investigator-assessed (INV) PFS was chosen as the primary outcome because 8-weekly scans could be assessed in real-time to inform the event-driven analysis of PFS. The primary analysis of INV PFS was based on a data cut-off of 9 February 2017.

Centralised assessment of PFS by an independent review committee (IRC), also according to RECIST v1.1, occurred at the same data cut-off to support PFS results by INV assessment. The ERG and its clinical experts considered PFS by IRC likely to be the less biased of the two PFS outcomes because of the open-label study design.

Time to CNS progression (CNS PFS) was a predefined secondary outcome in the ALEX trial that was not listed in the NICE final scope.[1] CNS PFS was measured in the ITT population to capture the growth or spread of baseline CNS metastases or the development of CNS metastases during the study. After consultation with clinical experts, the ERG considered that it was important to reflect CNS progressions in the review of cost effectiveness. As outlined in Sections 2 and 3.4, CNS progressions are a common site of progression in NSCLC with distinct clinical and cost implications, and the company propose the activity of alectinib in the CNS is an important benefit that is not captured adequately by the PFS endpoint.

During the clarification process, the company outlined that CNS progression could be picked up by either one of two separate IRC procedures: the main process for identifying systemic progression (based on RECIST v 1.1), and a second specifically to identify intracranial CNS progression using a modified version of RECIST (hereafter referred to as 'CNS RECIST'). At the clarification stage, the company submitted new PFS and CNS PFS results as their preferred analyses, incorporating events from either IRC procedure, which had implications on the clinical relevance and comparability of the results to related STAs (Section 3.4 and 4.3.2).

Response was also captured according to RECIST v1.1 criteria, and measures included objective response rate (ORR; total patients with either complete or partial response), complete response (CR), partial response (PR), and rates of stable disease (SD) and PD. Results in the CS were by INV assessment and the clinical study report (CSR)[35] included results by IRC. CNS response was also recorded for the subset of patients with CNS lesions at baseline, based on the modified CNS RECIST described above. Duration of response (DOR) was also reported, for all responders and separately for

those with CNS lesions at baseline, defined as the time from documented CR or PR to progressive disease or death from any cause. Full IRC and INV response data were available in the CSR.[35]

Patient-reported outcomes (PROs) were collected every four weeks until the end of treatment assessment, and included the EuroQol 5-Dimensions 3-Levels tool (EQ-5D-3L) for overall health status, the European Organisation for Research and Treatment of Cancer Quality of Life Core 30 questionnaire (EORTC QLQ-C30), and the EORTC lung cancer module (EORTC LC13).

Adverse effects (AEs) were recorded for all patients who received at least one dose of the study drug, which was all patients in the ITT population (n = 303). AEs were recorded by investigators who were aware of treatment assignment at each patient visit, until 4 weeks after the last dose of study drug (CSR,[35] pg 2033); severity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4 (NCI CTCAE v4).

As per Figure 2, treatment was planned until PD, unacceptable toxicity, withdrawal of consent or death. However, at the clarification stage, the company emphasised that patients with asymptomatic CNS progression could remain on treatment at the discretion of the investigator. While this is not indicated in the marketing authorisation for alectinib, the ERG considers that asymptomatic CNS progression may not be detected in clinical practice. The company anticipate that, in UK clinical practice, all patients will discontinue treatment at PD, irrespective of symptoms (see Section 3.2), but the ERG notes from clinical experts and related STAs (TA500 and TA422) that treatment with ALK-TKIs in UK clinical practice may be guided by symptoms rather than radiographic evidence of PD, particularly if it is at a single site and subsequent treatment options are limited. Information was not provided in the CS to assess how frequently patients were treated beyond asymptomatic CNS progression, but the ERG compared the curves for time to treatment discontinuation (TTD) with those for PFS, and did not note any large discrepancies for either treatment.

Crossover to the alternative treatment at PD, unacceptable toxicity or withdrawal of consent was not part of the study protocol but patients could receive the alternative treatment as subsequent therapy if it was available and clinically indicated at their local centre. After discontinuation of the study drug, the protocol stated that patients would be followed up for long-term survival and collection of subsequent therapy information. Subsequent therapy data were requested by the ERG at the clarification stage but the company confirmed they had only been captured for 41% of the 173 patients (68 alectinib and 105 crizotinib) who had progressed and permanently discontinued study treatment (Table 7). A higher proportion of patients who received 1L crizotinib received a TKI at 2L (31.4%) than those who received alectinib (19.1), a higher proportion of alectinib-treated patients received 2L platinum chemotherapy (23.5%) than those who received crizotinib (5.7%), and a similar number received the alternative study drug off protocol (7.6% alectinib to crizotinib and 8.8% crizotinib to alectinib, respectively). The ERG

recommends caution in interpreting any differences due to the incompleteness of the dataset, which limits what can be inferred about any possible imbalances and comparability to UK clinical practice. The full breakdown of subsequent therapies for the 41% is provided in Appendix 10.5. The possible impact of subsequent therapies is discussed in the context of OS in Section 4.3.5.1.

Table 7. Subsequent therapies captured in ALEX for 41%* of patients who have permanently discontinued study treatment (adapted from clarification response, Table 3)

	Alectinib		Crizotinib	
Treatment	**2nd line (n = 68)**	**3rd line + (n = 68)**	**2nd line (n = 105)**	**3rd line + (n = 105)**
Any subsequent anti-cancer therapy	31 (45.6%)	9 (13.2%)	40 (38.1%)	4 (3.8%)
TKI (ceritinib, crizotinib, alectinib, lorlatinib, brigatinib, gefitinib, entrectinib, erolotinib)	13 (19.1%)	5 (7.4%)	33 (31.4%)	3 (2.9%)
Platinum compound (carboplatin, cisplatin)	16 (23.5%)	3 (4.4%)	6 (5.7%)	0 (0.0%)
Antimetabolite (pemetrexed, gemicitabine)	14 (20.6%)	3 (4.4%)	6 (5.7%)	0 (0.0%)
Taxane (paclitaxel, docetaxel)	3 (4.4%)	0 (0.0%)	0 (0.0%)	1 (1.0%)
Immunostimulant (nivolumab)	0 (0.0%)	2 (2.9%)	0 (0.0%)	0 (0.0%)
Angiogenesis inhibitor (bevacizumab)	2 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other (cyclophosphamide, antineoplastic agent NOS, anti PD-L1, doxorubicin, vincristine)	3 (4.4%)	1 (1.5%)	1 (1%)	0

Abbreviations: NOS, not otherwise specified; PD-L1, programmed death-ligand; TKI, tyrosine kinase inhibitor
*Subsequent therapies are not known for the remaining 59% of patients who have permanently discontinued study treatment.

The ERG considers ALEX to be a well-conducted study that provides high quality evidence to support the decision problem. The open-label design has implications on the reliability of some outcomes and, where both are available, the ERG considers those captured by IRC to be more reliable than those assigned by INV. The CNS progression data presented in the CS could not be interpreted as a subset of PD as was initially done in the company's economic model, because CNS progression could be assigned by one of two separate IRC processes (RECIST or CNS RECIST); this issue was flagged by the ERG during the clarification process and an adapted model was submitted by the company based on alternative data for CNS PFS and PFS (Section 4.3.2). Treatment beyond asymptomatic CNS progression, which may not be detected in clinical practice, could continue until symptomatic CNS progression or systemic progression in ALEX.[25] The ERG notes from clinical experts and related STAs (TA500 and TA422) that treatment with ALK-TKIs in UK clinical practice may be guided by symptoms rather than radiographic evidence of PD, particularly if it is at a single site and subsequent treatment options are limited. The incomplete capture of subsequent therapies means it is difficult to assess the applicability of OS results to UK patients.

4.2.2 Baseline characteristics

Section 3.1 contains the ERG's critique of how well the ALEX population reflects the population outlined in the NICE final scope,[1] and patients in England who might be eligible for treatment with alectinib. The ERG's clinical experts considered the ALEX population largely reflective of UK patients

with ALK+ advanced NSCLC but highlighted that the patients may be considered somewhat healthier than would be seen in clinical practice.

Baseline characteristics of the ALEX population are reproduced in Table 66, Appendix 10.4, which showed characteristics were generally well balanced between groups. The ERG notes that patients in the alectinib group were slightly older (median 58 vs 54), had a higher prevalence of brain metastases at baseline than patients in the crizotinib group (42% vs 38%) and a smaller proportion had ECOG PS of 0 (28.3% vs 35.8) than of 1 (65.1% vs 57.6%); the same low proportion had PS of 2 in both groups (6.6%). The differences may suggest that the alectinib group may have had somewhat worse prognosis than the crizotinib group, but the company did not present statistical tests to assess the significance of the apparent differences. Subgroup analyses of IRC PFS provided at the clarification stage by age did not suggest the difference in age has a significant effect on PFS (< 65, ≥65 years), and while the results for presence of IRC-assessed CNS metastases at baseline and ECOG PS (separately for 0, 1 and 2) did show some differences in effect size, confidence intervals were all overlapping (Section 4.3.5).

The ERG's clinical experts confirmed that, compared with the wider lung cancer population, the relatively young population (~55 years), high proportion of women (56.4%) and non-smokers (61.7%), and significant proportion with CNS metastases at baseline (~40%) are all characteristic of the UK population affected by ALK+ NSCLC. The ERG notes that only patients with asymptomatic CNS metastases, or those who had completed radiotherapy 14 days prior to the trial, were eligible for ALEX. The percentage of patients with known CNS metastases at baseline is likely to be lower in UK clinical practice because asymptomatic patients are not scanned routinely. The ERG's clinical experts noted that the percentage of patients with ECOG performance score of two is lower than they would expect (7% in both groups), suggesting the ALEX population may be a relatively healthy subset of the full population who might be eligible for alectinib should it be approved for use in England.

Most patients in ALEX had adenocarcinoma histology (90% and 94% for alectinib and crizotinib, respectively) and stage IV disease (97% and 96%); a small proportion in both groups had stage IIIb, which is also classed as advanced disease. Around a quarter of patients in both groups had more than three lesions, but the majority had between one and three. The most common target lesions used for the RECIST assessment for PD were lung, pleura or pleural effusion (81.5% and 82.2% for alectinib and crizotinib, respectively), lymph nodes (47.0% and 50.7%), liver (23.2% and 17.8%) and CNS (8.6% and 11.8%).

Only three patients (1%) were recruited from UK centres, 97 (32%) from other Western European countries (Italy, Spain, Portugal, France and Switzerland), 42 from North America (14%), and 124 (41%) from Asian countries (South Korea, Hong Kong, Thailand, Singapore, Taiwan and China); other recruitment regions included Australasia, Eastern Europe and South America. The ERG's clinical

experts advised that the baseline characteristics suggest the ALEX population may be somewhat fitter than would be seen in UK clinical practice, but are nonetheless generally reflective of patients in England that would be eligible for alectinib. Furthermore, the prior non-systemic treatments received for NSCLC (e.g. radiotherapy or surgery) reflect what patients might have received prior to 1L systemic therapy for ALK+ advanced NSCLC.

4.2.3 Description and critique of statistical approach used

The power calculation for ALEX was based on the primary outcome, INV PFS. The calculation assumed 170 events, a median PFS of 10.9 months in the crizotinib group, a target HR of 0.65 for alectinib versus crizotinib, and non-linear recruitment over 24 months to yield 80% power of the log-rank test at a two-sided alpha level of 5% (CSR,[35] pg 55). Slightly fewer events had occurred at the primary data cut than planned (163 vs 170), but the observed median PFS for crizotinib was similar (11.1 months), and the HR showed a larger effect of alectinib than the assumption on which the calculation was based (HR 0.47). No interim efficacy or futility interim analyses were conducted. Analysis of secondary efficacy endpoints was conducted in a hierarchical sequence after INV PFS (IRC PFS, time to CNS progression, ORR, OS). A summary of how outcomes were defined, measured and analysed is provided in Table 8, including which were the company's and ERG's preferred analyses.

Table 8. Summary of ALEX efficacy outcomes included in the CS from clinical cut-off 9th February 2017

Outcome	Description	Measurement	Analysis	Preference	Pop	Subgroups
Outcomes covered by NICE final scope[1]						
Progression free survival (PFS)	INV: Time from randomisation to investigator-assigned date of first-documented PD or death (any cause)	RECIST v1.1, 8-weekly scans assessed real-time by the investigator	KM, stratified log-rank, stratified cox regression (HR, 95% CI)	Original	ITT	Age, sex, race, smoking status, ECOG PS, CNS mets at BL, prior brain radiation
		RECIST v1.1, 8-weekly scans assessed by IRC	KM, stratified log-rank, stratified cox regression (HR, 95% CI)	ERG	ITT	
	IRC: incorporating events based on CNS RECIST criteria	RECIST v1.1 + CNS RECIST combined	KM, stratified log-rank, stratified cox regression (HR, 95% CI)	Company	ITT	NA
Overall survival (OS)	Time from randomisation to the date of death (any cause)	NA	KM, stratified log-rank, stratified cox regression (HR, 95% CI)	NA	ITT	Subsequent tx, CNS at BL (*post-hoc*)
Objective response rate (ORR)	Percentage of patients with complete or partial response (CR or PR) by INV (IRC also available in CSR)	RECIST v1.1, based on 8-weekly scans	Clopper-Pearson with 95% CI for rates, Mantel-Haenszel for difference	NA	ITT	
Health-related quality of life (HRQoL)	EQ-5D-3L	4-weekly until PD, 8-weekly for 6 months, then 12-weekly	Mixed model (treatment, sex, age, rage, CNS mets at BL, PD as variables)	ERG and company	ITT	CNS mets at BL
	EORTC QLQ-C30 and LC 13	4-weekly until PD: symptoms, treatment/ disease burden	Time to deterioration, % with clinically meaningful improvement (≥10 points), mean change from BL (SD)	NA	ITT	NA
Additional outcomes not in NICE final scope						
Duration of response (DOR)	Time from first documented CR or PR to first documented PD or death	Based on ORR data, RECIST v1.1 8-weekly	KM, cox proportional regression (HR, 95% CI)	NA	CR or PR	CNS mets at BL
Time to CNS progression	Time from randomisation to radiographic evidence of CNS progression by IRC	RECIST v1.1 + CNS RECIST combined	Log-rank cumulative incidence, Gray's competing risks (non-CNS PD, death), stratified log-rank and cox regression.	Company	ITT	+/- pre-treatment radiation therapy for CNS lesions
		RECIST-only		ERG		
CNS ORR, PR and DOR	IRC-assigned intracranial response in those with CNS mets at BL	CNS RECIST	Clopper-Pearson with 95% CI for rates, Mantel-Haenszel for difference	NA	CNS mets at BL	NA

Abbreviations: BL, baseline; CI, confidence interval; CNS, central nervous system; CNS mets, CNS metastases; CSR, clinical study report; EORTC LC13, lung cancer module; EORTC QLQ30, EORTC core 30 questionnaire; EQ-5D-3L, ERG, evidence review group; HR, hazard ratio; INV, investigator-assessed; IRC, independent review committee; ITT, intent-to-treat; NA, not applicable; RECIST, Response Evaluation Criteria in Solid Tumours; SD, standard deviation, tx, treatment.

The intent-to-treat (ITT) population, including all randomised patients, was used for the INV PFS, IRC PFS, CNS PFS, ORR and OS analyses. The safety population was used for AE analyses, defined as all patients who had received at least one dose of study medication (which was the full ITT population). Duration of response (DOR) included all patients meeting RECIST criteria for partial response (PR) or complete response (CR), i.e. the ORR population. The ERG understands that CNS-specific ORR included only patients with CNS metastases at baseline, and CNS-specific DOR included patients with baseline CNS lesions that met criteria for CNS ORR by CNS RECIST.

PFS, OS and DOR were analysed using the Kaplan-Meier method to estimate medians with 95% confidence intervals (CIs) for each arm and survival curves. Stratified Cox proportional regression models including treatment were used to estimate relative treatment effects expressed as a hazard ratio (HR) with 95% CI. At the clarification stage, the company confirmed that the proportional hazards assumption does not hold for OS or PFS, supporting the fitting of independent curves for the review of cost-effectiveness.

IRC CNS PFS, which was not listed in the NICE final scope,[1] was originally analysed with the log-rank test including death and non-CNS progression as competing risks, to compare time to CNS progression only in patients who had not experienced prior non-CNS progression or died. The CS described the outcome as being based on RECIST criteria, but the company confirmed at the clarification stage that the analysis included the first CNS event from two separate IRC procedures: the main IRC assessment for PD based on RECIST v1.1, and a separate IRC assessment using CNS RECIST specifically to assess intracranial disease (see Section 4.2.1). The company confirmed that the different criteria for progression meant CNS progressions could not be interpreted as a subset of PD assigned by RECIST v1.1, which invalidated the way CNS progressions had been assumed as a proportion of all progressions for the assessment of cost effectiveness.

At the clarification stage, the company provided more information about trial procedures for assessing PD and CNS progression, and submitted revised analyses for PFS and CNS PFS (Table 9). The company's preferred analysis of PFS, hereafter referred to as 'adapted PFS', incorporated CNS events from the separate IRC CNS RECIST assessment to reflect their preferred analysis of CNS PFS and ensure internal consistency in the economic model. The company stated that the analyses based on IRC RECIST+IRC CNS RECIST are, "the most complete and robust analysis of the impact of CNS metastases", but accepted that events captured by CNS RECIST, "may be earlier than would be in clinical practice as CNS RECIST is not routinely used in the NHS" (company clarification response to question A10). The ERG considers PFS and CNS PFS based on RECIST-only events more applicable to UK clinical practice. The company did not provide sufficient detail about events that could occur in a sequence for individual patients, and how often this happened – e.g. CNS progression by CNS

RECIST preceding PD with CNS involvement by RECIST – for the ERG to confirm that events had been counted or censored appropriately in each analysis to avoid double counting.

Further uncertainty was introduced because neither CNS PFS analysis (RECIST+CNS RECIST and RECIST-only) censored patients who experienced non-CNS PD (i.e. PD not involving the CNS), meaning some CNS events in the analysis were secondary to systemic PD. The company justified this approach because censoring non-CNS PD caused the curves to cross the OS curve. The ERG does not understand why this would be the case (see Section 5.4.5.2) and considers the inclusion of secondary CNS progression a potential confounding factor in the CNS PFS analyses, particularly because, "after the first progression event, further progression events have not been systematically captured" (company response to CQ A9).

Table 9. Progression-free survival and CNS progression options (adapted from updated company clarification response to ERG question B1, Table 1)

Approach	Data source for PFS	Data source of CNS PFS	Censoring rules for CNS PFS
Original approach in CS with error	ALEX KM data for INV-assessed PFS from ALEX (RECIST v1.1)	Proportion of patients with IRC-assessed CNS progression from either RECIST or CNS RECIST applied as a percentage to PD in the model	Competing risks analysis censoring patients who had a prior non-CNS progression or died before CNS progression.
New company base case: RECIST v1.1 and CNS RECIST	New analysis using PFS as per IRC (RECIST v1.1 and CNS-RECIST)	New analysis using CNS PFS as per IRC (based on both RECIST and CNS-RECIST)	CNS progression = event Death = event Lost to follow-up = censor Time was the first of: •Measured CNS progression •Death •Lost to follow-up
Scenario analysis: RECIST only (ERG preference)	ALEX KM data for IRC-assessed PFS (RECIST v1.1)	New analysis using CNS PFS as per IRC (based on both RECIST and CNS-RECIST)	

Abbreviations: CNS, central nervous system; INV, investigator; IRC, independent review committee; KM, Kaplan-Meier; RECIST, Response Evaluation Criteria for Solid Tumours version 1.1.

The following subgroup analyses were reported in the CS for INV PFS, and were provided during the clarification process for IRC PFS at the ERG's request (CSR,[35] pg 60): age (< 65, ≥65 years), sex, race (Asian, non-Asian), smoking status, baseline ECOG PS, CNS metastases at baseline by IRC, and prior brain radiation. There were no prespecified subgroup analyses for OS but results were provided during the clarification process at the ERG's requested *post-hoc* analyses to explore the effect of subsequent therapies (any subsequent anti-cancer therapy versus no subsequent anti-cancer therapy, and subsequent tyrosine kinase inhibitor (TKI) vs subsequent non-TKI) and CNS metastases at baseline (present vs absent).

During clarification, the ERG also requested an analysis to explore how CNS progression during ALEX impacted OS. The company considered a regression analysis unreliable due to the immaturity of OS in ALEX, and instead conducted landmark analyses for 6 and 12-month PD in the CNS as a predictor of

OS. Two sets of landmark analyses were conducted to mirror the analysis options for PFS and CNS PFS, i.e. CNS progression based on RECIST only and based on RECIST+CNS RECIST.

Patient reported outcomes, including health-related quality of life, disease burden/morbidity, treatment burden/tolerability, and health status on the EuroQol 5 dimensions 3-levels questionnaire (EQ-5D-3L) were analysed and reported in a variety of ways in the CS and CSR. Analyses included percentage of patients with clinically meaningful improvement, time to confirmed clinically meaningful symptom deterioration. Only a narrative summary of results was provided in the CS but additional raw data were made available at the clarification stage.

Adverse events were reported as the number and percentage of patients experiencing at least one of a given type or severity of event. A variety of summary and specific measures were reported in the CS which gave a comprehensive overview of the safety profile of alectinib compared with crizotinib. Where between-group effects were reported, they were given as odds ratios (OR) with 95% CI using patients as the unit of analysis.

In summary, the ERG considers the statistical approach taken by the company mostly appropriate. However, insufficient information was submitted for the ERG to assess the reliability and internal consistency of the adapted analyses of PFS and CNS PFS. The company provided various exploratory analyses at the clarification stage to assess the robustness of key outcomes, and conducted *post-hoc* subgroup analyses to explore the effect of key moderators on IRC PFS and OS.

4.2.4 Summary statement

The company conducted a comprehensive SLR to identify relevant evidence to support the assessment of alectinib for ALK+ advanced NSCLC. While most of the studies listed as 'included' were not used in the CS, the ERG agrees that ALEX alone provides high quality and relevant evidence to support the decision problem. The ERG notes that retrospective chart reviews, which were not considered in the company's SLR, may provide useful real-world evidence with which to compare the efficacy of crizotinib in ALEX.

ALEX is a multicentre phase III randomised trial including 303 adults with untreated and histologically confirmed ALK+ advanced NSCLC. People who met the eligibility criteria were randomised to receive alectinib 600 mg twice daily (n = 152) or crizotinib 250 mg twice daily (n = 151). Randomisation was stratified by ECOG PS (0/1 vs 2), race (Asian vs non-Asian) and presence of CNS metastases at baseline (yes vs no). The ERG agrees with the company that ALEX provides appropriate head-to-head evidence that closely matches the population, intervention, comparator and outcomes listed in the NICE final scope for this STA.[1]

The ERG considers ALEX to be a well-conducted RCT that provides high quality direct evidence for alectinib compared with the relevant comparator, crizotinib. Evidence synthesis was not necessary because the design of ALEX covers the population, intervention, comparator and outcomes outlined in the NICE final scope.[1] The ERG notes that OS data from ALEX are immature and the open-label design has implications on the reliability of some outcomes; where both are available, the ERG considers those captured by IRC likely to be less biased than those assigned by INV. The ERG highlights that some aspects of the design of ALEX, namely rules regarding treatment beyond PD (treatment could be continued only beyond asymptomatic CNS progression, which may not be detected in clinical practice) and the incomplete capture of subsequent therapies, may affect the applicability of OS to patients receiving the treatments in England.

Only 1% of the ALEX population were recruited from UK centres. The ERG's clinical experts advised that baseline characteristics of the full ALEX population are, nonetheless, in line with the population outlined in the NICE final scope,[1] but are likely to represent a relatively healthy subset of UK patients who might receive a 1L ALK-TKI in UK clinical practice (ALEX included few patients with ECOG PS of 2). The ERG's clinical experts explained that, compared with the wider lung cancer population, the population of ALEX reflects that patients with ALK+ NSCLC are generally younger, more often female, non-smokers, and more commonly have CNS metastases at earlier stages of the disease. Characteristics were generally well balanced between groups, but some imbalances in ALEX (age, brain metastases at baseline, ECOG PS) may suggest the alectinib group were somewhat less healthy than the crizotinib group at baseline.

The ERG considers the statistical approach taken by the company generally appropriate. The ERG could not verify the company's preferred analyses of adapted PFS and CNS PFS, which were submitted at the clarification stage after an error was identified in the way CNS progression was presented. The company's preferred analyses incorporated events from two IRC procedures in ALEX – the main RECIST procedure and a separate procedure based on the modified CNS RECIST – into PFS and CNS PFS. The ERG preferred the analyses based on standard RECIST only (which were provided as a scenario analysis) because they are likely to be the most clinically relevant, and more comparable to other trials and NICE technology assessments.

4.3 Clinical effectiveness results

The company submitted clinical effectiveness results from ALEX for the following outcomes:

- OS;
- PFS: INV, IRC RECIST+IRC CNS RECIST and IRC RECIST-only;

- CNS PFS: IRC RECIST+IRC CNS RECIST and IRC RECIST-only (original competing risks analysis from CS not covered by the ERG because an error was identified);
- Response: ORR and DOR (INV and IRC), and CNS ORR and DOR for patients with CNS lesions at baseline;
- HRQoL: EORTC QLQ-C30 and EORTC LC13 and EQ-5D-3L;
- Adverse events.

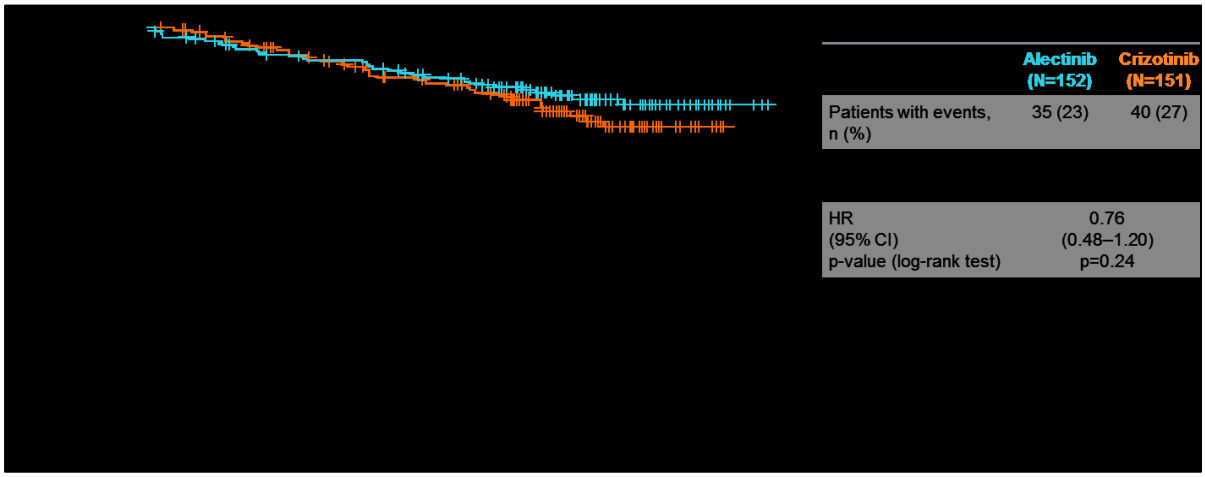
The ERG provides a critique of the submitted evidence from ALEX, with details of the company's and ERG's preference where more than one analysis was submitted for a given outcome. Full details of the analysis options and statistical approach are discussed in Section 4.2.3, and an overview is provided in Table 8.

4.3.1 Overall survival (OS)

At the February 2017 data cut-off, 35 patients (23.0%) in the alectinib group and 40 (26.5%) in the crizotinib group had died (KM plot reproduced in Figure 3). ALEX was not powered to detect a significant difference in OS and the median had not been reached in either group. Median follow-up at data cut-off was 18.6 months and 17.6 months in the alectinib and crizotinib groups, respectively (CS pg 32) and [redacted]

The hazard ratio (HR) for alectinib versus crizotinib lies in favour of alectinib but the difference is not statistically significant (HR 0.76; 95% CI: 0.48 to 1.20; p-value 0.24), and 12-month survival rates were similar at 84.3% for alectinib (95% CI: 78.4 to 90.2%) and 82.5% for crizotinib (95% CI: 76.1 to 88.9%). The HR should be interpreted with caution because an assessment provided at the clarification stage indicated proportional hazards (PH) do not hold (response to clarification question [CQ] B2).

Figure 3. KM plot of overall survival (OS) in ALEX stratified ITT analysis (reproduced from CS, Figure 5, pg 33)



Abbreviations: CI, confidence intervals; HR, hazard ratio; NE, not estimable; OS, overall survival.

The company propose that the long-term OS benefits of alectinib seen in the extrapolations for the review of cost-effectiveness is justified because the curves begin to separate at 18 months (Figure 3):

[…] "this trend is plausible, given the OS benefit and diverging KMs [Kaplan-Meier curves] observed within the trial (despite not being powered to demonstrate statistical improvement); the benefit derived from alectinib PFS and importantly, the protective CNS effect alectinib has demonstrated" (CS pg 59).

The ERG considers that a long-term OS benefit of alectinib versus crizotinib is currently unconfirmed by data from ALEX, and the ERG is unaware of any longer-term data for alectinib from other studies to support projections beyond the ALEX follow-up. The ERG's clinical experts did not consider the divergence of the curves at 18 months in Figure 3 demonstrated an OS benefit for alectinib over crizotinib, but do expect that the benefits of alectinib shown in ALEX for PFS and CNS metastases (Section 4.3.2) will translate to an OS benefit in clinical practice.

The ERG consulted clinical experts to assess the following:

- how closely crizotinib OS in ALEX reflects what is currently seen in UK practice;
- the relevance of longer-term data for crizotinib OS from PROFILE 1014 to this appraisal;
- the clinical plausibility of the extrapolation for alectinib and crizotinib for the review of cost-effectiveness.

The ERG's clinical experts did not have experience of alectinib because it is not yet available in the UK, and no real-life evidence has yet been published. For crizotinib, estimates from clinical experts suggested most people with ALK+ advanced NSCLC are expected to live for between 1 and 3 years

from initiation of treatment. The experts' experience is substantiated by a recent audit of crizotinib use for ALK+ advanced NSCLC at 20 UK centres since it was added to the Cancer Drugs Fund in 2012.[48] Median OS for the 99 patients in the audit was 13.5 months, which does not reflect the 1-year survival rates of over 80% for patients allocated to crizotinib in ALEX and PROFILE 1014,[37] or the 4-year survival in PROFILE 1014 of 56.6%.[28] Comparisons of OS in ALEX and PROFILE 1014 with the audit population are limited because the latter included 2L crizotinib use (and later), but the ERG nonetheless consider the audit data[48] a useful source of real-world evidence that was not considered in the CS.

More mature OS data for crizotinib for comparison with ALEX are available from PROFILE 1014 (median follow-up 46 months), which the company use to validate long-term OS for the review of cost-effectiveness (CS pg 62). Median OS for crizotinib has still not been reached in PROFILE 1014, though the company state that the population of PROFILE 1014 is generally healthier than that of ALEX, so median OS for crizotinib in ALEX is expected to be shorter. Comparing the crizotinib groups in ALEX and PROFILE 1014, the ERG notes the difference in the proportion of patients with brain metastases at baseline (38% in ALEX vs 26% in PROFILE 1014), and prior treatment for brain metastases (15% in ALEX vs 23% in PROFILE 1014), which may support the company's assertion, but considers other characteristics (i.e. age, ECOG performance status, stage of disease and smoking history) comparable between the two trials (Table 61).

The ERG thus highlights several factors that affect the applicability of OS from ALEX to UK clinical practice:

- Patients in ALEX (and PROFILE 1014) may be healthier than patients seen in UK clinical practice. The audit of crizotinib use in England[48] has not yet been published in full and so it is not possible to assess the comparability of its patient characteristics with the population of ALEX and PROFILE 1014. The percentage of patients with ECOG PS 0 or 1 was considerably lower in a French chart review of crizotinib use[27] (77.3%) than ALEX (93%) and PROFILE 1014 (94%).

- Subsequent treatment options may be more limited in the UK than in ALEX. The ERG's clinical experts expressed concern about the availability of appropriate 2L therapies for use after second-generation ALK-TKIs such as alectinib, whereas ceritinib is approved for use after 1L crizotinib in England. The potential impact of subsequent treatments after discontinuation of the study drug is discussed with results from subgroup analyses in Section 4.3.5.1.

- Continued treatment beyond asymptomatic CNS progression was allowed in both groups in ALEX at the discretion of the investigator (Section 3.2), but was stopped at symptomatic CNS progression or systemic PD. Observational evidence has shown treatment with crizotinib

beyond PD can lead to additional clinical benefit,[27, 49] but the ERG notes the practice was uncommon in both groups in ALEX (when TTD curves are compared with PFS curves). Treatment beyond PD is not indicated in the EPAR for alectinib, but TA422 (2L crizotinib) and TA500 (1L ceritinib) both suggest that ALK inhibitors are commonly used until symptomatic rather than radiological progression in UK clinical practice[10], particularly when subsequent treatment options are limited.

The ERG notes that OS data from ALEX are immature and does not consider the study to provide robust evidence for a long-term OS benefit of alectinib compared with crizotinib. For the reasons described above, comparative OS from ALEX may not be a reasonable reflection of what would be seen in UK clinical practice.

4.3.2 Progression free survival (PFS)

The company submitted three analyses of PFS based on data from ALEX, and all showed significant benefits of alectinib over crizotinib. INV PFS (RECIST; Figure 4) was the primary outcome of ALEX; the median was not reached in the alectinib group and was 11.1 months in the crizotinib group (95% CI: 9.1 to 13.1 months) based on median follow-up of 18.6 months in the alectinib group and 17.6 months in the crizotinib group (HR for alectinib vs crizotinib 0.47; 95% CI: 0.34 to 0.65, p-value < 0.0001). The ERG advises caution when interpreting HRs because an assessment conducted by the company suggest PH do not hold (response to CQ B2).

Median IRC PFS (RECIST; Figure 5), which was the ERG's preferred analysis, was 25.7 months for alectinib (95% CI: 19.9 months to not estimable) and 10.4 months for crizotinib (95% CI: 7.7 to 14.6 months; HR for alectinib vs crizotinib 0.50; 95% CI: 0.36 to 0.70, p-value < 0.0001).

Concordance data for INV PFS and IRC PFS in the CSR (Appendix 10.6, [redacted] The ERG considers IRC PFS likely to be less biased than the INV PFS due to the open-label design of ALEX.

Adapted IRC PFS (RECIST+CNS RECIST; Figure 6), submitted at the clarification stage, became the company's preferred analysis (see Section 4.2.3 and Table 9). The company did not provide descriptive data or a breakdown of events, meaning the impact of incorporating the additional CNS RECIST events could not be quantified fully. The difference in total number of events (i.e. PD and deaths) between IRC PFS (RECIST; [redacted]) and the adapted IRC PFS (RECIST+CNS RECIST; [redacted]) was [redacted]

events, indicating the [redacted].

Figure 4. KM plot of INV-assessed PFS (RECIST v1.1) in the ITT population (reproduced from CS Figure 3, pg 30)

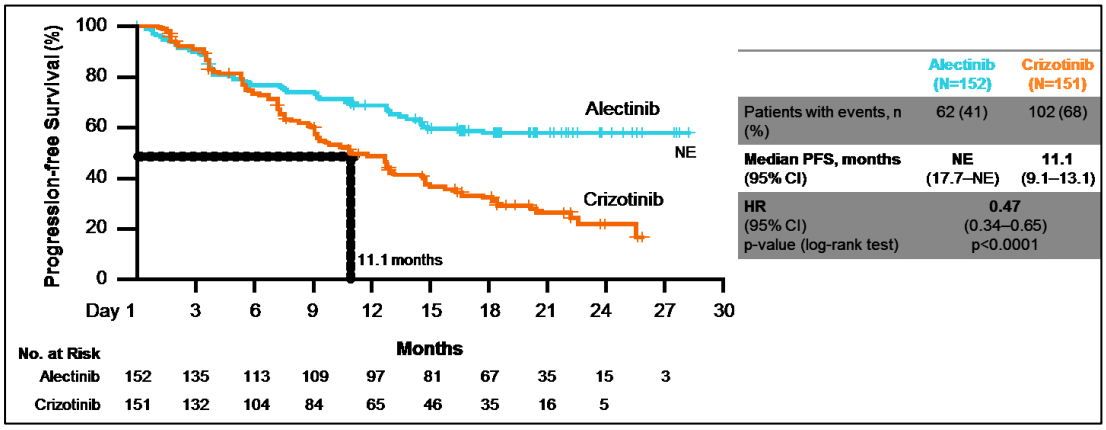


Figure 5. KM plot of PFS by IRC (RECIST v1.1) in the ITT population (reproduced from CSR Figure 5, pg 92)

REDACTED

Figure 6. Adapted PFS (IRC RECIST + CNS RECIST) Kaplan-Meier curves and extrapolation (reproduced from company clarification response to question B1, Figure 11)

REDACTED

The ERG is concerned that CNS RECIST is not widely used and may be a more sensitive than RECIST, and that incorporating events based on that assessment could lead to different conclusions than would be drawn based on IRC PFS (RECIST). As such., the ERG attempted to clarify how often patients had an event that met criteria for CNS progression by CNS RECIST before it met RECIST criteria for PD, and notes this happened more frequently in the crizotinib group than the alectinib group (24 vs 4, respectively; company response to CQ A9). Furthermore, the mean time between the events was 71 days and 43 days, respectively (company response to CQ A9). The company confirmed that events captured by CNS RECIST, "may be earlier than would be in clinical practice as CNS RECIST is not routinely used in the NHS" (response to CQ A10).

The ERG understands that any given patient could be represented differently in IRC PFS (RECIST) and adapted PFS analysis (RECIST+CNS RECIST) because patients could have more than one 'type' of progression event captured over the course of ALEX. The ERG considered that, if CNS progression was likely to meet CNS RECIST criteria before RECIST criteria, there would be inconsistency between IRC PFS (RECIST) and adapted PFS (RECIST) where both happened during ALEX. There is no inconsistency in scenarios where the first event captured was death or a PD by RECIST, which would be counted as the primary event in the company's and the ERG's preferred option.

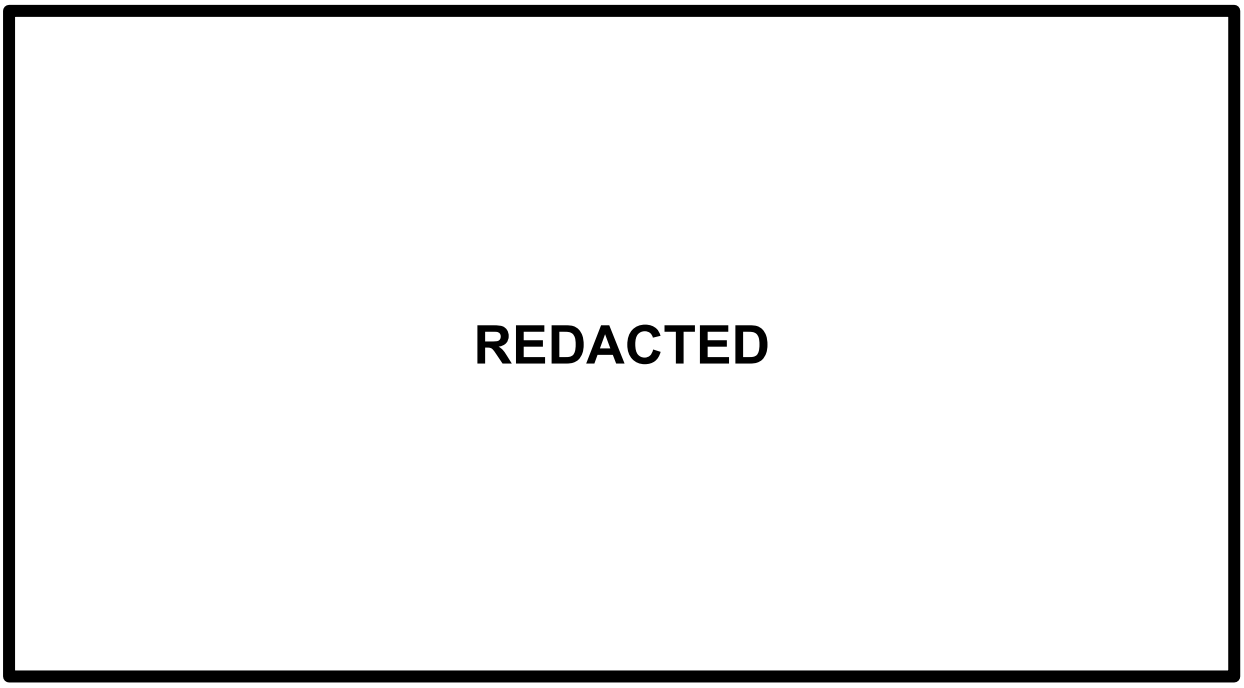
Given the reservations of the ERG's clinical experts about the clinical plausibility of OS observed in ALEX in the UK setting, the ERG compared the ALEX IRC PFS data (RECIST) with other RCTs, clinical expert opinion, and results from real-world cohorts. Median IRC PFS on crizotinib in ALEX is comparable to PFS observed for crizotinib in PROFILE 1014 (10.9 months), the J-ALEX study (10.2 months), and the audit of crizotinib use in England (9.8 months).[48] The ERG's clinical experts expected median PFS on crizotinib to be between 6 and 12 months, which is in line with the company's explanation that the curve divergence after 6 months most likely reflects where patients begin to relapse on crizotinib (CS pg 29). However, the experts expected that nearly all patients would have progressed on crizotinib by 24 months, [redacted].

The ERG's clinical experts did not have experience with alectinib because it is not yet available for use in any indication in the UK, but median IRC PFS was similar in ALEX and J-ALEX (25.8 and 25.9 months, respectively). As described in Section 3, the ERG does not consider J-ALEX relevant to the scope of this STA. The ERG did not identify any relevant real-world KM data for alectinib to substantiate the clinical plausibility of the company's PFS extrapolations for the company's review of cost-effectiveness.

4.3.2.1 CNS progression-free survival (CNS PFS)

The company's preferred analysis of CNS PFS mirrored their preferred analysis of PFS by incorporating events based on IRC RECIST and IRC CNS RECIST. A scenario analysis of CNS PFS based only on CNS events from the IRC RECIST assessment was also provided, which was the ERG's preference. Results from both analyses are shown in Figure 7. Descriptive statistics for the two CNS PFS options were not provided, but the curves for each demonstrate a benefit for alectinib compared with crizotinib. As with adapted PFS (RECIST+CNS RECIST), the difference between treatments [redacted] (blue solid line versus red dashed line; Figure 7) than when [redacted] (green solid line versus purple dashed line; Figure 7).

Figure 7. CNS PFS endpoints: RECIST+CNS-RECIST, versus RESIST only (reproduced from company's updated clarification response, Figure 13)



[redacted], but the measure may not reflect how progression is assessed and managed in UK clinical practice. As described above, the ERG understands CNS RECIST to be a more sensitive measure of intracranial lesions that may not meet criteria for PD by RECIST, which causes the same conflict described for PFS, i.e. patients could have both assigned over the course of the study and a different event for the same patient used in each analysis. As with adapted PFS, the ERG understands that the multiplicity of events means that any given patient could be represented differently in CNS PFS (RECIST) and CNS PFS (RECIST+CNS RECIST). It follows that there is no conflict between the analysis options in scenarios where the first event captured was death or a RECIST-defined PD, as the same event would be counted in the company's and the ERG's preferred options.

The ERG assumes that CNS progressions that met RECIST criteria represent a patient's systemic PD, and would have been counted in the PFS analysis. It follows that the number of events in the RECIST+CNS RECIST curve ( ) minus the number of events in the RECIST-only curve ( ), should leave the number of events that met CNS RECIST criteria but not RECIST criteria (both curves include primary deaths and secondary CNS events, see below). The numbers from this calculation are to the number of patients in each group recorded as having a CNS progression before systemic PD by IRC RECIST (4 and 24 patients in the alectinib and crizotinib groups, respectively; company response to CQ A9a).

Neither CNS PFS analysis (RECIST+CNS RECIST or RECIST-only) censored patients who had non-CNS PD (i.e. PD not involving the CNS) prior to a CNS event, meaning some CNS events in the analysis were secondary to systemic PD. The company justified this approach because censoring non-CNS PD caused the curves to cross the OS curve, but the ERG does not understand why this would be the case (see Section 5.4.5.2). The company did not provide a breakdown of the number of primary and secondary CNS events included in the analyses based on RECIST+CNS RECIST or RECIST-only, and the ERG could not use the data provided to calculate them with any certainty. The inclusion of secondary events may not be justified because there was inconsistency in the company's response to clarification regarding whether they were captured systematically. One answer stated that, "follow-up for additional progressions was not routinely conducted once the first progression was seen on RECIST" (response to CQ B1) and another that, "any patient who experiences a non-CNS-progression prior to CNS-progression is followed until the first of CNS progression or death or loss to follow-up" (response to CQ A10).

The ERG considers that CNS PFS (RECIST) and CNS PFS (RECIST+CNS RECIST) both demonstrate the protective effect of alectinib in the CNS. The ERG considers the CNS PFS (RECIST) to provide the most consistent analysis of CNS progression with PFS (RECIST), which are likely to be the most clinically relevant and comparable to other STAs. The ERG highlights that non-CNS PD was not censored in either analysis meaning secondary CNS events are represented, which makes the results difficult to interpret in relation to PFS.

4.3.3 Response

More patients in the alectinib group met criteria for ORR according to RECIST v1.1 than the crizotinib group according to the INV , but odds ratios (OR) indicate the difference between groups isn't statistically significant (Table 10).

[redacted] As with PFS, the ERG considers that the IRC assessment is likely to be less biased than the INV assessment, due to the open-label design of ALEX.

Table 10. Investigator-assessed (INV) and independent review committee (IRC) response according to RECIST v1.1 in the ALEX ITT population (adapted from CS Table 8, CSR Table 18 and CSR pg 576)

	INV assessment		IRC assessment	
Outcome	**Alectinib (n = 152)**	**Crizotinib (n = 151)**	**Alectinib (n = 152)**	**Crizotinib (n = 151)**
Objective response rate (ORR), n (%)	126 (82.9)	114 (75.5)	[redacted]	[redacted]
Stratified: OR (95% CI); p-value	1.62 (0.92 to 2.84); 0.09		[redacted]	
Unstratified: OR (95% CI); p-value	1.57 (0.90 to 2.76); 0.11		[redacted]	
Complete response (CR), n (%)	6 (3.9)	2 (1.3)	[redacted]	[redacted]
Partial response (PR), n (%)	120 (78.9)	112 (74.2)	[redacted]	[redacted]
Stable disease (SD), n (%)	9 (5.9)	24 (15.9)	[redacted]	[redacted]
Progressive disease (PD), n (%)	8 (5.3)	10 (6.6)	[redacted]	[redacted]
Missing or unevaluable, n (%)	9 (5.9)	3 (2.0)	[redacted]	[redacted]

Abbreviations: INV, investigator assessment; IRC, independent review committee; ITT, intention to treat; n, number of patients; RECIST, Response Evaluation Criteria in Solid Tumours
Factors for the stratified analysis were race (Asian vs. Non-Asian) and IRC CNS metastases at baseline (Yes vs. No).
Patients were classified as "Stable Disease" if assessment was at least 7 weeks from baseline/study entry. Patients were classified as "unevaluable" if all post-baseline response assessments were reported as not evaluable, or last assessment occurred within 7 weeks from baseline/study entry and was CR, PR or SD. Patients were classified as "Missing" if no post-baseline response assessments were available.

The company state that the similar ORRs for alectinib and crizotinib observed in ALEX are reflected in the overlapping PFS curves seen for the first six months ([redacted]), and that divergence of curves thereafter likely represents the point at which patients begin to relapse on crizotinib. Estimates of time to progression by the ERG's clinical experts support this explanation.

Median DOR among patients who met RECIST criteria for complete or partial response (i.e. ORR) was not estimable in the alectinib group and was 11.1 months in the crizotinib group (95% CI 7.9 to 13.0 months). The HR for alectinib versus crizotinib was 0.36 (95% CI: 0.24 to 0.53).

4.3.3.1 CNS response

The CS presents analyses of ORR and DOR for the subgroup of patients who had measurable and nonmeasurable CNS metastases at baseline, and for the subset of those patients who had received prior brain radiation (Table 11, from CS Appendix E). ORR was higher for patients treated with alectinib than those treated with crizotinib in all subgroups, but the difference was not statistically significant in patients with prior brain radiation because most patients in both groups responded. DOR was significantly longer for alectinib than crizotinib in the subgroup of patients who had measurable or nonmeasurable CNS lesions at baseline, but was not statistically significant when the analysis was restricted to patients who had only measurable CNS lesions at baseline (Table 11).

Table 11. Summary of CNS response outcomes from ALEX (adapted from CS Table 9, CS Appendix E Tables 20 and 21, and CSR Tables 20, 21, 23, 24 and 25)

	Measurable CNS lesions at BL		Measurable and nonmeasurable CNS lesions at BL		Prior brain radiation		No prior brain radiation	
	Alec	Criz	Alec	Criz	Alec	Criz	Alec	Criz
N	21	22	64	58	7	7	14	15
CNS ORR, n (%)	17 (81.0)	11 (50.0)	38 (59.4)	15 (25.9)	6 (85.7)	[redacted]	11 (78.6)	6 (40.0)
OR (95% CI) p-value	[redacted]		[redacted]		[redacted]		[redacted]	
CNS CR, n (%)	8 (38.1)	1 (4.5)	29 (45.3)	5 (8.6)	2 (28.6)	0 (0.0)	6 (42.9)	1 (6.7)
CNS PR, n (%)	9 (42.9)	10 (45.5)	9 (14.1)	10 (17.2)	4 (57.1)	5 (71.4)	5 (35.7)	5 (33.3)
CNS SD, n (%)	1 (4.8)	7 (31.8)	16 (25.0)	32 (55.2)	1 (14.3)	1 (14.3)	0 (0.0)	6 (40.0)
CNS PD, n (%)	2 (9.5)	3 (13.6)	4 (6.3)	6 (10.3)	0 (0.0)	0 (0.0)	2 (14.3)	3 (20.0)
Median DOR months (95% CI)	17.3 (14.8, NE)	5.5 (2.1, 17.3)	NE (17.3, NE)	3.7 (3.2, 6.8)	NR	NR	NR	NR
HR (95% CI) p-value	[redacted]		[redacted]		NR	NR	NR	NR

Abbreviations: Alec, alectinib; BL, baseline; CI, confidence interval; CNS CR, central nervous system complete response; CNS ORR, CNS objective response rate; CNS PD, CNS progressive disease; CNS PR, partial response; CNS SD, CNS stable disease; Criz, crizotinib; DOR, duration of response; NR, not reported.
The ERG noted an error in the reported CNS ORR for crizotinib-treated patients with prior brain radiation and provided the correct data from the CSR.
DOR was measured in the patients with CR or PR in that subgroup. Reported ORs and HRs are for the stratified analyses in CSR Table 20, 21, 23, 24 and 25.

The ERG understands that these analyses are based on the modified CNS RECIST criteria assessed by IRC, whereas the main ORR and DOR outcomes were based on RECIST by INV, which makes them difficult to compare. [redacted]

4.3.4 Health-related quality of life (HRQoL)

HRQoL data from ALEX had not been published at the time this report was written. HRQoL was measured with EuroQol 5-Dimensions 3-Levels tool (EQ-5D-3L) for overall health status, the European Organisation for Research and Treatment of Cancer Quality of Life Core 30 questionnaire (EORTC QLQ-C30), and the EORTC lung cancer module (EORTC LC13). Results from the EORTC scales, which include time-to-deterioration of lung cancer symptoms, patient functioning, treatment burden and tolerability, are discussed here, and results for the EQ-5D-3L are discussed in Section 5.4.8. Only the EQ-5D-3L data were incorporated in the review of cost-effectiveness, which the company does not believe to adequately capture the CNS benefit of alectinib.

A narrative summary of selected results was reported in the CS, mostly covering the number of patients experiencing clinically meaningful improvement or deterioration for subscales that showed a statistically significant difference between groups (CS pgs 33–34). Additional results provided at the

clarification stage were provided as the 4-weekly assessments for each subscale (mean, median, minimum and maximum scores, and change from baseline at 30 timepoints for 25 subscales), which could not be presented easily to give an overview of quality of life without further analysis. End of treatment scores were not reported, which may be because a significant proportion of patients remained on treatment at the primary data cut (84/152 in the alectinib group and 46/151 in the crizotinib group). As such, the ERG provides a critique of the narrative summary of results presented in the submission, supplemented by figures found in the CSR.

The CS describes that [redacted] alectinib-treated patients and [redacted] crizotinib-treated patients completed the baseline assessment. Questionnaire completion remained above 60% in the alectinib group until week 112, and until week 68 in the crizotinib group. The last assessment for which data were available for [redacted] of those with baseline assessments was [redacted] (CS page 33).

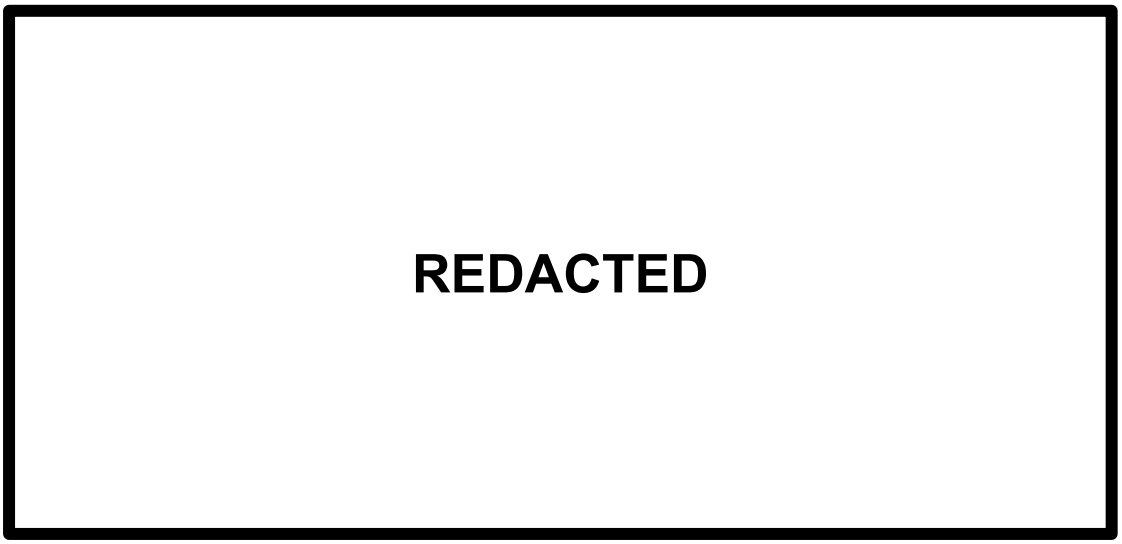
The CS states that [redacted] reported a confirmed clinically meaningful deterioration on a composite symptom endpoint based on EORTC LC13 (cough, chest pain, dyspnoea), and there was [redacted] in time to deterioration. The CS also states that [redacted] (CS page 34).

The CS states that results from the EORTC LC13 for commonly reported treatment-related AEs suggest [redacted] compared with crizotinib, and clinically meaningful improvement in [redacted] was observed for both treatment arms.

The CS reports [redacted] compared with crizotinib for Global Health Status/HRQoL on the EORTC QLQ-C30 ([redacted]). The KM plot for the outcome is reproduced from the CSR in Figure 8. The ERG does not consider there to be robust evidence for a meaningful difference between groups, particularly given the low questionnaire completion rates (described above) by the time the curves appear to diverge. The CS states that, on average, patients in the [redacted]

[redacted], though no numerical or graphical data were submitted to support this.

Figure 8. Time to deterioration in global health status/HRQoL on the EORTC QLQ-C30 (ITT population, reproduced from CSR Figure 15)



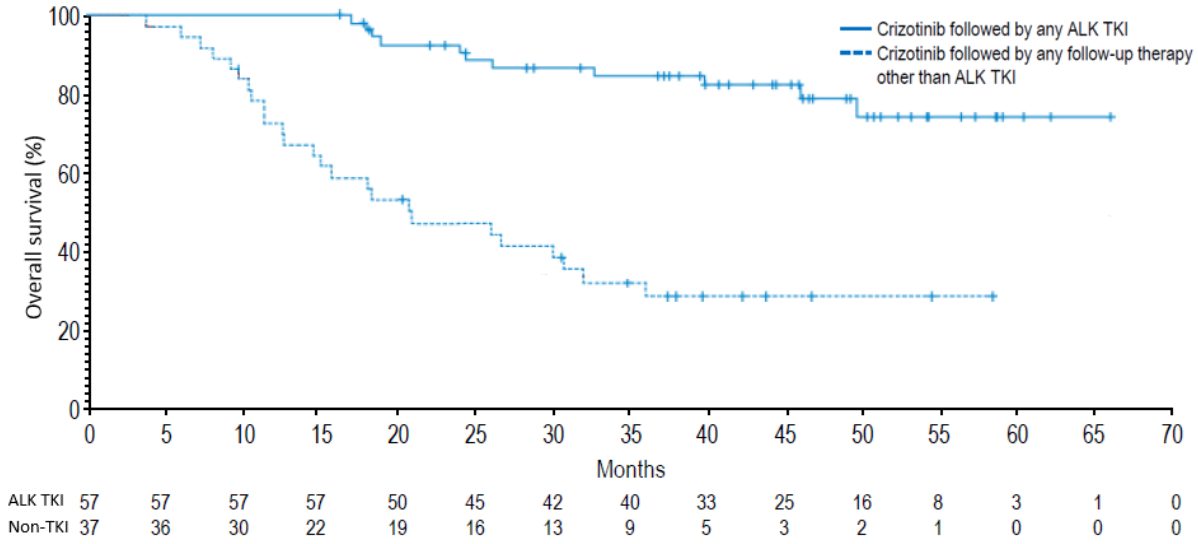
4.3.5 Subgroup analyses

No subgroups were listed in the NICE final scope.[1] However, the ERG's clinical experts highlighted that the presence of CNS metastases and ECOG PS can be important prognostic factors, and that subsequent therapies can have a significant impact on survival. Several *a priori* subgroup analyses were presented in the CS, primarily for PFS, and additional subgroup analyses were provided at the ERG's request at the clarification stage.

4.3.5.1 Subsequent therapies

The ERG notes that subsequent treatment with an ALK TKI can have a substantial impact on OS after a 1L TKI, which was recently shown in a subgroup analysis of PROFILE 1014 (Figure 9),[28] and in several real-world cohorts.[27, 50-52] As such, at the clarification stage, the ERG requested a full breakdown of subsequent therapies received after discontinuation of the study treatment in ALEX, and subgroup analyses to compare the OS of patients who received a subsequent TKIs with those who received non-TKI treatment.

Figure 9. Crizotinib OS by subsequent ALK-TKI or non-ALK-TKI use in PROFILE 1014 (adapted from Mok 2017[28]; comparison with chemotherapy not shown)



While crossover to the alternative treatment was not permitted in ALEX, nine patients in the alectinib group received crizotinib as a subsequent TKI, and 10 patients in the crizotinib received subsequent alectinib. The KM plots provided by the company (Figures 3 and 4 of the company's clarification response; [redacted].

The ERG explored the subsequent therapy data from ALEX provided by the company for possible imbalances that may have over- or underestimated the relative effect of alectinib compared with crizotinib in ALEX (Appendix 10.5, Table 67). Of the patients who have permanently discontinued treatment, 31/68 patients in the alectinib group (13 of which had a 2L TKI) and 40/105 patients in the crizotinib group (33 of which had a 2L TKI) had any 2L therapy recorded. The extent of missing information (54.4% of the alectinib group and 61.9% of the crizotinib group) means the full subsequent therapy profile could be substantially different to the subset; it is unknown what proportion of the missing data represents those who haven't received 2L therapy and what proportion have but haven't had it recorded. If it is assumed that none of the patients in the missing subset received 2L therapy after 1L crizotinib, the percentage (33/105; 31.4%) remains higher than the 18% of patients who received a second-generation TKI after crizotinib in the audit of crizotinib use in England.[48] The audit could be an underestimate because it is not limited to 1L crizotinib use.

4.3.5.2 Patients with CNS metastases

The ERG's clinical experts highlighted that patients with ALK+ NSCLC frequently experience progression in the CNS, which can have an important impact on OS and quality of life. A subgroup analysis of OS by presence of CNS metastases at baseline was not outlined in the NICE final scope[1] but the ERG considered it to be a valuable analysis considering the purported activity of alectinib in the CNS. The KM curves provided by the company at the clarification stage indicated shorter OS for alectinib and crizotinib patients who had brain metastases at baseline compared with those who did not, but the within-group differences were not statistically significant and the effect did not appear more distinct in one group than the other (Appendix 10.6).

The effect of alectinib on IRC PFS was larger in patients who had CNS metastases at baseline (HR 0.37, 95% CI: 0.22 to 0.60) than those who did not (HR 0.62, 95% CI: 0.40 to 0.96), but overlapping CIs between subgroups indicate the difference between subgroups is unlikely to be statistically significant (see Figure 10); the same pattern was seen for patients who had received prior brain radiation compared with those who had not (also shown in Figure 10).

The ERG also requested a regression analysis to explore OS for patients who developed CNS metastases during ALEX compared with those who did not, which the company were unable to provide because OS in ALEX is too immature. Instead, the company submitted landmark analyses for 6- and 12-month CNS progression as a predictor of OS. Two sets of landmark analyses were conducted to mirror the analysis options for PFS and CNS PFS (i.e. RECIST only and RECIST+CNS RECIST). Results from the landmark analysis for the ERG-preferred RECIST-only option are reproduced in Appendix 10.6. The analyses provide some indication that [redacted], as the company outline, patient numbers are too small to assess any differential impact reliably between arms (response to CQ A6). The company highlight that the 6- and 12-month landmarks are likely to reflect 'early progressors' that might be an aggressive subgroup, and recommend that caution be exercised when interpreting the curves. The ERG agrees that longer term data are required to capture any potential OS benefit that alectinib might have compared with crizotinib related to their differential effect in the CNS.

The company also presented subgroup data by presence of brain metastases at baseline for HRQoL, which showed a lower proportion [redacted]

[redacted]

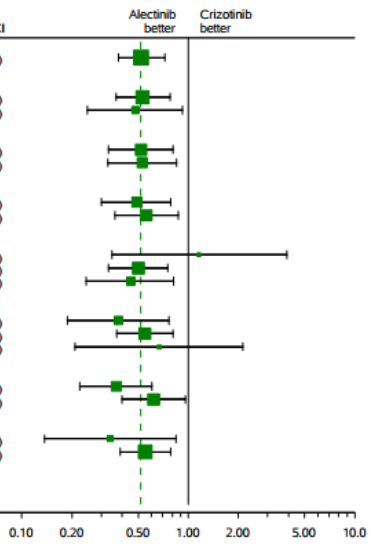
4.3.5.3 ECOG PS

The ERG's clinical experts highlighted that ECOG PS at baseline is likely to be an important prognostic factor. A subgroup analysis of INV PFS was one of several prespecified subgroup analyses in ALEX which was included in the CS, but the ERG requested to see a subgroup analysis of the IRC data given that it is likely to be the least biased of the two analyses. Figure 10 shows all subgroup analyses provided by the company for IRC PFS, which shows the benefit of alectinib is largest in patients with ECOG PS of 0. A formal assessment of subgroup differences was not submitted but the overlapping CIs across the subgroups (ECOG PS 0, 1 and 2) indicate the differences are not statistically significant.

Figure 10 shows that the benefit of alectinib over crizotinib for IRC PFS was relatively consistent across all predefined subgroups. The wide confidence intervals for active smokers and patients with ECOG PS of 2 indicate no significant difference between groups, but there was a small number of patients in both subgroups (17 and 20, respectively). Subgroup results for CNS metastases at baseline and those who had received prior brain radiation are discussed in Section 4.3.5.2.

Figure 10. Summary of subgroup analyses of independent review committee (IRC) PFS (reproduced from company's clarification response Figure 7, pg 17)

		Crizotinib (N=151)			Alectinib (N=152)				
Baseline Risk Factors	Total n	n	Events	Median (Months)	n	Events	Median (Months)	Hazard Ratio	95% Wald CI
All Patients	303	151	92	10.4	152	63	25.7	0.52	(0.38, 0.72)
Age Group (years)									
< 65	233	118	69	10.9	115	47	25.7	0.53	(0.37, 0.78)
>= 65	70	33	23	9.1	37	16	NE	0.48	(0.25, 0.92)
Sex									
Female	171	87	47	10.9	84	34	25.7	0.52	(0.33, 0.81)
Male	132	64	45	7.6	68	29	NE	0.53	(0.33, 0.85)
Race Category									
Asian	138	69	43	10.8	69	28	25.7	0.49	(0.30, 0.79)
Non-Asian	165	82	49	9.8	83	35	NE	0.56	(0.36, 0.87)
Smoking Status									
Active Smoker	17	5	4	10.4	12	8	3.7	1.16	(0.35, 3.90)
Non-Smoker	190	98	59	10.9	92	38	25.7	0.50	(0.33, 0.75)
Past Smoker	96	48	29	7.5	48	17	NE	0.45	(0.24, 0.82)
ECOG Performance Status									
0	97	54	28	16.7	43	11	25.7	0.38	(0.19, 0.76)
1	186	87	56	9.3	99	47	22.3	0.55	(0.37, 0.81)
2	20	10	8	6.1	10	5	3.7	0.67	(0.21, 2.13)
CNS Mets at Baseline (IRC)									
Yes	122	58	42	7.2	64	29	22.3	0.37	(0.22, 0.60)
No	181	93	50	14.8	88	34	NE	0.62	(0.40, 0.96)
Prior Brain Radiation									
Yes	47	21	13	7.5	26	9	25.7	0.34	(0.14, 0.84)
No	256	130	79	10.4	126	54	NE	0.55	(0.39, 0.78)



4.3.6 Adverse effects

Various categories of AE were presented in the CS or were available from other sources, including the published paper of ALEX[25] (e.g. specific AEs of any grade in at least 10% of patients in either group, AEs that occurred with a difference of 5% or more between groups, AEs of special interest (CS Table

11), rates of treatment-related AEs of any grade and of Grade 3 to 5, and serious adverse events [SAEs]). The ERG has collated the available AE data from ALEX into Table 12.

Table 12. Overview of the safety profile of alectinib compared with crizotinib in ALEX (compiled from Peters 2017, CS Table 10 and Table 11, and text on pgs 36–40).

	Alectinib (n = 152)	**Crizotinib (n = 151)**
All-cause (Grade 3–5)	97 (41)	97 (50)
Treatment-related	77	89
Serious	28	29
Fatal	3	5
Leading to discontinuation	11	13
Leading to dose reduction	16	21
Leading to dose interruption	19	25
AEs of any grade (Grade 3–5 in brackets); blue = favours crizotinib, orange = favours alectinib		
Anaemia	20 (5)	5 (1)
Myalgia	16 (0)	2 (0)
Increased blood bilirubin	15 (2)	1 (0)
Increased weight	10 (1)	0 (0)
Musculoskeletal pain	7 (0)	2 (0)
Photosensitivity reaction	5 (1)	0 (0)
Haematological abnormalities	24 (5)	17 (6)
Abnormal kidney function	18 (5)	9 (1)
Dysgeusia	3 (0)	19 (0)
Dizziness	8 (0)	14 (0)
Alopecia	1 (0)	7 (0)
Nausea	14 (1)	48 (3)
Diarrhoea	12 (0)	45 (2)
Vomiting	7 (0)	38 (3)
Peripheral oedema	17 (0)	28 (1)
Increased ALT	15 (5)	30 (15)
Increased AST	14 (5)	25 (11)
Eye disorders	8 (0)	33 (0)
Interstitial lung disease	2 (0)	6 (2)
Skin disorders	27 (1)	25 (0)
SAE Pneumonitis	1	3
SAE lung infection	2	0
SAE acute kidney infection	3	0
SAE pneumonia	3	3
SAE pulmonary embolism	1	2
SAE pyrexia	1	2

Abbreviations: AE, adverse event; ILD, interstitial lung disease
Specific AEs listed as more common in one group are those with at least 5 percentage point difference in the all-cause AE or 20 percentage point difference in the treatment-related AE (CS pgs 36–40). List of AEs are Grade 3–5 occurring in at least 3% of either group, any grade in at least 10% of either group, or SAE in at least 2% of either group.

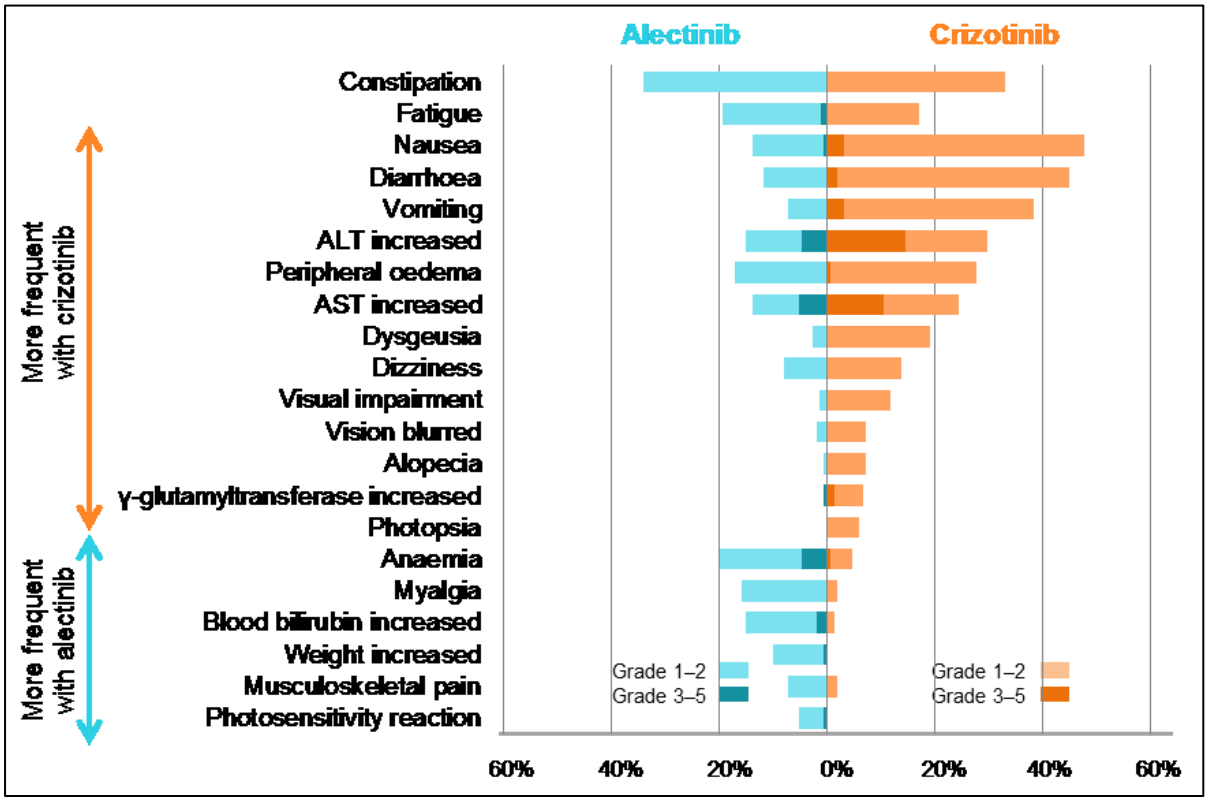
As described in the CS (pg 36), most patients in both groups reported at least one AE of any cause or grade (Table 12). The number of patients reporting at least one serious AE, Grade 3–5 AE, fatal AE, or AE leading to treatment discontinuation, were similar. AEs leading to dose reduction and dose

interruption were somewhat less frequent in the alectinib group (Table 12). The company highlight that median duration of treatment was longer in the alectinib group (17.9 months, range 0 to 29 months) than in the crizotinib group (10.7 months, range 0 to 27 months) which should be considered when interpreting the data in Table 12. The CS did not present information about whether AEs were more likely to occur at the beginning of treatment for either drug.

At the clarification stage, the company confirmed that safety assessments were conducted by study physicians who were aware of treatment assignment (response to CQ A21) and so there may be attribution bias, particularly in whether AEs were considered treatment-related. The ERG notes that the number of patients with at least one AE of any grade that was judged to be treatment-related was higher in the crizotinib arm (89%) than the alectinib arm (77%), despite rates of all-cause events being similar. Comparing rates of treatment-related AEs described in the CS (pg 37) with all-cause data compiled in Table 12, the ERG notes that some rates are similar (e.g. increased ALT and increase AST), but there were fewer treatment-related events for alectinib for other AEs (e.g. nausea, diarrhoea, vomiting, peripheral oedema). In each case, there was still a clear benefit of alectinib compared with crizotinib in the all-cause data which the ERG considers the more reliable assessment.

All-cause AEs that occurred more frequently at any Grade with alectinib than crizotinib were anaemia, myalgia, increased blood bilirubin, increased weight (noted as a new adverse drug reaction), musculoskeletal pain, and photosensitivity reaction (Table 12). All-cause AEs that were more common at any Grade with crizotinib than alectinib were nausea, diarrhoea, vomiting, peripheral oedema, dysgeusia, dizziness, alopecia, elevated liver enzymes (alanine aminotransferase [ALT] or aspartate aminotransaminase [AST]), eye disorders, and interstitial lung disease (tornado diagram shown in Figure 11). Grade 3–5 events were mostly infrequent in both groups, but some differences were noted in favour of crizotinib (anaemia and abnormal kidney function) and in favour of alectinib for elevated liver enzymes (Table 12). SAEs of lung and acute kidney infections were recorded with alectinib, and instances of pneumonitis, pulmonary embolism and pyrexia were recorded in both groups.

Figure 11. All cause adverse events of any grade reported in ≥10% of patients in ALEX, or ≥5% difference between alectinib and crizotinib (reproduced from CS Figure 6)



The safety profile of alectinib observed in ALEX is broadly in line with the SmPC for alectinib,[29] which is based on ALEX and two phase II trials of alectinib for ALK+ advanced NSCLC previously treated with crizotinib (NP28761 and NP28673).[53]. The SmPC advises that alectinib should be discontinued in the event of interstitial lung disease (ILD) or pneumonitis of any grade (which occurred in a small percentage of alectinib-treated patients in ALEX; Table 12), grade 4 bradycardia (not reported in ALEX), or severe hepatotoxicity (liver enzyme elevations were recorded relatively frequently in ALEX, though less frequently than in the crizotinib group). The SmPC advises interruption in the event of severe myalgia or creatine phosphokinase (CPK) elevation to > 5 times the upper limit of normal (ULN), which occurred more frequently in the alectinib group of ALEX than the crizotinib group. The increased rates of photosensitivity observed in the phase II trials was also noted in ALEX. The SmPC also list that anaemia, eye disorders, gastrointestinal disorders, skin disorders and oedema are common with alectinib, which were all recorded frequently in ALEX.

4.4 *Critique of the indirect comparison and/or multiple treatment comparison*

No indirect comparison was conducted by the company because direct evidence of alectinib versus crizotinib, the comparator of interest, was available from the ALEX study. The ERG considered the pros and cons of pooling the direct evidence between alectinib and crizotinib with indirect evidence via

one or more common comparators (e.g. best supportive care), and decided any potential for increased precision was likely to be outweighed by clinical heterogeneity introduced by incorporating indirect evidence.

As such, the ERG agrees with the company that the head-to-head ALEX study provides the most reliable evidence to inform the decision problem of interest to this STA. Where there was uncertainty in the robustness or clinical plausibility of evidence from ALEX, the ERG consulted its clinical experts and referred to related studies identified in the company's systematic literature review (SLR; see Section 4.1).

4.5 Summary and conclusions of clinical effectiveness sections

- A positive opinion was recommended by the CHMP on 12 October 2017, and marketing authorisation granted on 18 December 2017, to extend the existing marketing authorisation for alectinib after 1L crizotinib to include 1L treatment. The updated EPAR concludes that, "the superiority of alectinib over crizotinib in treatment-naïve patients with advanced ALK-positive NSCLC has been further substantiated" by the primary results of ALEX.

- Evidence from the multicentre phase III randomised trial, ALEX, closely matches the NICE final scope for this STA[1]:

    - Population: 303 adults with untreated, histologically confirmed ALK+ advanced NSCLC;

    - Intervention: alectinib 600 mg twice daily (n = 152), in line with the MA;

    - Comparator: crizotinib 250 mg twice daily (n = 151), in line with the MA;

    - Outcomes: OS, PFS, response, (ORR and DOR) HRQoL and AEs. In addition, time to CNS progression (CNS PFS) and CNS response are presented, which, on the advice of clinical experts, the ERG considered appropriate to capture the CNS activity of alectinib. CNS metastases are common for patients with ALK+ NSCLC and impact prognosis and quality of life.

- The ERG considered direct results from ALEX to cover the scope sufficiently. While precision may have been increased for some outcomes by pooling results from ALEX with indirect evidence identified in the company's SLR (i.e. via one or more common comparators in related RCTs of alectinib and crizotinib), any benefit was likely to be outweighed by added clinical heterogeneity.

- ALEX was of good methodological quality but patients and investigators were aware of treatment assignment. Randomisation was carried out centrally and was stratified by ECOG PS, race and presence of CNS metastases at baseline. Where available, the ERG prefers IRC-assessed PFS, CNS PFS and ORR likely to be less biased than the INV equivalents. HRQoL and safety assessments may also be subject to bias related to the open-label design.

- The population of ALEX reflects that ALK+ NSCLC affects a younger population who are more often female, and with less distinct smoking history than the wider NSCLC population. Characteristics were generally well balanced between groups. The population of ALEX may represent a relatively healthy subset of all patients with ALK+ advanced NSCLC, but generally reflect UK patients despite the small proportion recruited from UK centres (1%). The proportion of patients with CNS metastases at baseline (42% and 38% for alectinib and crizotinib, respectively) is higher than seen in UK clinical practice because asymptomatic patients are not scanned routinely.

- The ERG's preferred measure of PFS (IRC RECIST) showed a statistically significant and clinically meaningful benefit of alectinib compared with crizotinib; median PFS 25.7 months for alectinib (95% CI: 19.9 months to not estimable) and 10.4 months for crizotinib (95% CI: 7.7 to 14.6 months). The alectinib benefit was statistically significant across all predefined subgroups (age group, sex, race category, smoking status, ECOG PS, CNS mets at baseline and prior brain radiation) except those based on very small numbers (active smokers and ECOG PS 2).

- The company's preferred measure of PFS was based on their chosen analysis of CNS PFS, both including events from two separate IRC assessments: RECIST v1.1 and a CNS RECIST specifically to identify intracranial lesions. Median PFS and CNS PFS and associated CIs were not reported by the company for analyses based on RECIST+CNS RECIST but all options demonstrate a clear benefit of alectinib over crizotinib.

- ALEX was not powered to detect a statistically significant difference in OS between groups. At the February 2017 data cut-off, median follow-up was 18.6 months in the alectinib group and 17.6 months in the crizotinib group; a similar number of patient in each group had died (35 in the alectinib group and 40 in the crizotinib group; HR 0.76; 95% CI: 0.48 to 1.20; p-value 0.24) and median OS had not been reached in either group. One-year survival rates were similar at 84.3% for alectinib (95% CI 78.4 to 90.2%) and 82.5% for crizotinib (95% CI 76.1 to 88.9%). [redacted].

- The ORR benefit of alectinib compared with crizotinib was not statistically significant by INV (82.9% vs 75.5%, respectively) [redacted]; median DOR was immature but favoured alectinib (not estimable) over crizotinib (11.1 months; HR for alectinib versus crizotinib: 0.36, 95% CI: 0.24 to 0.53).

- There was a significant CNS ORR benefit of alectinib compared with crizotinib in patients with measurable CNS lesions at baseline (81.0% vs 50.0), and the combined subgroup of patients measurable or nonmeasurable CNS lesions at baseline (59.4% vs 25.9%). DOR was longer in the combined subgroup (HR 0.23; 95% CI: 0.10 to 0.53). The benefit of alectinib for CNS response was larger in patients who had not had prior brain radiation than those who had.

- Within the HRQoL and patient reported outcomes (PROs), there was [redacted]

- Significant differences in PROs favouring alectinib were [redacted]; in general, numerical or graphical data were not provided to substantiate the differences.

- Most patients in both groups reported at least one AE of any cause or grade (Table 12) and the number of patients reporting at least one serious AE, Grade 3–5 AE, fatal AE, or AE leading to treatment discontinuation, were similar. AEs leading to dose reduction and dose interruption were somewhat less frequent in the alectinib group despite longer median treatment duration for alectinib than crizotinib (17.9 vs 10.7, respectively).

- The rate of TRAEs was higher in the crizotinib arm (89%) than the alectinib arm (77%), but may be subject to attribution bias because safety assessments were conducted by study physicians. The CS did not present information about whether AEs were more likely to occur at the beginning of treatment for either drug.

- The safety profile of alectinib observed in ALEX is broadly in line with the SmPC for alectinib[29] All-cause AEs that occurred more frequently at any grade with alectinib than crizotinib were

anaemia, myalgia, increased blood bilirubin, increased weight (noted as a new adverse drug reaction), musculoskeletal pain, and photosensitivity reaction.

- All-cause AEs that were more common at any grade with crizotinib than alectinib were nausea, diarrhoea, vomiting, peripheral oedema, dysgeusia, dizziness, alopecia, elevated liver enzymes, eye disorders, and interstitial lung.

- Grade 3–5 events were mostly infrequent in both groups, but some differences were noted in favour of crizotinib for anaemia and abnormal kidney function, and in favour of alectinib for elevated liver enzymes. SAEs of lung and acute kidney infections were recorded with alectinib, and instances of pneumonitis, pulmonary embolism and pyrexia were recorded in both groups.

4.5.1 Clinical issues

- ALEX has not demonstrated that the statistically significant increase of alectinib in PFS or CNS PFS outcomes translate to an OS benefit. The [redacted].

- The company's preferred analyses of PFS and CNS PFS include events from CNS RECIST which may not reflect how PD would be assessed and managed in UK clinical practice. PD not involving the CNS was not censored for CNS PFS so the analysis includes patients experiencing secondary CNS progression. The ERG could not verify the methods of analysis fully. Variation in the extent of benefit could not be quantified because summary statistics were not available for all analyses, [redacted].

- Treatment beyond asymptomatic CNS progression, which may not be detected in clinical practice, could continue until symptomatic CNS progression or systemic progression in ALEX.[25] The ERG notes from clinical experts and related STAs (TA500 and TA422) that treatment with ALK-TKIs in UK clinical practice may be guided by symptoms rather than radiographic evidence of PD, particularly if it is at a single site and subsequent treatment options are limited. Comparison of ALEX TTD and PFS curves suggest treatment beyond PD was uncommon in both groups.

- Subsequent therapies were not recorded systematically in ALEX, which limits the conclusions that can be drawn about comparability of OS from ALEX to the UK treatment pathway.

Subgroup analyses

[redacted]

5 COST EFFECTIVENESS

5.1 Introduction

This section provides a structured description and critique of the systematic literature review and the *de novo* economic evaluation submitted by the company. Due to changes made to the company's model in reply to the clarification stage, the company provided an updated version of the Microsoft Excel®-based economic model. The focus of the Evidence Review Group's (ERG's) report is therefore on the second, updated, economic model.

5.2 Summary of the company's key results

According to the company's updated base case analysis, the incremental cost-effectiveness ratio (ICER) for alectinib compared with crizotinib is £72,544 per QALY gained. When the patient access scheme (PAS) for alectinib is applied to the economic results, the final ICER decreases to [redacted] per QALY gained. The probabilistic sensitivity analysis ICERS are £72,651 for the list price analysis and [redacted] when the PAS for alectinib is used.

5.3 ERG comment on company's review of cost-effectiveness evidence

The company carried out a systematic literature review (SLR) to identify cost-effectiveness, health related quality of life (HRQoL) and health state utility value (HSUV) evidence, in the first-line treatment of patients with ALK+ advanced or metastatic NSCLC. The cost-effectiveness search was originally carried out in August 2015, while the HRQoL search was first run in December 2015. Both searches were updated in March 2017. Additionally, the company carried out a SLR in June 2017 to identify the resource use and costs associated with the management and treatment of ALK+ NSCLC.

When conducting the SLR for the cost-effectiveness and HRQoL evidence, the company searched the following electronic databases: MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE, EMBASE, OVID EconLit and the Cochrane Library incorporating: Cochrane Database of Systematic Reviews (Cochrane Reviews), the Database of Abstracts of Reviews of Effects (DARE), the Cochrane Central Register of Controlled Trials (CENTRAL), the Health Technology Assessment Database (HTA), the NHS Economic Evaluation Database (NHS EED). In addition to electronic databases, conference proceedings, submission documents from HTA agencies, additional databases and the references lists of included publications were searched. No date limits were imposed on the original search, but a limit of 2006 was applied to full text reviews as this represents the time of the first description of ALK positivity. Search strategies for the original and updated searches are provided in Appendix G and Appendix H of the CS, for the cost-effectiveness and the HRQoL evidence, respectively. In summary, the search terms combined the population (patients with advanced or metastatic lung cancer) with the economic and HRQoL outcome terms, which the ERG considers to be

inclusive. Nonetheless, the ERG notes that quality of life terms were somewhat confined as these did not include terms for QoL instruments such as the EQ-5D or forms of the SF-36.

In order to conduct the SLR of resource use and costs, the company searched the same sources used for the economic evidence SLR in addition to the American College of Physicians (ACP) journal club, reference lists of included studies, conference proceedings over the past two years (2014-2016) and additional sources including the Cost-Effectiveness Analysis (CEA) Registry, Research Papers in Economics (RePEc), NICE and the Scottish Medicines Consortium (SMC). Search strategies for the search are provided in Appendix I of the CS. The search terms combined the general ALK+ NSCLC population with resource use and cost terms.

The cost-effectiveness search identified 4,740 studies, while the HRQoL search identified 18,469 studies, following the removal of duplicates. Of those, 274 texts from the cost-effectiveness search and 135 from the HRQoL search were evaluated for inclusion using the criteria provided in Table 22, Appendix G of the CS. Additionally, 411 resource and cost use studies were identified, 42 of those were evaluated for inclusion using the criteria provided in Table 54, Appendix I of the CS. The ERG considers the inclusion criteria used by the company to be reasonable.

Overall, a total of 29 publications were included from the cost-effectiveness search, covering 21 unique studies. Lists of the 145 and 100 studies excluded on full text from the original search and update, with reasons for exclusion, are provided in Tables 31 and 32, Appendix G of the CS, respectively. Six of the included cost-effectiveness studies considered a first-line setting, including three economic evaluations[54-56] and three HTA submissions.[57-59] Four of those six studies assessed patients with ALK+ advanced NSCLC.[54-56, 58] The remaining two studies included patients with ALK+ advanced NSCLC or unknown statuses of advanced NSCLC given the inclusion of testing strategies.[57, 59] All six studies compared crizotinib to chemotherapy regimens. A summary of those six studies is provided in Table 14 of the CS. To focus on the scope of this appraisal, the company did not report the results of studies which considered a second-line setting. It is unclear if the methods of those studies were considered by the company when the pathway for progressed disease was modelled. However, the ERG considers that the company is likely to have considered economic evidence relevant to the modelling approach as the key features of the company's *de novo* analysis were compared with the recent NICE TA submission for the first-line treatment of ALK+ advanced NSCLC (TA406).[55] A summary of the model developed for TA406 is given in Table 69 of Appendix 10.7.

With regards to the HRQoL search, a total of 11 publications were included, covering five unique studies. A list of the 103 studies excluded on full text from the updated search, with reasons for exclusion, is provided in Table 45, Appendix H of the CS. A list of studies excluded on full text from the original search was not available. Two of the 11 included publications considered a first-line setting

and focused on the first-line treatment of advanced ALK+ NSCLC patients in the PROFILE 1014 trial (Felip *et al.* 2015; Solomon *et al*. 2014).[37, 60] Both studies estimated HSUVs from patients who completed the EQ-5D and compared first-line treatment crizotinib with chemotherapy. The ERG noted a copying error in the company's initial data extraction of these studies (Table 25 of the CS), which was corrected by the company at clarification and is reported in Table 70 (Appendix 10.7). Furthermore, the ERG asked the company to extract Blackhall *et al.* 2014 (described as the parent study of seven included publications relating to the PROFILE 1007 trial, and in the second-line treatment setting) at clarification.[61] The methods and results of Felip *et al.* 2015; Solomon *et al*. 2014 and Blackhall *et al*. 2014 provided by the company at clarification are summarised in Table 70 (Appendix 10.7) and discussed further in Section 5.4.8.1.1. [37, 60, 61]

Finally, four HTA publications relating to three separate assessments were included in the resource and cost use search results.[55, 62, 63] Data obtained from the HTA publications are summarised in Table 32 of the CS. A list of the 38 studies excluded on full text from the search, with reasons for exclusion is provided in Tables 56 and 57, Appendix H of the CS.

Overall, the ERG considers the searches carried out by the company to be appropriate, and sufficient to identify published studies for treatments of ALK+ NSCLC. Due to time constraints, the ERG was unable to replicate the company's searches and appraisal of identified abstracts.

5.4 Overview and critique of company's economic evaluation

5.4.1 NICE reference case checklist

Table 13 summarises the ERG's appraisal 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 3.

Table 13. NICE reference checklist

Attribute	**Reference case**	**Does the *de novo* economic evaluation match the reference case?**
Decision problem	The final scope developed by NICE	Partially. The ERG is unclear to what extent the subsequent treatments received after alectinib might have influenced trial outcomes, and to which extent these are representative of subsequent treatments available in the UK.
Comparator(s)	Alternative therapies routinely used in the NHS	Unclear. The ERG is unclear to what extent the subsequent treatments received after crizotinib might have influenced trial outcomes, and to which extent these are representative of subsequent treatments available in the UK. Time to treatment discontinuation and progression-free survival curves were fairly similar to each other, across both treatment arms in ALEX. While the ERG is unclear if alectinib would be given beyond disease progression, there seems to be a reasonable evidence base suggesting that the majority of patients will receive crizotinib beyond treatment progression in clinical practice. Therefore, if crizotinib was given for a shorter period of time in ALEX than it would in clinical practice, there might be a negative bias in ALEX's results towards crizotinib.
Perspective costs	NHS and Personal Social Services	Yes.
Perspective benefits	All health effects on individuals	Yes.
Form of economic evaluation	Cost-utility analysis	Yes.
Time horizon	Sufficient to capture differences in costs and outcomes	Yes.
Synthesis of evidence on outcomes	Systematic review	Yes.
Outcome measure	Quality adjusted life years	Yes.
Health states for QALY	Described using a standardised and validated instrument	Yes.
Benefit valuation	Time-trade off or standard gamble	Yes.
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	Yes.

Discount rate	An annual rate of 3.5% on both costs and health effects	Yes.
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes.
Sensitivity analysis	Probabilistic sensitivity analysis	Partially. The company did not provide the PSA results for the RECIST analysis (only for the RECIST+CNS RECIST analysis).
Abbreviations used in the table: EQ-5D, EuroQoL 5-Dimension; HRQoL, health-related quality of life; HUI, health utility index; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life year; SF-36, 36-Item Short Form Survey; TTO, time trade-off.		

5.4.2 Population

The population considered by the company comprises adults with untreated anaplastic lymphoma kinase positive (ALK+) advanced non-small-cell lung cancer (NSCLC). The modelled population was based on the ALEX population data, for both alectinib and crizotinib and while the company's original model was an appropriate reflection of the NICE final scope, it did not explicitly differentiate between systemic progression with CNS involvement (hereafter referred to as CNS progression), from systemic progression without CNS involvement (hereafter referred to as non-CNS progression), other than to account for the costs and benefits associated with the overall percentage of CNS progressions as a one-off estimation.

Based on clinical expert opinion provided to the ERG, the clinical experts' statements to NICE and the company's views reported in the CS, one of alectinib's main advantages is its effect on delaying and/or potentially preventing CNS progression. As such, the ERG considers it is crucial to assess this group of patients in detail. Even though CNS disease presented itself in two ways in the ALEX population: baseline CNS disease, and CNS progression (regardless of CNS involvement at baseline), the ERG's focus is on the latter more than on the former. As discussed in Section 4, the presence of baseline CNS is unlikely to influence the effectiveness of alectinib when compared with crizotinib, in terms of overall survival and progression-free survival.

Upon a clarification request from the ERG, the company used the ALEX data to explicitly model CNS progression in the model. The CNS data have some issues due to the study design of ALEX; thus the company's updated analysis of this population has some shortcomings. This issue is further discussed in Section 5.4.5.2.

The ERG's clinical experts considered the ALEX[2525] population broadly reflective of UK patients with ALK+ NSCLC disease. However, the ERG's clinical experts considered there may be a higher proportion of detected CNS metastases in ALEX than would be seen in UK clinical practice because patients are not routinely scanned for these, unless symptomatic. Only three patients (1%) were

recruited from UK centres, with other countries including Western Europe countries, North America, Asia, Australasia, Eastern Europe and South America. The ERG's clinical experts advised that the baseline characteristics and prior non-systemic therapies are nonetheless reflective of patients in England, but highlighted that the provision of subsequent therapies after discontinuation of the randomised treatment is unlikely to be similar.

Finally, the ERG's clinical experts advised that the baseline characteristics in ALEX may suggest a somewhat healthier population than what would be seen in UK clinical practice, which is not uncommon in the clinical trial setting. This issue is further discussed in Section 5.4.5.

5.4.3 Interventions and comparators

The intervention and comparator considered in the economic model reflect those set out in the NICE final scope. The intervention under consideration is alectinib, administrated orally in 150mg capsules, to be taken as 600mg twice daily (amounting to a total of 1200mg per day). The comparator considered in the analysis is crizotinib (250mg) administered orally, twice daily. Both treatment regimens are modelled accordingly in the economic analysis.

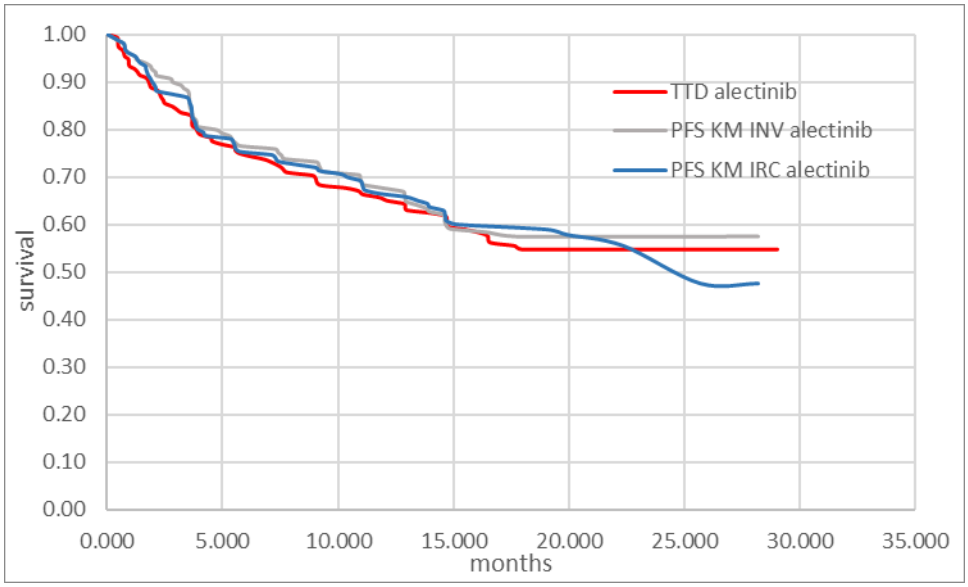
Treatment discontinuation was not explicitly modelled, but instead captured through the progression-free survival (PFS) curve as patients were assumed to receive treatment until disease progression.

5.4.3.1 Treatment beyond progression with alectinib

In their response to clarification request A8, the company outlined a discrepancy between the design of ALEX and the marketing authorisation for alectinib, stating that: "*whilst a patient with asymptomatic isolated CNS progressive disease could, at the discretion of the investigator, remain on treatment in the ALEX trial, there are no such criteria in the anticipated license of alectinib. As such, in UK clinical practice, all patients will discontinue treatment at progressive disease, irrespective of symptoms*."

With regards to comparability to the UK clinical practice, continuing treatment beyond the detection of an asymptomatic, isolated CNS does not seem problematic at face value (as these patients' CNS progression would not be captured in routine clinical practice). The company provided alectinib's time to discontinuation (TTD) curves after the ERG's request for clarification, and comparing these to the PFS curves (Figure 12) suggests that time to disease progression and TTD were fairly similar in ALEX, for alectinib. To note is that the PFS curve only shows systemic disease progression, and not necessarily asymptomatic CNS progression.

Figure 12. Progression-free survival and TTD for alectinib



It remains unclear to the ERG if clinicians will use alectinib beyond disease progression in the UK. For example, there seems to be evidence suggesting that patients with ECOG PS (0 or 1) at initial progression are more likely to receive and derive additional clinical benefit from continued treatment with crizotinib beyond disease progression compared with those who are given an alternative therapy at progression, or who receive no additional treatment.[27, 49] Furthermore, treatment beyond progression has been raised as an issue in the related appraisals of first-line crizotinib (TA406) and ceritinib (TA500).[55, 64] In both associated pivotal trials (PROFILE 1014 and ASCEND-4 for crizotinib and ceritinib, respectively), approximately 75% of patients continued treatment beyond progression with either crizotinib and ceritinib. The final appraisal determination (FAD) document for ceritinib TA500 states that clinical experts' view is that, "*it might be appropriate to continue treatment with ALK inhibitors after disease progression, for example if there is evidence of disease progression at only 1 tumour location but otherwise the disease is well-controlled*." The clinical experts also explained that they would wait until the disease has progressed at multiple sites before changing treatment, because there are limited alternative options for these patients. It was added that people taking ceritinib are more likely to continue treatment beyond disease progression than people taking crizotinib. This is because the only option after ceritinib is chemotherapy, whereas people on crizotinib can switch to ceritinib. The clinical experts suggested that in the future, as more treatment options become available, people might switch to an alternative therapy more quickly. The Committee concluded that in current practice, treatment with ceritinib, and to a lesser extent crizotinib, continues beyond disease progression.

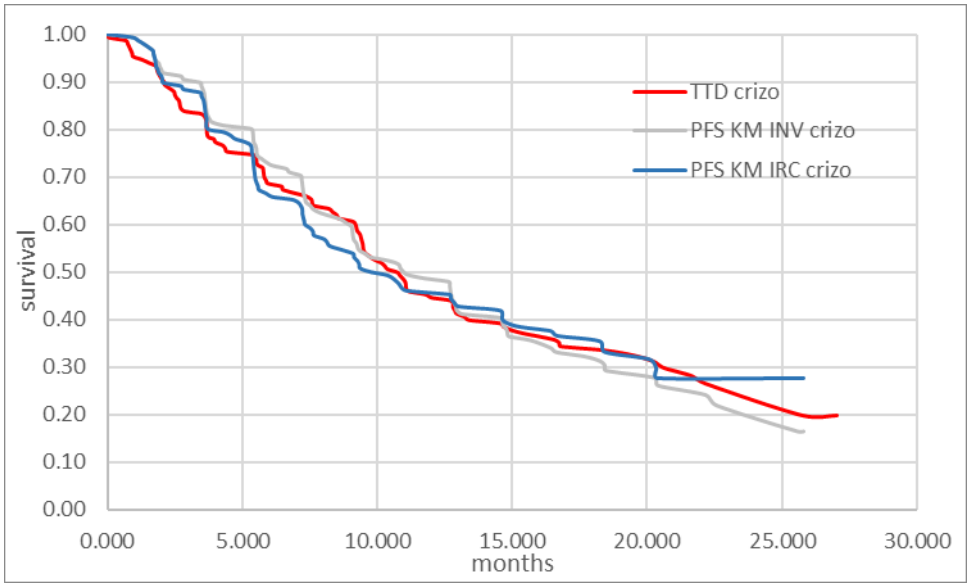
Even though the marketing authorisation for alectinib does not allow for treatment beyond progression, treating patients with (the same) ALK inhibitor beyond disease progression seems established practice in the UK. This also relates to the availability of subsequent therapies, although if alectinib is

recommended by NICE, there will be no available guidance to support alectinib as a second-line treatment. At the moment, the only available TKI treatment available after alectinib is crizotinib. However, there was uncertainty within the ERG's clinical experts and experts consulted for TA500 (ceritinib),[10] about whether crizotinib, a first-generation ALK-TKI, would be used as a second line treatment after a second-generation ALK-TKI such as alectinib. Given the acknowledged differences between first- and second-generation ALK-TKIs, some clinical experts considered it counterintuitive that crizotinib would be given after failure on a superior class of therapy.

5.4.3.2 Treatment beyond progression with crizotinib

Figure 13 reports the TTD and PFS curves for crizotinib, which suggest that there was considerable consistency in time to disease progression and TTD. Although the TTD curve lies above the PFS curve in some instances, these are mainly similar. The consequences of this are twofold: from a point of view of balance in the ALEX trial outcomes, it seems that TTD and PFS curves were fairly similar to each other, across both treatment arms. However, the ERG is concerned with the implications of this compared to crizotinib's actual use in clinical practice. While the ERG is unclear if alectinib would be given beyond disease progression, there seems to be a reasonable evidence base suggesting that the majority of patients (over 75% of patients in ASCEND-4 and PROFILE 1014) will receive crizotinib beyond treatment progression in clinical practice. Therefore, if crizotinib was given for a shorter period of time in ALEX than it would in clinical practice, there might be a negative bias in the results from ALEX against crizotinib. Without knowing how alectinib would be prescribed in clinical practice, it is difficult to anticipate the extent, direction, or even existence of a bias in terms of relative effectiveness. However, if alectinib is given according to the marketing authorisation, then it could be argued that ALEX is a fair representation of time on treatment for alectinib but potentially underestimates the time on treatment with crizotinib, compared with clinical practice. This will also have implications for the cost of treatment, which is likely to be underestimated for crizotinib in the economic analysis, if crizotinib is given for longer in clinical practice.

Figure 13. Progression-free survival and TTD for crizotinib



5.4.3.3 Subsequent treatments

The ERG finds it imperative to emphasize that any analysis of subsequent therapies in ALEX and its impact on trial outcomes is very incomplete and flawed, as subsequent therapies were not systematically captured in ALEX. As a result, of all patients who discontinued study treatment, only 41% of these have data regarding subsequent treatment. The type, or in fact existence, of subsequent treatments for the remaining 59% of the ALEX population is unknown. This, of course, means that the data available for 41% of patients in ALEX might (or might not) present a very skewed picture of subsequent treatments regimens in the trial.

As mentioned in the previous subsection, the likelihood of prolonging treatment beyond progression with the same TKI is highly linked to the availability of subsequent treatments in clinical practice. At the moment, there is no NICE-approved second-generation TKI for use after alectinib should it be recommended for ALK+ advanced NSCLC, whereas ceritinib can be used after crizotinib.

The protocol for ALEX stipulated that after treatment discontinuation, patients would be followed up for long-term survival and collection of subsequent therapy information. Nonetheless, the company confirmed that the latter was not captured systematically. Subsequent therapy data were requested by the ERG at the clarification stage, and is presented in Table 14, for the 41% of patients (68 alectinib and 105 crizotinib) who had subsequent treatment data collected. Crossover to the alternative treatment was not part of the study protocol but patients could receive the alternative treatment as a subsequent therapy if it was available, and clinically indicated, at their local centre. At least nine patients in the alectinib group received crizotinib as a subsequent TKI, and 10 patients in the crizotinib received

subsequent alectinib. As only 41% of the data are known, it is not possible to assess if more patients "crossed over".

Although it is not advisable to derive final conclusions from Table 14, as it does not represent the whole picture of subsequent treatments received in ALEX (in terms of number of patients, treatments received or balance across treatment arms), it can be noted that 40% of patients who received crizotinib as first-line treatment received ceritinib (13 out of 33) subsequently, while 24% of patients received alectinib (8 out of 33) as a subsequent treatment. It is not possible to anticipate the extent of the impact that subsequent therapies had on trial outcomes, given the incompleteness of the data.

Table 14. Subsequent therapies captured in ALEX for 41%* of patients who have permanently discontinued study treatment (adapted from clarification response, Table 3)

	Alectinib		**Crizotinib**	
Treatment	**2nd line (n = 68)**	**3rd line + (n = 68)**	**2nd line (n = 105)**	**3rd line + (n = 105)**
Any subsequent anti-cancer therapy	31 (45.6%)	9 (13.2%)	40 (38.1%)	4 (3.8%)
Any TKI	13 (19.1%)	5 (7.4%)	33 (31.4%)	3 (2.9%)
Ceritinib	2 (2.9%)	2 (2.9%)	13 (12.4%)	1 (1.0%)
Alectinib	0 (0.0%)	0 (0.0%)	8 (7.6%)	2 (1.9%)
Crizotinib	6 (8.8%)	3 (4.4%)	2 (1.9%)	0 (0.0%)
Other (lorlatinib, brigatinib, gefitinib, entrectinib, erolotinib)	5 (7.4%)	1 (1.5%)	10 (9.5%)	0 (0.0%)
Platinum compound (carboplatin, cisplatin)	16 (23.5%)	3 (4.4%)	6 (5.7%)	0 (0.0%)
Antimetabolite (pemetrexed, gemicitabine)	14 (20.6%)	3 (4.4%)	6 (5.7%)	0 (0.0%)
Taxane (paclitaxel, docetaxel)	3 (4.4%)	0 (0.0%)	0 (0.0%)	1 (1.0%)
Immunostimulant (nivolumab)	0 (0.0%)	2 (2.9%)	0 (0.0%)	0 (0.0%)
Angiogenesis inhibitor (bevacizumab)	2 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other (cyclophosphamide, antineoplastic agent NOS, anti PD-L1, doxorubicin, vincristine)	3 (4.4%)	1 (1.5%)	1 (1%)	0

Abbreviations: NOS, not otherwise specified; PD-L1, programmed death-ligand; TKI, tyrosine kinase inhibitor
*Subsequent therapies are not known for the remaining 59% of patients who have permanently discontinued study treatment.

5.4.4 Modelling approach and model structure

After a clarification request from the ERG, the company differentiated CNS from non-CNS progression in the economic model, however the details of the updated model were only described in a short document provided and therefore the ERG based its critique on the latter and on inspection of the economic model.

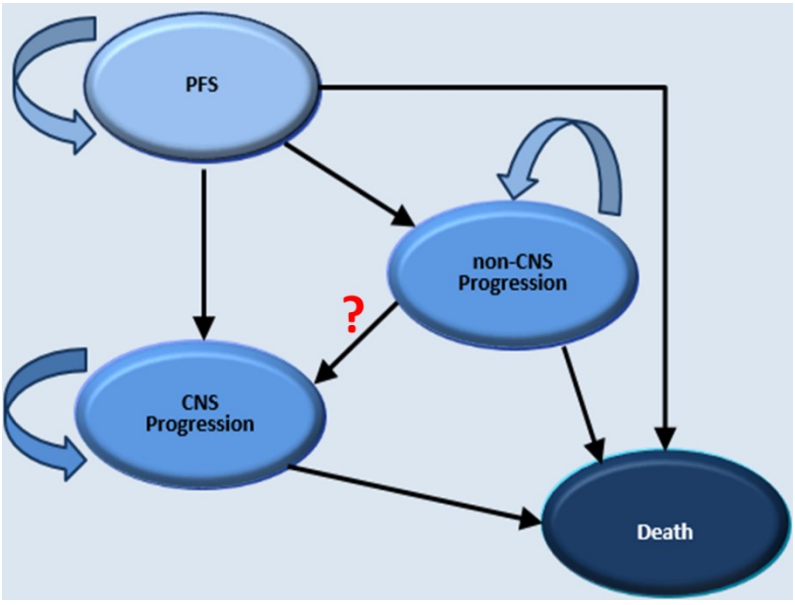
The company developed a *de novo* model in Microsoft Excel® to assess the cost-effectiveness of alectinib in comparison with crizotinib in patients with ALK+ NSCLC. The model is a cohort-based partitioned survival model, (presented in Figure 14), which includes four health states: progression-free survival (PFS), non-CNS progressed disease (PD), CNS progressed disease (CNS PD), and death. Patients receive treatment with alectinib or crizotinib until disease progression or unacceptable toxicity.

The cohort is allocated to the PFS state at the beginning of the economic analysis and is assumed to initiate treatment with alectinib or crizotinib. Patients occupying the PFS state are at risk of disease progression or death. Patients can experience CNS or non-CNS progression from the PFS state. Patients in the PD and in the CNS-PD state are also at risk of death and cannot enter remission in the model. The company, in their reply to the ERG's clarification questions, state that, "*patients with progression but no CNS progression can then subsequently progress into either progression with CNS progression or death*". As the model does not explicitly differentiate between primary and secondary disease progression, the ERG's interpretation of the company's statement relates with the ERG's interpretation of the CNS data provided by the company, which the ERG assumes includes primary and secondary events. By secondary events, it is meant that patients could have a systemic non-CNS progression, and then experience CNS metastases.

All progressed patients are assumed to receive subsequent treatments in the economic analysis. The partitioned survival (or area under the curve [AUC]) approach means that the proportion of patients modelled in each health state is based on parametric survival curves for each clinical outcome. A description of how the survival curves were estimated and implemented in the model is provided in detail in Section 5.4.5.

A life time horizon of 30 years is adopted in the model and time is discretised into weekly cycles. A half-cycle correction was applied in the model. The analysis was carried out from an NHS and Personal Social Services (PSS) perspective. Costs and health effects are discounted at an annual rate of 3.5%, in line with the NICE Reference Case.[65]

Figure 14. Company's model structure (taken from the company's Excel model)



5.4.4.1 ERG critique

The ERG is generally satisfied with the model structure and the patients' flow through the model. Patients who have progressed are assumed to receive subsequent treatments, which is in line with clinical expert opinion provided to the ERG. The company's assumptions of subsequent therapies carry some issues, which the ERG discuss in Section 5.4.3.3 and in Section 5.4.9.

The partitioned survival approach employed by the company is appropriate. The starting age in the model is 55 years. Approximately 30 years into the model (when patients would be 85 years old), 1% of patients are still alive in the alectinib arm of the model, and 14 years after treatment initiation 1% of patients have not progressed yet. On the crizotinib arm, 100% of patients are dead at 25 years (by the time they are 80 years old) and all patients have progressed by year 5. This seems unrealistic from a clinical point of view, especially in the alectinib arm of the model, where patients seem to live with advanced ALK+ NSCLC for over 30 years. This suggests an overestimation of the survival tails in the long-term of the economic analysis. This issue is further discussed in Section 5.4.5.1 and Section 5.4.7 of the ERG report.

Considering the short duration of the model cyclesPo (seven days), the ERG does not see the need for the half-cycle correction applied by the company, however acknowledges that removing the half-cycle correction from the model is likely to have a negligible impact on the final ICER.

5.4.5 Treatment effectiveness

Treatment effectiveness within the model was implemented through a partitioned survival method, which uses the estimated OS, PFS and CNS PFS data from the ALEX RCT to determine mortality and disease progression in the economic model.

In order to extrapolate OS, PFS and CNS PFS data into the model time horizon, the company fitted a variety of parametric curves to the ALEX Kaplan-Meier (KM) data. The company reports fitting clinical data with exponential, Weibull, Gompertz, log-logistic, lognormal and generalised gamma models in accordance with guidance from NICE Technical Support Document (TSD) 14.[66] The fit of each parametric model was compared with the observed KM data and statistical fit was assessed using the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC).

The company also explored the option of including KM curves with different parametric tails used for extrapolation. In response to the ERG's clarification questions, the company explained that the option of using KM data with parametric tails consists on fitting the parametric model to the entire dataset in order to inform the shape of the extrapolated curve and only then replacing the tail of the KM curve by a fitted/extrapolated curve, according to the user defined timepoint. The company also incorporated an alternative scenario, allowing for piecewise models to be used in the analysis.

Once the best-fitting model was selected, survival curves for alectinib and crizotinib were derived through the use of survival functions and were then used to estimate the proportion of patients in each health state for every cycle of the economic model. The proportion of patients in each health state of the model were derived through the following equations:

- PFS = P(PFS);
- Non-CNS PD = P(CNS PFS) – P(PFS);
- CNS PD = P(OS) – P(CNS PFS);
- Death = 1– P(OS).

Where P(PFS) is the proportion of progression-free patients taken from the PFS curve, P(CNS PFS) is the proportion of CNS-progression-free patients taken from the CNS PFS curve and P(OS) is proportion of patients alive taken from the OS curve.

Given the RCT design of ALEX, the company used the trial data to obtain OS, CNS PFS and PFS data for alectinib and crizotinib. The CS states that given that head-to-head evidence was available, it was not necessary to rely upon the proportional hazards (PH) assumption and thus treatment curves were fitted independently in the model.

5.4.5.1 ERG critique

The ERG discusses the modelling of each individual clinical outcome (CNS PFS, PFS and OS) in the following sections of the report.

Overall, the ERG agrees with the independent fit approach taken by the company as the assessment of the PH assumption undertook by the company shows that PHs do not hold for OS or PFS data. Nonetheless, the company did not assess the PH assumption for the CNS PFS (RECIST-assessed) data.

5.4.5.2 Central nervous system progression-free survival

After a clarification request from the ERG, the company used the ALEX data to differentiate systemic progression with CNS involvement (CNS progression), from systemic progression without CNS involvement (non-CNS progression) in the economic analysis.

In order to carry the CNS data analysis, the company had to ensure the consistency across the PFS KM and the CNS KM data, so that progression events were not double counted in the analysis, and that one dataset could be accounted as a subset of the other. This is necessary to ensure that in every model cycle, the total percentage of patients in the four health states (described in Section 5.4.4) accounts for 100% of the model cohort.

During the clarification process, the company advised that an error had been found in the original CS as the latter stated that CNS progression had been captured in ALEX using only the RECIST criteria, when in fact CNS progression had been measured with two different criteria (aggregated into one outcome): RECIST and also CNS RECIST (more details of these measurements can be found in Section 4). This created the following problem: as the PFS endpoint in ALEX was only measured by the RECIST criteria this resulted in an inconsistent data set available for PFS and CNS outcomes when analysed together. That is, CNS progression could not be considered a subgroup of PFS given the difference in the assessment methods.

Therefore, in order to incorporate CNS progression in the updated model, the company has included two options for analysis in the economic model:

1. Add CNS RECIST outcomes to the PFS KM data (company's base case in the updated model);

2. Separate RECIST and CNS RECIST-assessed CNS outcomes and only use RECIST-assessed CNS outcomes, so that the original PFS KM data could be used in the model.

Furthermore, time to CNS progression in ALEX was only captured by the independent review committee (IRC) and not by the investigators (INV). Thus, to assure further consistency across CNS and PFS outcomes, the company used the IRC PFS instead of the INV PFS data in their updated analysis.

The company chose option 1 as they deemed it to be the most complete and robust analysis of the impact of alectinib on CNS metastases, but recognised that events captured by CNS RECIST, "*may be earlier than would be in clinical practice as CNS-RECIST is not routinely used in the NHS*". The ERG does not consider the RECIST+CNS RECIST analysis (the company's base case) to be a robust method of assessment of CNS events. This is mainly because the detection of CNS RECIST-assessed events is not aligned with clinical practice in the UK. Also, in the model, it is not clear to the ERG how the CNS RECIST outcomes are "added" to the PFS KM curve. Therefore, the focus of the ERG report and analysis, is on RECIST-assessed outcomes from ALEX.

The details of the updated model including the CNS data analysis were described in a short document provided by the company after clarification; therefore, the ERG based its critique on the latter and on inspection of the economic model. The limited information available in the document shed some light on CNS data collection in the trial but is not entirely transparent and so the ERG is still unclear on a few aspects of the company's analysis. The ERG had to make assumptions with regards to the data, which are discussed in this section, however, further clarification from the company might be necessary on some aspects for the Committee to reach final conclusions.

Furthermore, the ERG could not validate the company's estimates to their full extent (the number of events in KM curves, the ALEX CSR and the company's two documents containing replies to the clarification questions do not appear to match for all outcomes) but acknowledges that, although not explained (or mentioned) by the company, inconsistencies might come from different data cut-offs in the analysis, or different measurements used for CNS events.

The ERG's understanding of the data has two foundations: firstly, the way KM data were used in the economic model (described through the equations reported in Section 5.4.5); secondly, in the company's statement that patients in the CNS PFS curve (the curve capturing the proportion of patients free from CNS progression) were followed until the first CNS progression, death or follow-up, regardless of whether a non-CNS progression event was observed. This implies that non-CNS progression events were not censored in the CNS PFS KM curve (represented by the beige circle and curve in Figure 15). These same events would, of course, be accounted for in the PFS curve (represented by the yellow circle and curve in Figure 15). What was unclear to the ERG from the company's reply was how CNS events were accounted for in the PFS curve, considering the fact that CNS events did not necessarily include systemic progressions in ALEX, but could equally be accounted as such.

In order for the company's manipulation of the clinical data to be correct, in particular for the two equations: non-CNS PD = P(CNS PFS) – P(PFS); and CNS PD = P(OS) – P(CNS PFS) to be correct, the ERG had to assume that all RECIST-assessed, first CNS events were also systemic progressions, and therefore captured in the PFS curve. This seems plausible, as the RECIST assessment of progression is used to evaluate systemic progression, rather than localised tumour growth. If the company confirms the ERG's assumption is correct, then subtracting the proportion of patients on the CNS PFS curve from the OS curve (represented by the red circle and curve in Figure 15) will leave the proportion of patients with CNS progression. Equally, if the ERG's assumption is valid, then subtracting the number patients on the PFS curve from the patients on the CNS PFS curve gives the proportion of patients with systemic progression outside the CNS (i.e. non-CNS disease progression).

The ERG also remains unclear as to how secondary CNS events were dealt with in the CNS PFS curve. In their reply to clarification question A9, the company states that, "*after the first progression event, further progression events have not been systematically captured"*. In an apparently contradictory statement, the company's reply to question A10 states that, "*any patient who experiences a non-CNS progression prior to CNS-progression is followed until the first of CNS progression or death or loss to follow-up*". The ERG is therefore concerned with how secondary CNS events (i.e. CNS events captured in the CNS PFS curve occurring after a systemic progression outside the CNS) were captured in the data and were subsequently modelled. It is likely that these events were not systematically captured, therefore potentially introducing some degree of bias in the analysis of secondary events across treatment arms.

The ERG is equally concerned with the company's statement which reports that when primary non-CNS events were censored in the CNS PFS curve, that lead to the OS and the CNS curves crossing. The ERG is unclear if the company means the KM curves from ALEX or the extrapolated curves used in the economic analysis. If the former is true, that is extremely worrying, as OS and CNS PFS KM curves should never cross if the data are robustly estimated. If the company means the latter, then the ERG does not consider this to be a valid justification for not censoring secondary events, as OS and CNS PFS estimated curves still cross in the company's model (this is further discussed in Section 5.4.5.2.2).

With regards to the modelling of secondary CNS events, even though these are not explicitly modelled, the ERG does not anticipate this creates a problem because a CNS progression always "trumps" a systemic disease progression captured in the PFS curve (see Figure 15) in the model. Therefore, all costs and QALYs are appropriately captured. When these patients experience their first event (a non-CNS progression) they begin to accrue disease progression costs and a lower utility value. However, when the same patients experience a secondary CNS event (because these transitions are not explicitly modelled), they will be captured in the model as a new CNS progression.

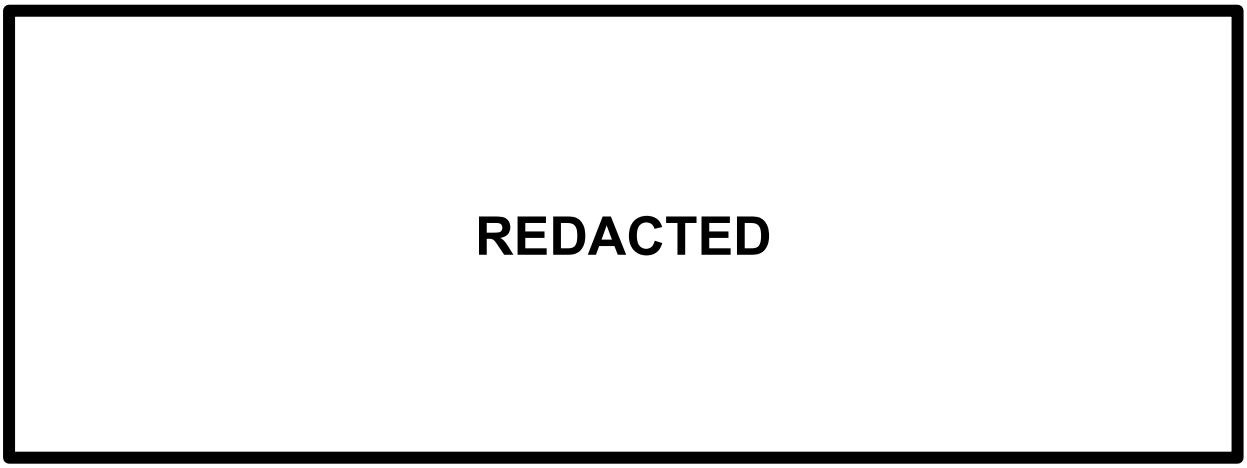
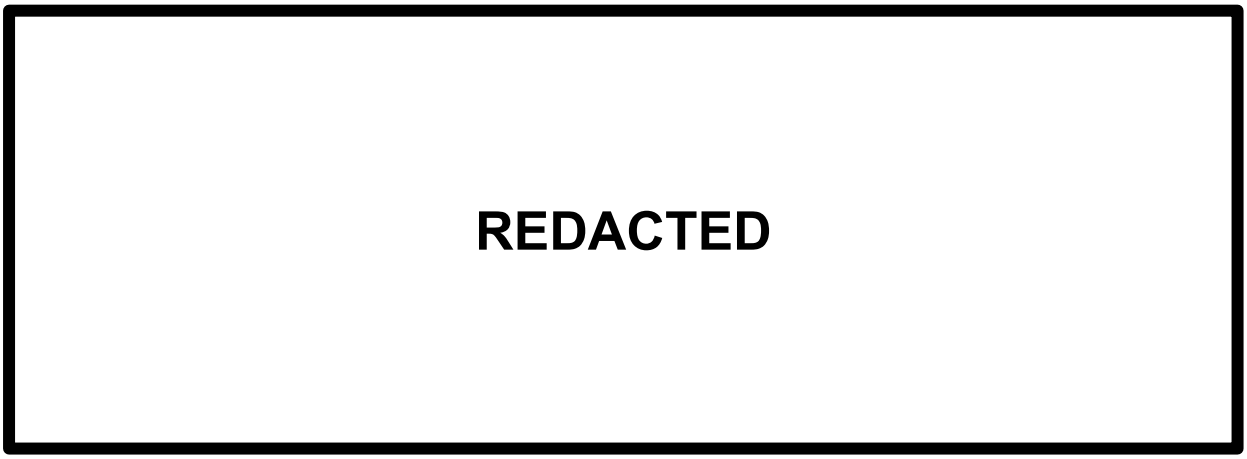


Figure 15. ERG's understanding of company's updated data analysis



It is important to caveat the ERG's assumptions regarding the company's data. If the ERG's assumptions are not correct, and if not all RECIST-assessed primary CNS progressions are also systemic progressions, then the company's model is flawed as the manipulation of the data in the economic analysis is likely to be incorrect.

In conclusion, the ERG remains unclear on the validity of the incorporation of clinical data into the economic model. It is vital that the company validates/clarifies the following issues:

1. All RECIST-assessed primary CNS events were simultaneously systemic progressions;
2. How were secondary CNS events captured in the CNS PFS KM curves (i.e. systematically or not systematically);
3. How can OS and CNS PFS curves (and whether these are KM or extrapolated curves) cross when primary non-CNS events were censored from the CNS PFS curves.

5.4.5.2.1 Extrapolation of CNS data in the model

The company's scenario analysis, which includes the RECIST-assessed CNS and PFS outcomes, uses the Gamma distribution to extrapolate the CNS PFS KM data. The company states that the Gamma distribution is the most suitable one due to the, "*levelling off of cumulative CNS metastasis incidence in the long term, demonstrated by the poster presented by Betts* et al. *at the 2016 AMCP Managed Care & Specialty Pharmacy Annual Meeting in San Francisco* [67]". The company adds that the poster likely underestimates CNS progression for crizotinib given the healthier population included in the poster's analysis.

The RECIST-assessed CNS PFS KM curves provided by the company are shown in Figure 16 and Figure 17, for crizotinib and alectinib, respectively. The figures also show the respective PFS KM curves. As discussed in the previous subsection, the CNS PFS KM curves sit above the PFS curves as there were more non-CNS events than CNS events, and the CNS PFS KM curves do not censor the non-CNS systemic progressions. Figure 18 compares the CNS PFS KM curves for alectinib and crizotinib.

Figure 16. Crizotinib CNS PFS KM curve and PFS curve (RECIST-only)

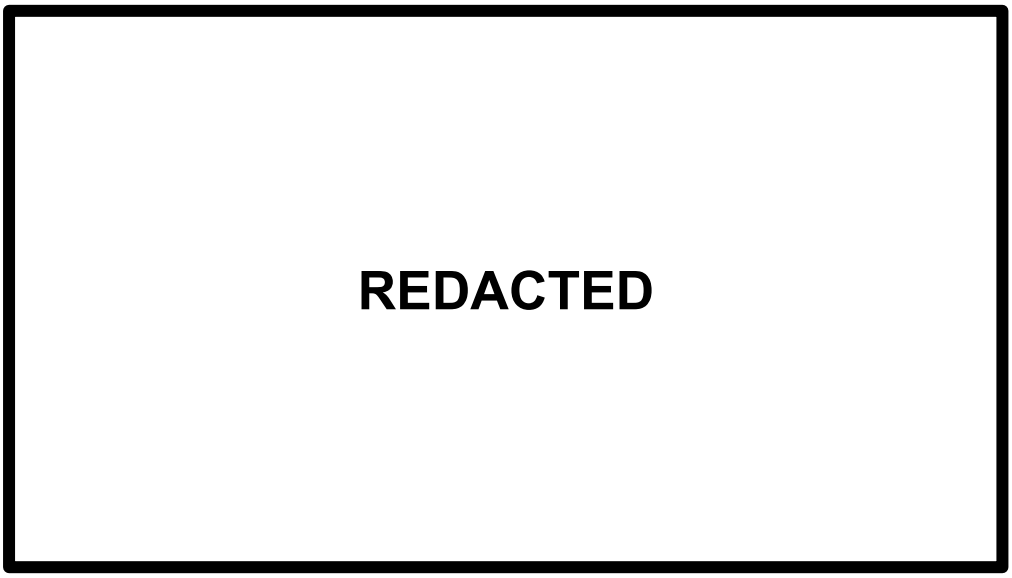


Figure 17. Alectinib CNS PFS KM curve and PFS curve (RECIST-only)

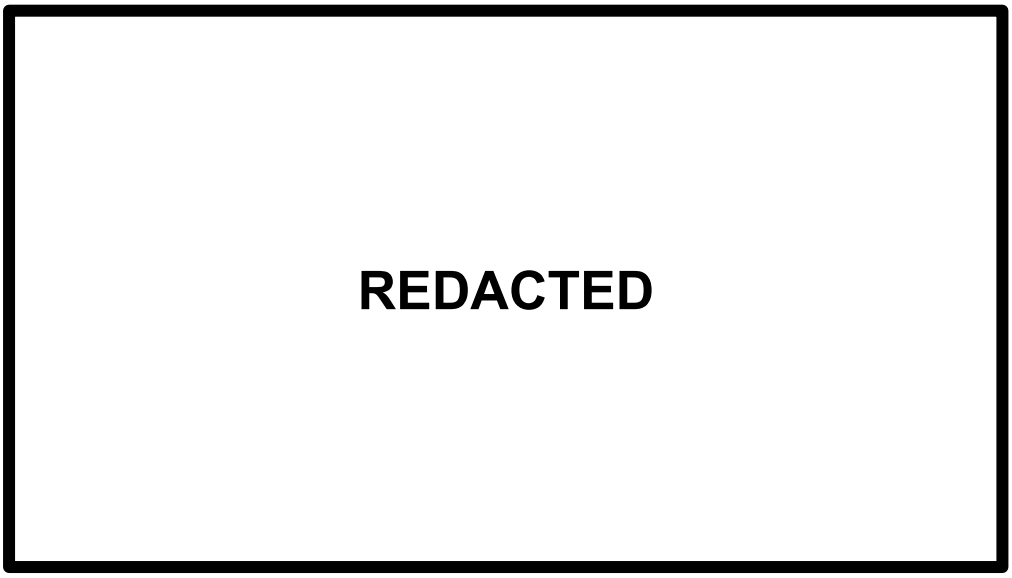
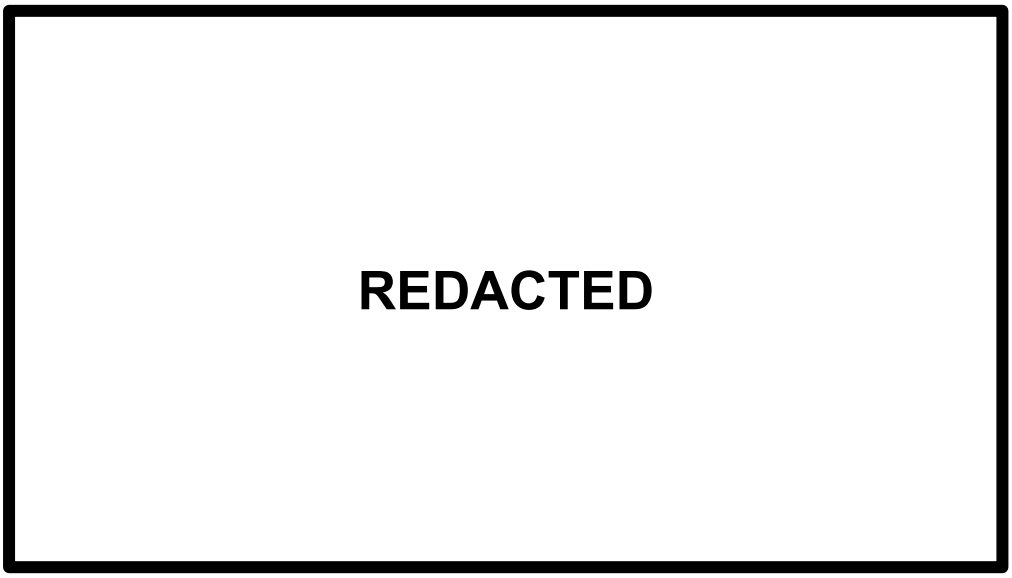


Figure 18. Alectinib and crizotinib CNS PFS KM curves (RECIST-only)



Even though the company selected the Gamma distribution to fit and extrapolate CNS PFS KM data in the alectinib and crizotinib arms of the model (measures of fit reported in Table 15), the curves were also adjusted by the relative risk of the OS curves. The ERG notes that the company did not report this adjustment in any written document provided to the ERG. Therefore, the ERG's description of the company's approach is based on model investigation, and the rationale behind the company's decision in unknown.

Table 15. Goodness of fit statistics for CNS PFS KM data

	Alectinib		**Crizotinib**	
Distribution	AIC	BIC	AIC	BIC
Exponential	273.12	276.14	322.43	325.45
Weibull	274.41	280.46	319.79	325.83
Log-normal	273.51	279.56	312.96	318.99
Gamma	275.51	284.58	313.97	323.02
Log-logistic	274.16	280.21	316.30	322.33
Gompertz	275.12	281.16	323.54	329.57
Abbreviations used in the table: AIC, Akaike information criteria; BIC, Bayesian information criteria				

In order to estimate the final CNS PFS curve in the model, the company began by fitting a Gamma distribution to the KM CNS PFS data. Following on from that, the company estimated the risk of CNS progression in each cycle (by diving the proportion of patients in the CNS PFS curve in t+1 by the proportion of patients in the CNS PFS curve in t) and compared it to the risk of death of ALK+ NSCLC patients (the proportion of patients in the OS curve in t+1 divided by the proportion of patients in the OS curve in t), and the risk of death in the general UK population, in each model cycle, by treatment arm. The company then took the minimum value between the underlying risk in each cycle for the OS, the background survival and the CNS PFS curves, and used it to estimate the proportion of patients in

the CNS PFS curve in that cycle. The ERG reports the equation used by the company in Equation 1 for transparency purposes.

Equation 1. Company's estimation of CNS PFS patients in the model

$$Nr\ pts\ in\ the\ CNS\ curve = \%\ CNS\ PFS_t * \left(minimum\ \left(\frac{\%\ CNS\ PFS_{t+1}}{\%\ CNS\ PFS_t}, \frac{\%\ OS_{t+1}}{\%\ OS_t}, \frac{\%\ BS_{t+1}}{\%\ BS_t} \right) \right)$$

The company's updated analysis also estimated newly progressed patients (only for CNS progression). The company states that the proportion of transitions out of the CNS PFS curve which were (and were not) deaths in ALEX was used to track the proportion of patients in each cycle which enter the progressed CNS heath state. These proportions were assumed to be fixed throughout the analysis as the company considered that a stratified analysis would lead to an excessive subdivision of the data and result in a biased analysis. Therefore, the company used the number of CNS events captured by the RECIST+CNS RECIST analysis ([redacted]) and the number of deaths as first events ([redacted] as per Table 4 in company's reply to clarification question B1) and estimated that for crizotinib, [redacted]% of transitions out of the CNS PFS curve were not deaths ([redacted]) and for alectinib, [redacted]% of transitions out of the CNS PFS curve were not deaths ([redacted]). The ERG found a discrepancy between the company's analysis and the results reported in the company's reply to clarification question B1, as the number of CNS events in the crizotinib arm were [redacted] and not [redacted]. The ERG corrected this in the company's model and presents the results in Section 6. The company used the estimated number of newly progressed CNS patients (Equation 2) to calculate the marginal costs of CNS progression in the economic analysis.

Equation 2. Company's estimation of newly progressed patients in the model

$$Newly\ progressed\ patients = \%\ CNS\ PFS_t * \left(1 - \frac{\%\ CNS\ PFS_{t+1}}{\%\ CNS\ PFS_t}\right) * fixed\ \%\ of\ events,$$

where the fixed proportion of events was 62% and 88% for alectinib and crizotinib, respectively.

5.4.5.2.2 ERG critique

The ERG notes that the Gamma distribution seems to be one of the worst fitting curves, according to the AIC and BIC criteria reported by the company. The lognormal or the log-logistic curves seem to provide better measures of fit. In the company's base case analysis, replacing the Gamma curve by the lognormal or log-logistic has a negligible impact on the model results. The ERG agrees with the company's assessment, even when the ERG changed the capping method in the analysis.

The ERG disagrees with the method used by the company to cap the CNS PFS data. Figure 19 shows the underlying risk throughout the economic model timeframe, in the OS curve (estimated with an exponential distribution), the CNS PFS curve (estimated with the Gamma distribution) and the

background population survival. Given that the company took the minimum risk each cycle to determine the proportion of patients in the CNS PFS curve, the risk for death (taken from the OS curve) was used from month 20 (approximately) to estimate the CNS PFS curve in the model for alectinib. Figure 21 shows that the risk of death was used from month 50 (approximately) to estimate the CNS PFS curve in the model for crizotinib.

Nonetheless, Figure 20 shows that the OS and CNS PFS curves for alectinib do not cross until 42 months. A similar situation is observed for the crizotinib model, where the OS and CNS PFS curves do not cross until 163 months (Figure 22). The ERG does not see a reason why the risk of events in the CNS PFS curve should not be higher than the risk of events in the OS curve. In fact, the CNS PFS curve includes death and progression events, and therefore the risk of events in the curve should, on average, be higher than the risk of events in the OS curve.

Alternatively, the company should have capped the CNS PFS curve by the OS curve when these cross, as the OS curve cannot be below the CNS PFS curve (yielding a negative proportion of patients in the model). The ERG replaced the company's approach by capping the CNS PFS curve by the OS curve. Results are reported in Section 6.

Figure 19. Relative risk for OS, CNS PFS and background survival for alectinib

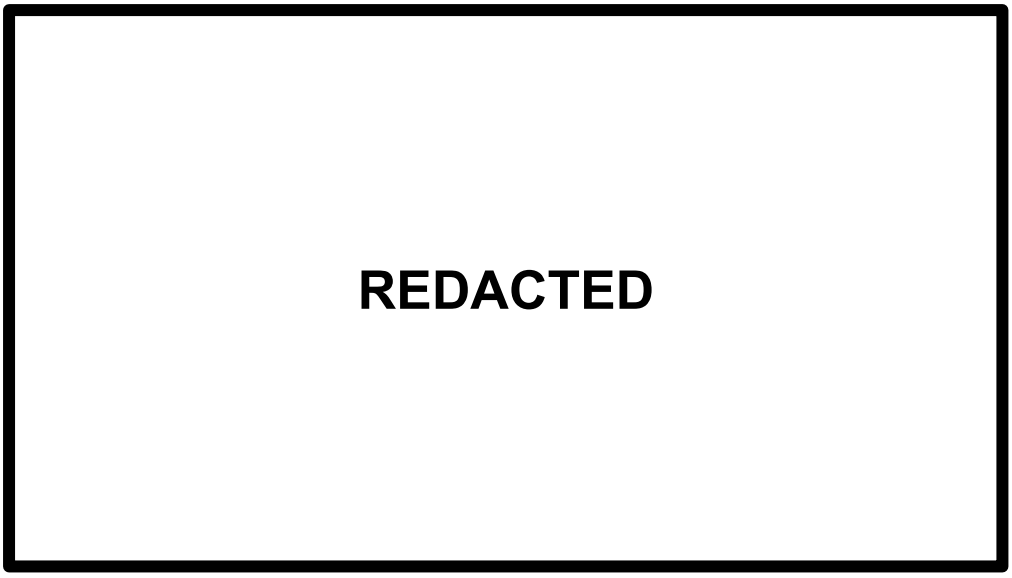


Figure 20. Survival curves for alectinib

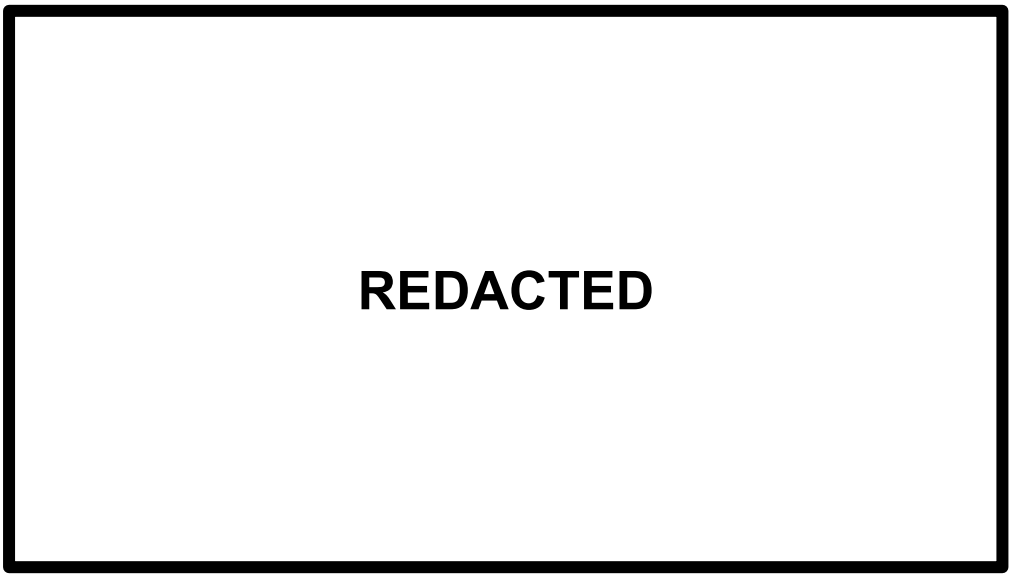


Figure 21. Relative risk for OS, CNS PFS and background survival for crizotinib

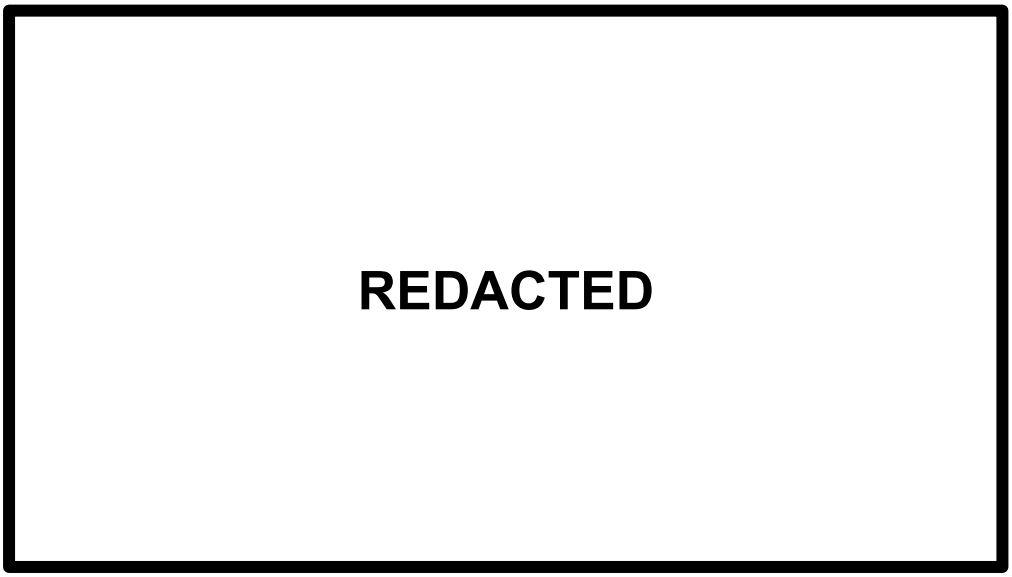
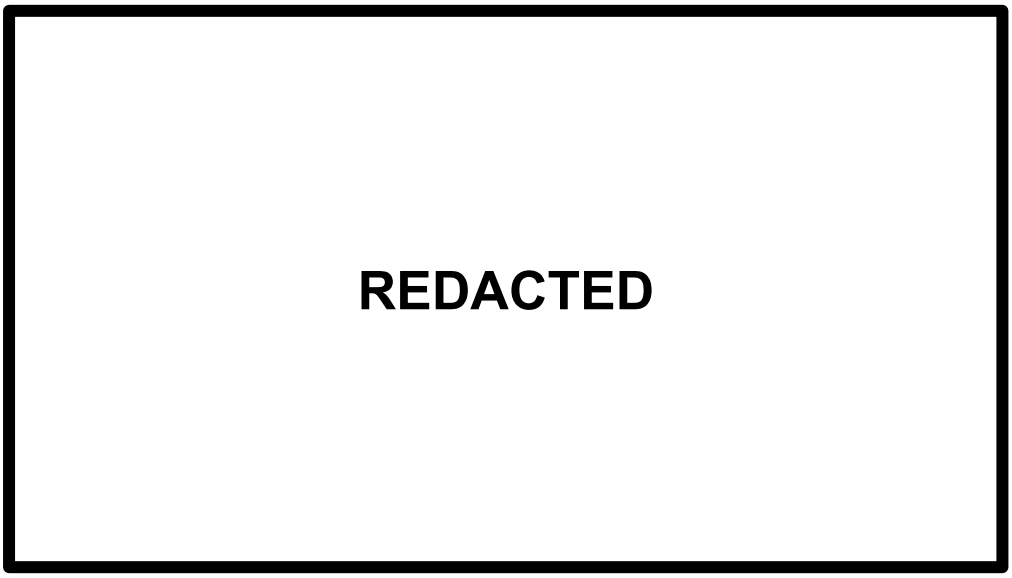


Figure 22. Survival curves for crizotinib



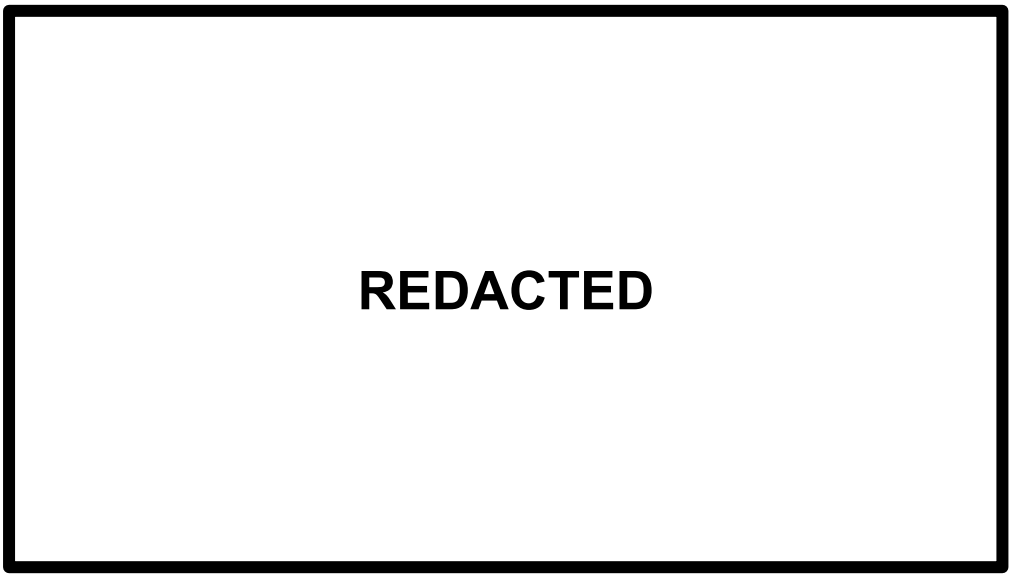
The ERG disagrees with the method used for the estimation of newly progressed patients in the model as it uses a fixed proportion of CNS events (captured by the RECIST+CNS RECIST measure) throughout the analysis. A more robust approach would have been to estimate the number of newly progressed patients every cycle, instead of relying on a fixed proportion. Therefore, the ERG replaced the company's method (Equation 2) with the formula below. The results are reported in Section 6.

$$(CNS\ PD_{t+1} - CNS\ PD_t) + (1 - OS_{t+1}/OS_t) * (CNS\ PD_t)$$

5.4.5.3 Progression-free survival

The company originally chose the INV PFS outcomes for its base case analysis. However, as a result of the clarification stage, the company changed the PFS data in its base case model to reflect the IRC-assessed PFS. The KM PFS curve for the IRC PFS is shown Figure 23.

Figure 23. Kaplan-Meier plot of IRC-assessed PFS, ITT analysis (Figure 5, CSR)



The company reports that the lognormal, log-logistic and Gamma distributions have the best statistical fit (Table 16). Nevertheless, the company deemed these distributions to be clinically implausible as using these resulted in the PFS curves crossing the OS curve. The clinical experts advising the company concluded that the Weibull produced unrealistic survival estimates, with 10% of patients being progression-free at 10 years. Therefore, the company selected the exponential distribution. Given the poor fit of the exponential curve to the KM data, the company used the KM curves up to 18 months (where the company reports that censoring increases), and then replaced the tail of the KM curve by a fitted/extrapolated exponential curve.

Table 16. Goodness of fit statistics for PFS KM data

	Alectinib		**Crizotinib**	
Distribution	AIC	BIC	AIC	BIC
Exponential	381.93	384.96	384.40	387.42
Weibull	378.95	385.00	384.30	390.34
Log-normal	371.85	377.90	370.73	376.77
Gamma	369.76	378.83	369.26	378.31
Log-logistic	376.07	382.12	375.01	381.04
Gompertz	383.93	389.98	386.40	392.44
Abbreviations used in the table: AIC, Akaike information criteria; BIC, Bayesian information criteria				

5.4.5.4 ERG critique

Median IRC PFS on crizotinib in ALEX (10.4 months) is comparable to PFS observed for crizotinib in PROFILE 1014 (10.9 months), the J-ALEX study (10.2 months), the Davis *et al.* 2015 (9.6 months) and the audit of crizotinib use in England (9.8 months).[68,69] The ERG's clinical experts expected median PFS on crizotinib to be between 6 and 12 months and that nearly all patients would have progressed on

crizotinib by 24 months. The ALEX data suggest that around 25% of crizotinib patients remain progression-free at this timepoint (by IRC; Figure 23).

Given the short-term experience with crizotinib in UK clinical practice (as it entered the CDF in 2012) and the fact that alectinib is not yet used in clinical practice, the validation of survival estimates from ALK+ NSCLS trials in terms of clinical plausibility, is challenging. The FAD for ceritinib (ID1117) states that, "*the clinical experts noted that the survival rates in PROFILE 1014 were higher than in real-world studies. They suggested that this could be because a substantial proportion of people in PROFILE-1014 had subsequent lines of therapy, noting that survival rates have improved considerably in recent years. The clinical experts agreed that the population in PROFILE-1014 was generalisable to clinical practice and, on balance, considered that the survival estimates from PROFILE-1014 could be realistic*." [64]

Overall, it is likely that survival outcomes from ALEX are overestimated, when compared with clinical practice. The ERG agrees with the company's approach of selecting the exponential tail as it provided the most conservative scenario, from a clinical point of view, for alectinib (Figure 24). While for crizotinib (Figure 25), the exponential curve is the second most conservative (with the Weibull curve predicting the lower survival), the ERG considers that choosing different distributions to model PFS across treatment arms is not justified in this case. Furthermore, the combination of using the exponential curve for alectinib and crizotinib, is in itself a conservative approach, as the Weibull curve would have predicted a lower survival for crizotinib.

Given that the exponential curve was the worst fitting distribution to the KM PFS data, the ERG sees the benefit of using the KM PFS curves for the initial period of the model. However, the exponential tail of the curve was still derived from fitting an exponential distribution to the KM curve, which proved to be a bad fit. Hence, the portion of the curve used after 18 months is still based on a badly fitting curve. The ERG undertook some initial exploratory analysis to assess the impact of using more flexible modelling options (for example, using spline models). Nonetheless, because the shape of the KM curves (Figure 23) exhibits a plateau from about 15 months for alectinib, where the number of patients at risk in the KM curve is still generally robust (83 patients; 55% for alectinib), all exploratory analysis conducted by the ERG produced curves with very long (and clinically implausible) tails.

Another consequence of using an exponential curve is the fact that at 18 months (where the exponential tails are used in the model), the hazard ratio between the alectinib and crizotinib PFS curves becomes proportional. This is because the underlying hazard in each curve will remain constant throughout the rest of the model. There is no clinical justification for this and, in fact, the company's assessment of PH indicated that the PH assumption is unlikely to hold for PFS data.

Overall, the ERG considers that the company's solution is a reasonable compromise between statistical fit and clinical plausibility of the survival curves (the same issue applies to the OS data, discussed in Section 5.4.7). However, the intrinsic assumption of PH after 18 months is unlikely to be reflective of clinical practice, and of the underlying clinical data.

Finally, the ERG considers that the choice of the cut-off point (18 months) for the KM data used by the company is quite arbitrary. This should have been better substantiated, and some sensitivity analysis should have been undertaken by the company to reflect the impact of changing this parameter in the analysis. At 18 months, there are 22% and 45% of patients at risk in the crizotinib and alectinib curves, respectively. The company reports that censoring increases after this point. However, the same could be argued for other cut-off, and more importantly, the alectinib and crizotinib curves do not necessarily have the same "appropriate" cut-off points. For example, while at 18 months there are still 45% of patients at risk in the alectinib curve, the (approximately) equivalent figure for the crizotinib curve is observed at 9 months (49% of patients at risk). When 9 months are used as the cut-off point in the crizotinib curve (and 18 months for the alectinib curve), the ICER increases from £72,544 to £74,554 per QALY gained.

Figure 24. Progression-free survival curves for alectinib

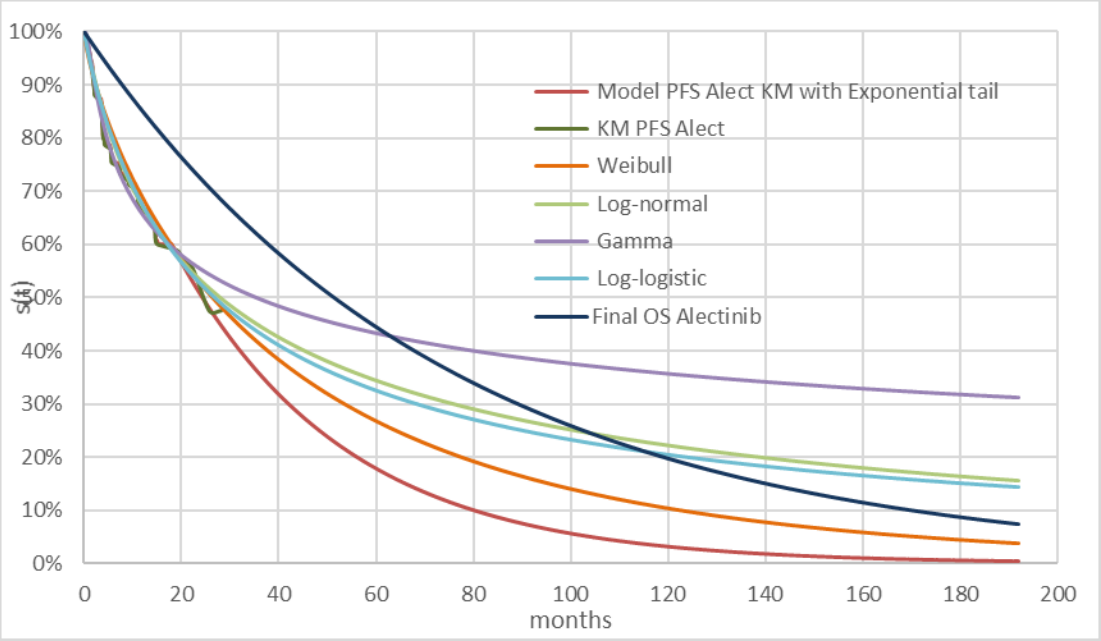
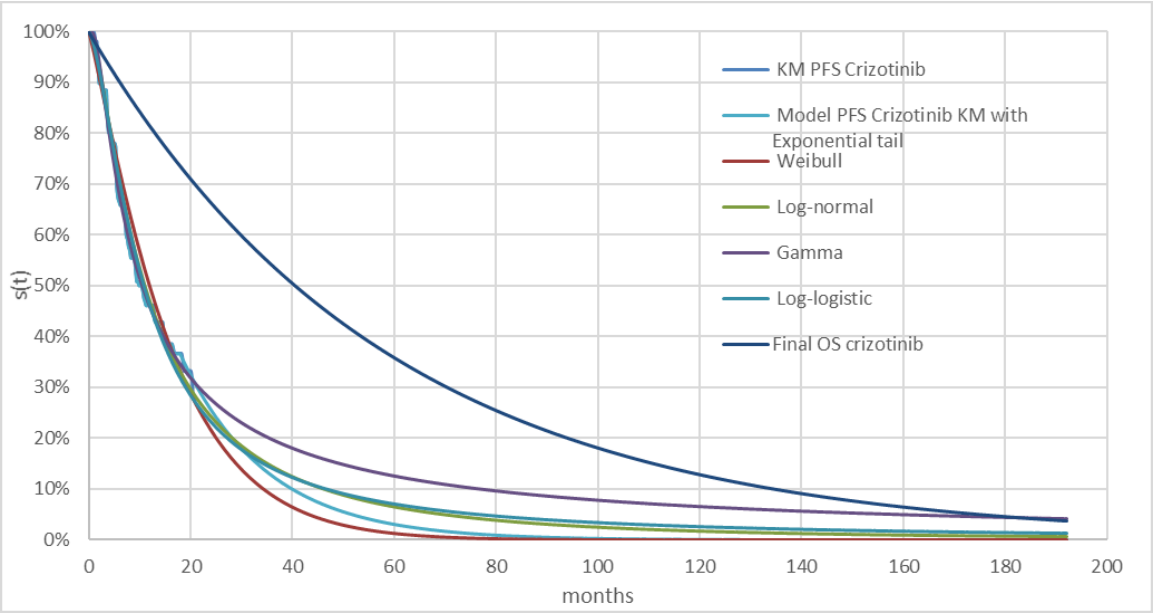


Figure 25. Progression-free survival curves for crizotinib



5.4.6 Adverse events

In the base case analysis, the company included all grade 3 and 4 treatment-related adverse events (TRAEs) with an incidence of ≥ 3% in either arm of the ALEX trial, and all grade 5 TRAEs irrespective of incidence.

To account for the weekly cycle length in the model, the company calculated the rate of each TRAE and transformed it into a weekly probability, as summarised in Box 1. The resulting TRAEs and probabilities included in the economic model are shown in Table 17.

Box 1. Company's calculation of TRAE probabilities

weekly rate = – (LN (1 – p))/t
p= number of events observed during follow-up divided by patient years at risk of TRAE
t = number of weeks per year i.e. 52.1786
weekly probability = 1 – EXP (– weekly rate)

Table 17. TRAEs included in the economic model (adapted from Table 27 and Table 46 of the CS)

TRAE	Alectinib (n=152)			Crizotinib (n=151)		
	Occurrence	%	Probability of event (per week)	Occurrence	%	Probability of event (per week)
Alanine Aminotransferase Increased	7	4%	0.0007	25	14%	0.0035

Aspartate Aminotransferase Increased	10	5%	0.0010	17	9%	0.0023
Cardiac Arrest (G5)	0	0%	0.0000	1	1%	0.0001
QT interval prolongation	0	0%	0.0000	6	3%	0.0008
Neutropenia	0	0%	0.0000	13	3%	0.0018
Pneumonitis (G5)	0	0%	0.0000	3	2%	0.0004
Abbreviations used in the table: G5, grade 5; TRAE, treatment-related adverse event						

The impact of TRAEs on patients' quality of life is considered in the model and is described further in Section 5.4.8.1.3, while the costs of managing TRAEs are discussed in Section 5.4.9.

5.4.6.1 ERG critique

The ERG considers the company's estimation of adverse events to be reasonable. The ERG's clinical experts confirmed that all the relevant TRAEs associated with alectinib and crizotinib have been included in the economic analysis.

The company did not include adverse events related with second line treatments in their analysis. For completeness, the ERG asked the company to justify this decision. The company, in their reply to the ERG, stated that their approach to exclude adverse events of second line treatments was consistent with the methodology used in TA406. The company also added that the inclusion of adverse events was expected to have a negligible impact on the ICER. The ERG agrees that this simplification is generally reasonable and likely to have little impact on the model results.

5.4.7 Mortality

The company used the exponential distribution to model the OS curves for alectinib and crizotinib (Table 18). The company recognised the lack of maturity of the OS data (Figure 26) and, therefore, sought external validation from more mature OS data, available for crizotinib. The company used the PROFILE 1014 study although warned that patients in PROFILE 1014 were generally healthier and therefore expected to perform better. After conducting a naïve comparison of the PROFILE 1014 data to the extrapolated curves (Figure 27), the company concluded that even though the Gamma distribution was the closest curve to the PROFILE 1014 predictions, it led to an overestimation of survival in the long-term. The company reported that the exponential distribution was the second-best fit to the to the PROFILE 1014 data, and resulted in a more conservative estimation of survival for both crizotinib and alectinib (when the same distribution is used for both curves), and thus it was the chosen distribution for the company's base case.

Table 18. Goodness of fit statistics for OS KM data

	Alectinib		Crizotinib	
Distribution	AIC	BIC	AIC	BIC
Exponential	246.59	249.61	234.24	237.26
Weibull	247.98	254.03	232.71	238.74
Lognormal	247.97	254.02	230.88	236.91
Gamma	249.79	258.86	232.79	241.84
Log-logistic	247.91	253.96	232.10	238.13
Gompertz	248.59	254.63	234.72	240.76
Abbreviations used in the table: AIC, Akaike information criteria; BIC, Bayesian information criteria				

Figure 26. Kaplan-Meier plot of OS, ITT analysis (Figure 2, CS)

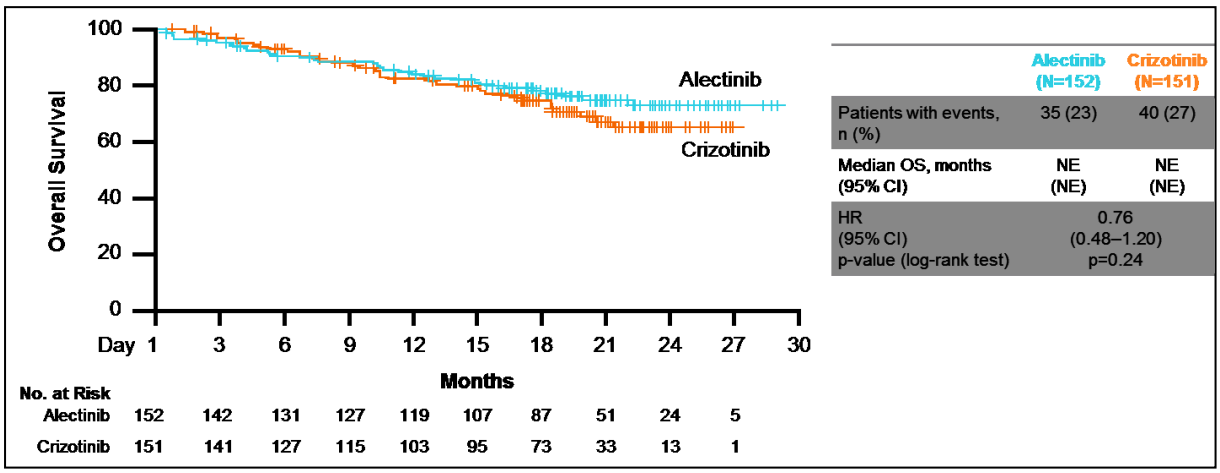
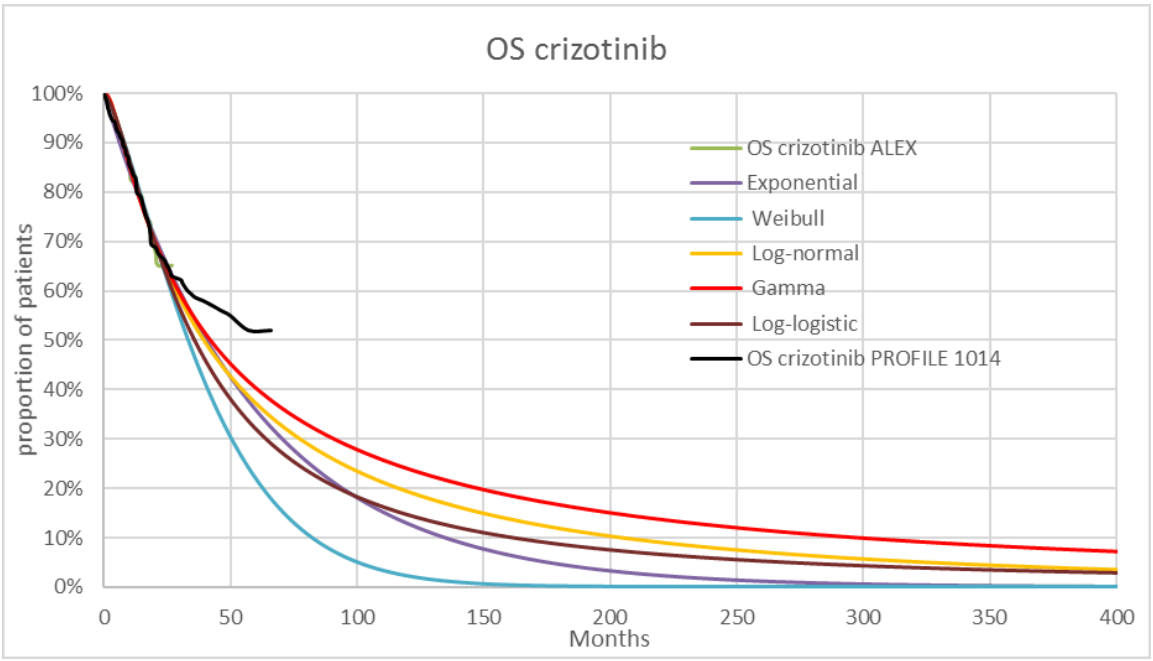


Figure 27. Extrapolated crizotinib OS curves from ALEX and crizotinib KM OS curve from PROFILE 1014



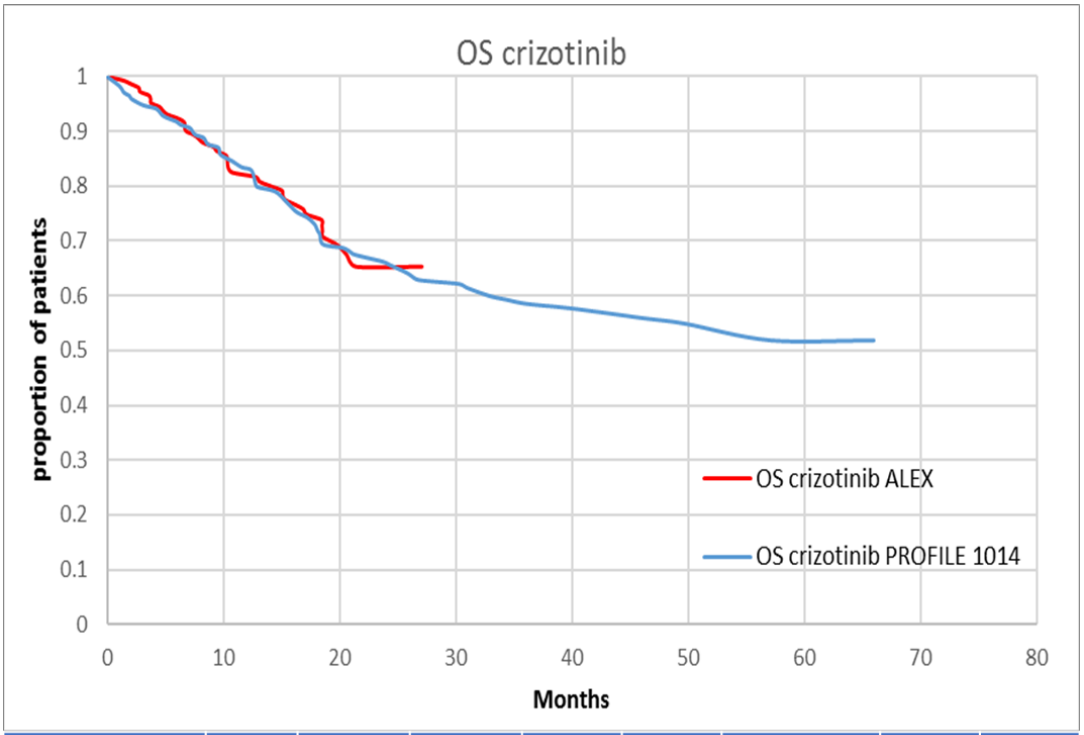
5.4.7.1 ERG critique

The ERG's clinical experts suggested most people with ALK+ advanced NSCLC are expected to live between 1 to 3 years from initiation of treatment with crizotinib. The experts' experience is substantiated by a recent audit of crizotinib for ALK+ advanced NSCLC at 20 UK centres since it was added to the Cancer Drugs Fund in 2012, although not limited to its use as a first line therapy.[69] Median OS for the 99 patients in the audit was 13.5 months, which compares to approximately 80% of crizotinib patients being alive at 12 months in ALEX and in PROFILE 1014 (Figure 28). The more mature PROFILE 1014 data shows a 4-year survival of 56.6%, which again is a very different estimate to the clinical experts' expectations.

The company considered that a naïve comparison of the ALEX and the PROFILE 1014 studies is inappropriate as patients in PROFILE 1014 are considered to be healthier and therefore, perform better. However, the ERG finds these populations comparable, to some degree. Comparing the crizotinib groups in ALEX and PROFILE 1014, the ERG notes the difference in the proportion of patients with brain metastases at baseline (38% in ALEX vs 26% in PROFILE 1014), and prior treatment for brain metastases (15% in ALEX vs 23% in PROFILE 1014), which may support the company's assertion, but considers other characteristics (age, ECOG performance status, stage of disease and smoking history) comparable between the two trials (see Section 4.3 for more details). In fact, Figure 28 shows a reasonable overlap of OS curves for crizotinib in ALEX and in PROFILE 1014.

As discussed in Section 4, different factors need consideration with regards to the estimated survival in ALEX, the most important one being the availability of subsequent therapies in the trial. As discussed in Section 4.3.5.1, there is considerable evidence that subsequent treatment with an ALK TKI have a substantial impact on OS after a first-line TKI. It is therefore, crucial that an analysis comparing subsequent treatments received by patients in ALEX, and the availability of such treatments in UK clinical practice is conducted. Unfortunately, such analysis is not possible, as of all patients who discontinued study treatment in ALEX, only 41% have data regarding subsequent treatment received. The type, or in fact existence, of subsequent treatments for the remaining 59% of the ALEX population is unknown and therefore any analysis of subsequent therapies in ALEX and its impact on trial outcomes is very incomplete and so flawed, as the data available for 41% of patients from ALEX might (or might not) present a very skewed picture of subsequent treatments regimens in the trial.

Figure 28. Kaplan-Meier OS data and numbers at risk from PROFILE 1014



Months	0	10	20	30	40	50	57	66
Left	172	143	110	88	72	54	34	0
Percentage at risk	100%	83%	64%	51%	42%	31%	20%	0%

In the previous appraisals of crizotinib and ceritinib there seems to have been a consensus that survival estimates in PROFILE 1014 were generally overestimated. Nonetheless, the FAD for ceritinib (ID1117) states that, "*the clinical experts noted that the survival rates in PROFILE 1014 were higher than in real-world studies. They suggested that this could be because a substantial proportion of people in PROFILE-1014 had subsequent lines of therapy, noting that survival rates have improved considerably in recent years. The clinical experts agreed that the population in PROFILE-1014 was generalisable to clinical practice and, on balance, considered that the survival estimates from PROFILE-1014 could be realistic*."[64]

To note is that in the previous appraisal of first-line crizotinib (TA406), the FAD reports that, "*to generate more realistic survival estimates relevant to the UK population, the company had adjusted PROFILE 1014 data to reflect the characteristics of patients in a retrospective cohort study from the US and Canada (Davis* et al. *2015). The committee discussed whether the characteristics of patients in the study reflected those of patients in England and noted from the company's sensitivity analyses that the assumptions were conservative. The committee concluded that it was satisfied with the company's approach*."[55]

The OS curve for PROFILE 1014 shown in Figure 28 shows the unadjusted trial data. The analysis performed in TA406 to adjust PROFILE 1014 data to real-life data, resulted in a median OS for

crizotinib of 21.7 months and a mean adjusted OS of 29 months. This compares to the approximately 68% of patients still alive in the unadjusted OS curve for PROFILE 1014 at 22 months (note that median OS was not reached in the unadjusted OS curve). Although it is not possible to draw final conclusions from this naïve comparison, it could be argued that if ALEX data were to be adjusted to real-life data, the survival predictions for crizotinib would be more conservative.

The ERG considers that ALEX does not provide robust evidence to substantiate a long-term OS benefit of alectinib compared with crizotinib. Furthermore, comparative OS data from ALEX may not be a reasonable reflection of what would be seen in UK clinical practice because treatment beyond PD may differ for alectinib and crizotinib in practice, and subsequent therapies available to patients in ALEX do not reflect the UK pathway for ALK+ advanced NSCLC.

5.4.7.1.1.1 Extrapolated survival curves

Overall, the ERG finds the company's description of the curve selection process slightly unclear. Nonetheless, the ERG agrees with the company's approach of selecting the exponential curves as these provide the most conservative pair of curves in terms of estimating relative treatment effectiveness (Figure 29).

The Committee for the ceritinib STA supported the use of an exponential distribution to model OS for crizotinib. The FAD states that, "*the company explained that recently published data from PROFILE-1014 suggested that 56.6% of patients who had crizotinib would be alive at 4 years and 44% would be alive at 5 years, which supports using the exponential function to extrapolate survival in the model*." Figure 29 is reasonably supportive of these estimates, with 5-year survival for crizotinib being approximately 40% in the model.

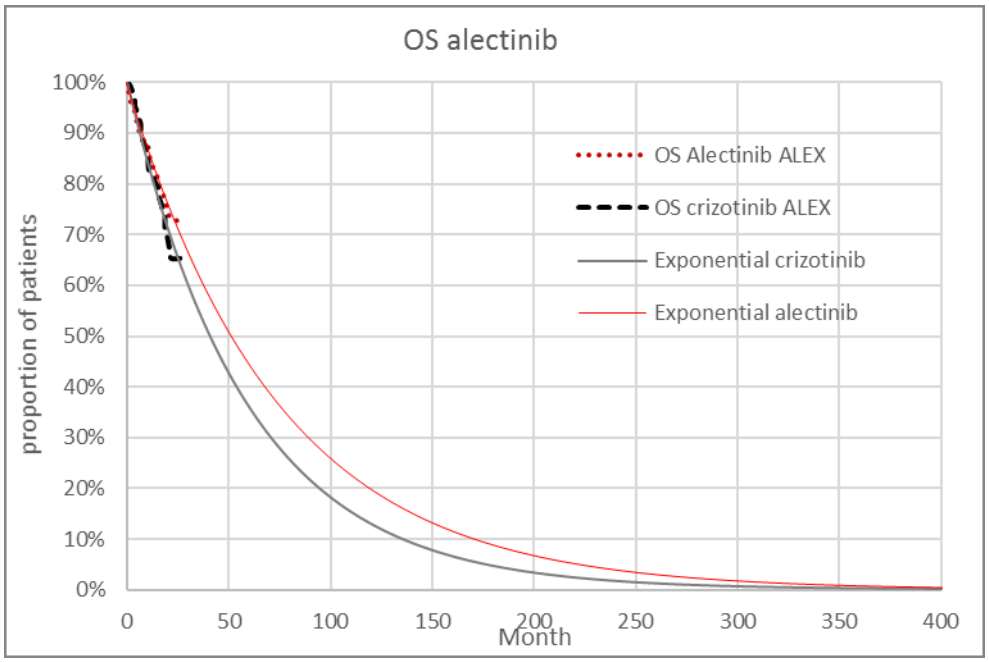
Nonetheless, the exponential distribution was the second-worst fitting distribution to the KM OS data for crizotinib. Additionally, using the exponential distribution to fit both treatment arms implicitly assumes PHs, which the company demonstrated is not a valid assumption for the observed OS data. Therefore, in the interest of consistency with the approach taken for the PFS data, the ERG requested that the company used the KM OS curve for the initial period of the model, where the fit of the exponential curve to the KM data was not very good. The company incorporated this scenario in their updated model (results are reported in Section 5.5 and Section 6).

The ERG emphasizes that the same caveats noted for the PFS approach apply to using the KM+exponential curves in the OS data. That is, the exponential tail of the curve was still derived from fitting an exponential distribution to the KM curve, which proved to be a bad fit for the crizotinib data; at 18 months (where the exponential tails are used in the model), the hazard ratio between the alectinib and crizotinib OS curves becomes proportional; the choice of the cut-off point (18 months) for the KM

data should have been better substantiated, and some sensitivity analysis should have been undertaken by the company to reflect the impact of changing this parameter in the analysis.

Similar to the PFS data analysis, the ERG undertook some initial exploratory analysis to assess the impact of using more flexible modelling options (for example, using spline models) to estimate OS in the model. Nonetheless, because the shape of the KM OS curves (Figure 26) exhibits a long plateau, all good-fitting curves are likely to produce very long tails. The spline curve fitted and extrapolated by the ERG did not produce dissimilar results from the exponential curves (from a visual assessment point of view). Given the spline model does not assume PHs, it might be of interest to assess what is the impact of including a spline model in the economic analysis on the final ICER.

Figure 29. Company's base case modelling of OS



5.4.8 Health-related quality of life

5.4.8.1 Health-related quality of life data used in cost-effectiveness analysis

The company estimated utility values associated with the PFS and the non-CNS PD health states in the economic model, through the use of ALEX data. The company also incorporated CNS PD utility data in the analysis, however these were estimated from different literature sources. In the model, utility values were assumed to be constant over time, although age-related utility decrements published in Ara and Brazier 2010 were incorporated into the analysis.[70] The company also accounted for the impact of adverse events and post-progression treatments on patients' quality of life in a scenario analysis. The company's analysis of HRQoL data in the economic model is outlined in Sections 5.4.8.1.1 to 5.4.8.1.4, and critiqued by the ERG in Section 5.4.8.2.

5.4.8.1.1 Health-related quality of life data obtained from the clinical trial

During the ALEX trial, patients completed the EQ-5D-3L questionnaire at trial entry (week 0) and thereafter every 4 weeks (in line with treatment administration) until disease progression. Upon disease progression, the EQ-5D was administered at the post-treatment visit (4 weeks after permanent treatment discontinuation), and then every follow up visit (every 8 weeks for the first 6 months, thereafter every 12 weeks). Table 19 summarises the EQ-5D data collected in ALEX at each time point.

Table 19. EQ5D in ALEX: Mean (SD) and number of observations collected at each time point (reproduced from the company's response to clarification Table 21)

Analysis Visit Window	Alectinib			Crizotinib		
	Number of observations	Mean	SD	Number of observations	Mean	SD
BASELINE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 32	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 44	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 52	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 56	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 60	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 64	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 68	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 72	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 76	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 80	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 84	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 88	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 92	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 96	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 100	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 104	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 108	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 112	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Week 116	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 120	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 124	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations used in the table: NR, not reported; SD, standard error						

Using these data, EQ-5D utilities were derived with a linear mixed effects model which included clinically relevant predictors of quality of life identified by the company. The relevant variables analysed in the model were chosen based on clinical reasoning, and included treatment (alectinib vs crizotinib); gender (male vs female); age; race (Asian vs non-Asian); CNS metastasis at baseline (IRC); and progressed vs non-progressed disease.

The company decided to exclude treatment type from the model as it was not found to be a statistically significant predictor of patients' quality of life. At clarification, a stepwise approach, excluding all variables with a p-value > 0.1 was provided to the ERG. The final model in the stepwise approach showed that treatment type, gender and CNS at baseline were not statistically significant predictors of patients' quality of life. Nonetheless, the company stated that excluding treatment type from the model (base case model in Table 20) and using a model including only statistically significant predictors of quality of life (final model in Table 20) yielded very similar results in terms of the estimated utility values (Table 21).

Table 20. Models used to estimate utility

Covariate	Estimate	SE	DF	P value
Base case mixed effects model				
Intercept	0.9208	0.05541	239	<0.0001
Gender (Female) [a]	-0.02641	0.02322	237	0.2566
Age [b]	-0.00189	0.000910	239	0.0385
Race (Asian) [c]	0.04726	0.02303	236	0.0412
CNS metastasis at baseline (yes) [d]	-0.02446	0.02352	239	0.2995
Disease Progressed (Yes)	-0.08911	0.009547	4357	<0.0001
Final model using stepwise approach (requested by the ERG)				
Intercept	0.8956	0.05270	240	<0.0001
Age [b]	-0.00190	0.000909	241	0.0380
Race (Asian) [c]	0.04857	0.02300	237	0.0357
Disease Progressed (Yes)	-0.08918	0.009546	4361	<0.0001
Abbreviations used in the table: DF, degrees of freedom; SE, standard error [a] 56% female, [b] mean age 55 years, [c] 46% Asian, [d] 41% CNS metastasis at baseline				

Table 21. Utility estimates from ALEX for the full patient population

Health state	Utility	SE
Final utility estimates (base case analysis)		
PFS	0.8138	0.012
PD	0.7247	0.014
Final utility estimates (stepwise approach requested by the ERG)		
PFS	[redacted]	[redacted]

PD	[redacted]	[redacted]
Abbreviations used in the table: PD, progressed disease; PFS, progression-free survival; SE, standard error		

Compared to the HRQoL evidence identified in the SLR, PFS-related utility estimates for crizotinib are consistent with those derived from ALEX. Utility estimates related with the PD state were not reported in the studies included in the company's SLR for HRQoL evidence, however, the company compared the utility estimates derived from ALEX to the values reported in the HTAs undertaken for crizotinib for the first-line treatment of advanced ALK+ NSCLC (Table 22). Following this, the company noted that the PD state (and simultaneously second-line treatment) associated utilities identified in the literature were lower than the PD state utilities derived from ALEX. The company relates this to the availability of TKIs as subsequent therapies in ALEX, and added that PD state utilities are not as inconsistent once a utility associated with CNS progression is incorporated in the analysis (Section 5.4.8.1.2).

Table 22. Summary of utilities from identified health technology appraisals (reproduced from Table 26 of the CS)

Study	Population details	Mean HSUVs		
		Pre-progression	Post-progression	Other
pCODR crizotinib resubmission 2015[54]	Locally advanced or metastatic ALK+ NSCLC	NR	NR	NR
NICE TA406 2016[55]	Locally advanced or metastatic ALK+ NSCLC	Crizotinib: redacted Pemetrexed + platinum: redacted Treatment beyond progression with crizotinib: redacted	Docetaxel (2L): 0.66 BSC (3L): 0.47	Disutilities associated with AEs: Elevated transaminases: 0.00 Neutropenia: 0.09 Anaemia: 0.07 Leukopenia: 0.09 Thrombocytopenia: 0.09
SMC 1152/16[56]	Advanced ALK+ NSCLC	Crizotinib: 0.81 Pemetrexed + platinum: 0.72	Docetaxel (2L): 0.66 BSC (3L): 0.47	
Abbreviations used in the table: 2L, second-line; 3L, third-line; AE, adverse event; ALK+, Anaplastic lymphoma kinase positive; HSUV, health state utility value; NSCLC, non-small cell lung cancer; NR, not recorded; pCODR, pan-Canadian Oncology Drug Review; SMC, Scottish Medicines Consortium				

5.4.8.1.2 Impact of CNS progression on patients' quality of life

Based on the analysis of the EQ-5D data obtained from ALEX, the presence of CNS metastases at baseline does not show a statistically significant impact on the quality of life of patients (Table 20). The company attributed this to the fact that the EQ-5D might not be sensitive enough to capture changes in the CNS and to the fact that the group of patients with CNS at baseline in ALEX might not accurately represent CNS patients in clinical practice, as these had to be well enough to participate in the trial. Nonetheless, the company's clinical experts advised that CNS metastases have a negative impact on patients' wellbeing and therefore, the company sought the literature to identify utility data on CNS metastases in patients with ALK+ NSCLC.

As part of the clarification process, the ERG asked the company to explore the impact of CNS metastases further, by undertaking a subgroup analysis of the EQ-5D data collected in ALEX for the group of patients experiencing CNS progression. To reflect the base case utility analysis, the mixed model provided by the company at clarification considered the same clinically relevant predictors. Two CNS PFS analyses were made available to the ERG: one based on IRC RECIST plus IRC CNS RECIST criteria, and another based only on IRC RECIST criteria.

The analyses provided by the company showed CNS-progressed disease utility (Table 23) to be higher than the progressed disease utility for any progression location (Table 21). The company attributed this result to the low number of observations in the CNS progressive disease subgroup (73 in alectinib and 432 in crizotinib, compared with 2341 and 1690 in the non-CNS progression group, respectively) and the limited length of follow up post-progression. The company concluded there was insufficient evidence available from the ALEX trial to demonstrate the detrimental impact of CNS progressions on patients' quality of life.

Table 23: Utility estimates from ALEX for the group of patients experiencing CNS progression

Health state	Utility	SE
CNS PFS (IRC, RECIST + IRC CNS-RECIST) utility estimates		
PFS	[redacted]	[redacted]
CNS-progressed disease	[redacted]	[redacted]
CNS PFS (IRC, RECIST) utility estimates		
PFS	[redacted]	[redacted]
CNS-progressed disease	[redacted]	[redacted]
Abbreviations used in the table; PFS, progression-free survival; SE, standard error		

Therefore, the company concluded that literature should be sought to appropriately capture quality of life for these patients and used the Roughley *et al.* 2014 paper which measured HRQoL using the EQ-5D in 498 patients in France and Germany with NSCLC in one metastatic site, either brain, contralateral lung, adrenal gland, bone or liver. Roughley *et al.* 2014 estimated utility values for each metastatic site, including a value of 0.52 for brain metastases, which the company applied to all patients entering the CNS-progressed disease state in the economic model.[71]

5.4.8.1.3 Adverse events

The model includes all grade 3 and 4 TRAEs with an incidence of ≥ 3% in either arm of the ALEX trial, and all grade 5 TRAEs irrespective of incidence. The proportions of patients experiencing each TRAE in the model have been previously reported in Section 5.4.6.

In the base case, the company assumed AE-related disutilities were implicitly incorporated into the PFS and PD utilities derived from the EQ-5D data in ALEX, and therefore considered that incorporating an additional disutility could lead to double counting. However, as a scenario analysis, the company

explored the possibility that averaged trial-derived utilities underestimated disutilities associated with adverse events, and applied additional disutilities to TRAEs (neutropenia and pneumonitis), which clinical experts expected to impact patients' quality of life. Table 24 summarises the disutilities due to TRAEs applied by the company as a scenario analysis.

Table 24. Disutilities due to TRAEs: scenario analysis (adapted from Table 28 of the CS)

TRAE	Utility decrement	Duration (days)	Source
Neutropenia	-0.09	5	Nafees *et al.* 2008[72]
Pneumonitis (G5)	-0.20	5	Utility: Beusterien *et al.* 2010[73] Duration: assumption, equivalent to neutropenia
Alanine aminotransferase increased	0	NA	Assumption based on clinical expert feedback
Asparatate aminotransferase increased	0	NA	Assumption based on clinical expert feedback
Cardiac Arrest (G5)	0	0	Assumption immediate transition to death
QT interval prolongation	0	NA	Assumption based on clinical expert feedback
Abbreviations used in the table: G5, grade 5; NA, not applicable; TRAE, treatment-related adverse event			

5.4.8.1.4 Subsequent therapies

The impact of subsequent therapies in patients' quality of life was only captured in a scenario analysis undertaken by the company. As ALEX did not capture the length of time that patients spent on subsequent therapies, the company derived the time on second line treatment using a targeted literature search for the pivotal trials of subsequent treatments in the second line treatment setting (Table 25). While on the CNS PD or the non-CNS PD states (considered to be the second line treatment phase), patients were allocated to either a TKI (29%) or a non-TKI (71%) treatment after alectinib; or to a TKI (28%) or a non-TKI (72%) treatment after crizotinib. Patients were then attributed a TKI or non-TKI-related utility (Table 26).

Table 25. Duration of utility estimates (scenario analysis) (adapted from Table 30 of the CS)

Health state	Duration 2nd line (weeks)	Source	Comment
TKI-treatments 2L PPS			
Ceritinib	41.89	ASCEND-5[38]	2L PPS TKI-utility is applied in PD state for a duration equal to the average estimated mean weeks in PFS of ceritinib in the crizotinib-failure setting (as derived from the ASCEND 5 trial based on a median PFS by INV of 6.7 months)
Alectinib	60.20	ALUR [74]	2L PPS TKI-utility is applied in PD state for a duration equal to the average estimated mean weeks in PFS of alectinib in the crizotinib-failure setting (as derived from the ALUR trial based on a median PFS by INV of 9.6 months). ALUR was identified as opposed to PROFILE 1007 to provide information in a prior TKI setting, as opposed to prior chemotherapy setting.
Crizotinib and other TKIs	48.14	PROFILE 1007 [75]	2L PPS TKI-utility is applied in PD state for a duration equal to the average estimated mean weeks in the

			post-chemotherapy setting (as derived from the PROFILE 1007 trial based on median PFS by INV of 7.7 months)
Average TKI-related duration	50.1	-	-
Non-TKI-treatments 2L PPS			
Chemotherapy	8.8	ALUR [74]	2L PPS non-TKI utility is applied in PD state for a duration equal to the estimated mean PFS of patients on chemotherapy in the crizotinib-failure setting (as derived from the ALUR trial based on a median PFS by INV of 1.4 months)
3L PPS			
BSC (3L)	Remaining time to death	Assumption	-
Abbreviations used in the table: BSC, best supportive case; PFS, progression-free survival; PPS, post-progression survival; TKI, tyrosine-kinase inhibitor			

Table 26. Utility estimates (scenario analysis) (reproduced from Table 29 of the CS)

Health state	Utility	Variance	Source
PPS 2nd line in PD for TKI	0.7247	0.014	ALEX mixed model
PPS 2nd line in PD for non TKI	0.6600	0.040	PROFILE 1007 - Docetaxel arm
PPS 3rd line in BSC	0.4700	0.101	Nafees *et al.*2008[72]
Abbreviations used in the table: BSC, best supportive case; PPS, post-progression survival; TKI, tyrosine-kinase inhibitor			

5.4.8.2 ERG critique

The company measured changes in HRQoL directly from patients in the ALEX trial, using a generic preference-measured measure (EQ-5D), therefore, following the key components of the NICE reference case. Overall, the ERG finds the EQ-5D data captured in ALEX to be informative. Nonetheless, the ERG is concerned with the low compliance rates seen for both treatment arms (62% for alectinib and 52% for crizotinib patients). Furthermore, the ERG asked the company what the mean age of responders was in the EQ-5D analysis, and the company replied that the mean age of responders was considered equivalent to the mean age of the trial (55 years).

The ERG has two main concerns regarding the company's modelling approach including: the utility value applied to patients with CNS metastases and the quality of life of patients on subsequent therapies. Each of these issues is discussed in turn below.

5.4.8.2.1 Impact of CNS progression on patients' quality of life

The HSUV associated with CNS progression were taken from Roughly *et al.* 2014[71], which observed no statistically significant difference in utility values between brain and bone metastases. Clinical experts advised the ERG that although brain metastases severely impact patients' quality of life, the development of metastases in other locations also affects patients' wellbeing. For completeness, the ERG asked the company to provide the number of patients in ALEX with bone metastases at data cut

off as per the IRC endpoint, by treatment arm. The company, in their reply to the ERG's clarification question, stated bone metastases data are not currently available from ALEX.

Furthermore, Roughley *et al.* 2014 is a conference abstract, providing a limited description of methods and results.[71] Consequently, the ERG could not investigate in detail the data used, and it was not possible to compare patient demographics with the population in ALEX, as advised by the TSU (DSU document 12).[76]

Given the company's conclusion that the PD state-related utilities identified in the literature are generally lower than the PD state utilities derived from the ALEX trial (which the company attributed to the availability of TKIs as subsequent therapies in the trial), and because Roughley *et al.* 2014 did not report the utility associated with progressed patients without brain metastases, it is not possible to assess if the utility values related with general disease progression (without CNS metastases) are comparable in ALEX, and in the paper. It is possible the utility values for overall progressed patients in Roughley *et al.* 2014 are lower than in ALEX, which would mean that using an unadjusted CNS utility value from Roughley *et al.* 2014 potentially overestimates the impact of CNS metastases on patients' quality of life. This would, in its turn, lead to an overestimation of the benefit of alectinib, considering its advantageous profile in preventing CNS progression.

During the clarification stage, the company explained that targeted literature searches were carried out in PubMed, *Value in Health* and previous TAs in NSCLC submitted to NICE, in order to find the appropriate evidence sources for informing the impact of CNS progression on patients' quality of life. The ERG considers the search terms and reasons for exclusion to be sufficient, and agrees that the best available sources were chosen to inform the model. Nonetheless, the source used is not without its faults, thus the ERG flags the value of conducting additional research to identify the impact of CNS metastasis on patients' quality of life, to reduce the current uncertainty.

To explore this issue, and considering that CNS-related utility value is one of the key drivers of the economic results, the ERG ran a scenario where the utility associated with CNS progression was varied by a range of values. The detailed results of these analyses are presented in Section 6.

5.4.8.2.2 Subsequent therapies

The company, in their clarification response, explained that quality of life data by type of subsequent therapy received was not directly available from the trial; hence, differentiating utility by type of subsequent therapy was explored only as scenario analysis. The company added that this scenario analysis did not account for the impact of CNS metastases, and required a number of assumptions to determine the duration of time for which each utility should be applied.

The company used the merged ALEX data on second and third line treatment (Table 14) to estimate the proportion of patients receiving treatment after alectinib or crizotinib. The combined values, reweighted to account for the fact that not all patients had their data collected on subsequent therapies, is reported in Table 27.

Table 27. Estimation of subsequent therapies in the company's model

	Alectinib (N=152, n=68)		Crizotinib (N=151, n=105)	
Treatment	**n**	**%**	**n**	**%**
Any subsequent anti-cancer therapy	40	59%	44	42%
Any TKI	19	48%	36	82%
Ceritinib	4	10%	14	32%
Alectinib	0	0%	10	23%
Crizotinib	9	23%	2	5%
Other (lorlatinib, brigatinib, gefitinib, entrectinib, erolotinib)	6	13%	10	23%
Platinum compound (carboplatin, cisplatin)	19	48%	6	13%
Antimetabolite (pemetrexed, gemicitabine)	17	43%	6	13%
Taxane (paclitaxel, docetaxel)	3	8%	1	2%
Immunostimulant (nivolumab)	2	5%	0	0%
Angiogenesis inhibitor (bevacizumab)	2	5%	0	0%
Other (cyclophosphamide, antineoplastic agent NOS, anti PD-L1, doxorubicin, vincristine)	4	10%	1	2%
Total	66	165%	50	114%
Patients on TKIs	-	**29%***		**72%'**
Patients on non-TKIs	-	**71%^**		**28%+**

Abbreviations: NOS, not otherwise specified; PD-L1, programmed death-ligand; TKI, tyrosine kinase inhibitor
* 48% divided by 165%
^ 1 minus 29%
' 82% divided by 114%
+ 1 minus 72%

Not surprisingly, the incremental QALYs gained with alectinib reduce in this scenario analysis, as a higher proportion of crizotinib patients receive a subsequent TKI, compared with the proportion of patients receiving a TKIs in the alectinib arm. As a result, the impact of the company's scenario analysis was large, with the ICER increasing from £72,544 to £95,820 using list prices. Due to the incompleteness of data on subsequent treatments received across treatment arms in ALEX, the scenario analysis provided by the company needs to be interpreted with extreme caution.

The ERG considers the estimates used in the economic model are likely to be a poor reflection of clinical practice. With regards to crizotinib, the England audit data[48] available suggests that 18% of patients who received crizotinib, received a second-line TKI (Section 4). Nonetheless, the audit estimates could be underestimated because the audit was not limited to first line crizotinib, and as the clinical experts advising the ERG have explained, clinical practice has been rapidly evolving in this setting, with more patients getting access to more subsequent treatment options. This estimate differs greatly from the 72% assumed by the company in their analysis. Furthermore, clinical expert opinion provided to the ERG

indicated that (although there is not clinical consensus on how to treat progressed patients after alectinib), it would appear plausible that alectinib patients would be fitter than crizotinib patients, and therefore more likely to tolerate subsequent treatment with a TKI than crizotinib patients. The clinical experts added that the reason why in the UK a relatively low percentage of patients receives TKI treatment after crizotinib is related to the development of CNS metastases, which leave the patients too ill to receive a further TKI, therefore only having chemotherapy as an option. As clinical experts anticipate that alectinib will have a protective effect on the CNS, compared with crizotinib, it is likely that a higher percentage of alectinib patients receive a subsequent TKI. Again, this is contradictory to the data used by the company in the model, where a considerably higher proportion of patients receives a TKI after crizotinib than after alectinib (72% vs 28%).

The ERG also agrees with the company that this scenario analysis is flawed by not including the impact of CNS on patients' quality of life, therefore underestimating the benefit of alectinib. Another important point, is the possibility that people continuing treatment beyond disease progression may have a better quality of life than those with progressed disease who switch treatment.

Overall, the ERG considers that the impact of subsequent therapies on patients' quality of life is potentially a key model driver. The company did not run a scenario analysis to portray the distribution of patients across subsequent therapies reflecting clinical practice in the UK. Therefore, the ERG ran three scenario analyses to reflect the uncertainty around the changes in clinical practice if alectinib is recommended. These scenarios consist of the following:

1. Assuming patients on alectinib are more likely to receive a subsequent TKI than crizotinib patients;

2. Assuming patients on alectinib are equally likely to receive a subsequent TKI as crizotinib patients;

3. Assuming patients on alectinib are less likely to receive a subsequent TKI than crizotinib patients.

All patients not receiving a TKI as subsequent treatment were assumed to receive a non-TKI (i.e. 100% of patients receive subsequent treatment in the ERG's analysis). As clinical experts could not find a consensus on the likely proportion of patients to allocate to these scenarios, the ERG used the ALEX trial data and the England audit data as a form of validation. Given the ERG's concerns that the proportions used by the company (approximately 70% of crizotinib patients receive a subsequent TKI and 30% of alectinib patients receive a subsequent TKI) are not reflective of clinical practice, the ERG had to make some assumptions with regards to the missing data on the 59% of patients and their subsequent treatments in ALEX. Given the England audit data suggests 18% of patients receive a

second-line TKI after crizotinib, the ERG assumed that the 31.4% (Table 14) receiving a TKI after crizotinib in ALEX could be a reasonable approximation to the UK clinical practice. In order to estimate the proportion of patients receiving a TKI after alectinib, the ERG assumed the following:

1. For scenario 1 described above, it was assumed that 64% of patients receive a TKI after alectinib. This estimate assumes that all the 97 alectinib patients with missing data on subsequent treatments in ALEX received a TKI. To these 97 patients add the 13 patients for whom there are data, and are known to have received a subsequent TKI (Table 14);

2. For scenario 2, it was assumed that 31.4% of patients get a TKI after alectinib;

3. For scenario 3, the ERG took the minimum know value from ALEX, which is based on the 13 alectinib patients receiving a second-line TKI (Table 14). This amounts to 19.1% (13 divided by 152) of patients receiving a post-alectinib TKI.

This analysis is caveated by the fact that CNS impact on patients' quality of life has not been included in the analysis, and that the sources for utility values and treatment duration related with subsequent therapies are derived from various literature sources.

Furthermore, these analyses need to be accompanied by the respective costs of receiving subsequent therapies, which are discussed in Section 5.4.9. In their scenario analysis, the company included a third line treatment option in the model, with respective QALYs. However, in the cost analysis, patients in the model only receive up to two treatment lines. For consistency purposes, the ERG removed the third-line treatment option from the QALY analysis, when combining the cost and QALY analysis together (Section 6).

5.4.9 Resources and costs

The costs included in the economic model are listed below and discussed in detail in this section:

- Acquisition and administration costs associated with the intervention and comparator (Section 5.4.9.1);
- Acquisition and administration costs associated with subsequent treatments (Section 5.4.9.2);
- Disease management costs (Section 5.4.9.3);
- Costs of managing adverse events (Section 5.4.9.4);
- Other costs (Section 5.4.9.5).

5.4.9.1 Acquisition and administration costs associated with the intervention and *comparator*

Drug acquisition costs used in the model for alectinib and crizotinib are presented in Table 28 using list prices; however, both treatments are associated with confidential PASs. For alectinib, there is a simple PAS of [redacted] discount from the list price. The current list price for alectinib is £5,032 per pack, with resulting net price following PAS application of [redacted] per pack. The discount for alectinib applies to all populations within the anticipated marketing authorisation.

The dosing schedule modelled by the company for alectinib was 1200mg per day (600mg twice daily) and for crizotinib 500mg per day (250mg twice daily), in line with the SmPC[29] for those treatments, and with the dosages received in ALEX. To reflect the marketing authorisation, alectinib was administered until disease progression in the model, although in ALEX patients could continue alectinib or crizotinib after disease progression at the investigator's discretion. While a discontinuation rule for crizotinib is not specified in the SmPC, the same rule for administration was implemented in the model (i.e. until disease progression).

Clinical experts advising the company reported that alectinib and crizotinib would be provided as full-packs at a specified lung cancer clinic, every 4 weeks by a pharmacist, with patients then self-dosing until their next appointment (Table 29). This was incorporated into the economic model by applying the full-pack cost and administration cost, up-front, every 4 cycles (i.e. every 4 weeks) to patients in the PFS health state. Therefore, if a patient died or discontinued between appointments, the remaining pack is considered 'waste'. However, the company ran a scenario analysis without wastage by applying the acquisition and administration costs every cycle (i.e. 1 week) to patients in the PFS state.

Table 28. Drug acquisition costs (list prices) used in the cost-effectiveness model (adapted from Table 33 of the CS)

Drug	Pack concentration (per tablet)	Pack volume	Dose per pack	Cost per pack	Cost per unit	Cost per mg	Source
Alectinib	150 mg	224	33,600 mg	£5,032.00	£22.46	£0.15	BNF
Crizotinib	250 mg	60	15,000 mg	£4,689.00	£78.15	£0.31	BNF
Abbreviations used in the table: BNF, British National Formulary							

Table 29. Drug administration costs used in the cost-effectiveness model (adapted from Table 38 of the CS)

Drug	Administration type	Source	Administration cost	Cost per week
Alectinib	12 minutes of pharmacist time every 4 weeks (hospital pharmacist band 6)	PSSRU 2016[77]	£9.20	£2.30
Crizotinib	12 minutes of pharmacist time every 4 weeks (hospital pharmacist band 6)	PSSRU 2016[77]	£9.20	£2.30
Abbreviations used in the table: PSSRU, Personal Social Services Research Unit				

5.4.9.2 Subsequent therapy costs

The company's updated base case model includes a "basket" of subsequent treatments to reflect the ALEX treatment regimen, as opposed to the anticipated market share of ceritinib, crizotinib and docetaxel obtained from the company's clinical experts (used in the company's original model). However, it is important to note that subsequent therapy data were only available for 41% of the 173 patients (68 alectinib and 105 crizotinib) in ALEX who progressed and permanently discontinued study treatment. Moreover, acquisition costs were not available for three developmental products (loratinib, brigatinib and entrectinib) received by 13 patients (6 alectinib and 7 crizotinib) in ALEX as subsequent therapies, therefore the company disregarded these for costing purposes.

Based on the available treatment options in ALEX, summarised in Table 30, the company calculated a weighted average cost per cycle on the assumption that 100% of patients in the model receive second line treatment. The company also assumed all subsequent treatments are mutually exclusive and second line treatments, although some were received as combination treatments and as third or further line therapies in ALEX.

At clarification, the company also provided an additional scenario analysis to address the ERG's clinical expert's view that docetaxel is not the only chemotherapy agent used to treat ALK+ NSCLC in the UK, as modelled by the company in their initial submission. In this scenario, also summarised in Table 30, the company assumed pemetrexed and docetaxel are given as single therapies, and pemetrexed in combination with carboplatin (or cisplatin) are given as combination therapies. The composition of the chemotherapy market share was also adjusted to reflect the company's expected values, but the market shares for second line ceritinib, alectinib, crizotinib and overall chemotherapies remained equal to the company's initial submission.

As described in Section 5.4.8.1.4, the company derived the mean time on subsequent treatment from alternative clinical trials and published literature in the second line setting, as ALEX did not accurately capture the length of time patients spent on subsequent therapies. Following this, all chemotherapies were assumed to incur the same time on treatment as docetaxel and all other TKIs were assumed to have the same treatment length as crizotinib.

Table 30. Subsequent therapy shares and time on treatment (reproduced from the economic model provided at clarification)

Drug	Alectinib n (%)	Crizotinib n (%)	Mean duration (weeks)	Duration source
Revised base case				
Ceritinib	4 (7%)	14 (24%)	41.89	ASCEND - 5 [38]
Alectinib	0 (0%)	10 (17%)	60.20	ALUR [74]
Crizotinib	9 (15%)	2 (3%)	48.14	PROFILE 1007 [75]
Gefitinib	0 (0%)	2 (3%)	41.89	ASCEND - 5 [38]

Erlotinib	0 (0%)	1(2%)	41.89	ASCEND - 5 [38]
Cisplatin	7 (12%)	5 (8%)	8.83	ALUR [74]
Carboplatin	12 (20%)	1 (2%)	8.83	ALUR [74]
Pemetrexed	15 (25%)	5 (8%)	8.83	ALUR [74]
Gemcitibine	2 (3%)	1 (2%)	8.83	ALUR [74]
Paclitaxel	3 (5%)	0 (0%)	8.83	ALUR [74]
Docetaxel	0 (0%)	1 (2%)	8.83	ALUR [74]
Nivolumab	2 (3%)	0 (0%)	9.97	NICE TA484*
Bevacizumab	2 (3%)	0 (0%)	25.13	Heist et al. 2008*[78]
Cyclophosphamide	1 (2%)	0 (0%)	8.83	ALUR [74]
Doxorubicin	1 (2%)	0 (0%)	8.83	ALUR [74]
Vincristine	1 (2%)	0 (0%)	8.83	ALUR [74]
Scenario analysis				
Ceritinib	0%	90%	41.89	ASCEND - 5 [38]
Alectinib	0%	0%	60.20	ALUR [74]
Crizotinib	60%	0%	48.14	PROFILE 1007 [75]
Chemotherapy	40%	10%	8.83	ALUR [74]
Composition of chemotherapy				
Docetaxel	85%	85%	8.83	ALUR [74]
Pemetrexed	5%	5%	8.83	ALUR [74]
Pemetrexed + carboplatin	5%	5%	8.83	ALUR [74]
Pemetrexed + cisplatin	5%	5%	8.83	ALUR [74]

*Bevacizumab and nivolumab have a maximum number of cycles defined within the product SPC or NICE recommendations, however are applied for simplicity until progression. Mean duration = median duration * number of weeks per month

The acquisition cost of subsequent therapies in Table 31 reports the list price, however, ceritinib, alectinib, crizotinib, gefitinib, erlotinib and nivolumab are subject to confidential PASs. Based on the average weight (66.6kg) and height (164.7cm) of patients included in ALEX, a body surface area of 1.73m^2 was assumed for patients in the model to calculate doses dependent on surface area, or body weight.

Table 31. Drug acquisition costs used in the cost-effectiveness model for subsequent therapies (reproduced from updated economic model)

Drug	Composition	Pack volume	Price per pack	Cost per unit	Frequency	Source	Weekly cost*
Alectinib (oral tablet)	150 mg/ tablet	224	£5032	£22.5	1200mg daily	Alectinib dose: 600mg administered orally twice-daily from day 1 (total: 1200mg). List price: Alecensa 150mg x 224 Capsules: £5032.00 [79]	£1,262
Crizotinib (oral tablet)	250 mg/ tablet	60	£4689	£78.2	500 mg daily	Crizotinib dose: 250 mg administered orally twice-daily from day 1 (total: 500mg). List price: £4689	£1,098

						per 60 capsules (200mg and 250mg) [79]	
Ceritinib (oral tablet)	150 mg/ tablet	150	£4923	£32.8	750mg daily	Ceritinib dose: 750 mg administered orally once-daily from day 1. List price: 150mg x 150 capsules: £4923.00 [79]	£1,153
Gefitinib (oral tablet)	250mg/ tablet	30	£2168	£72.3	250mg once daily	List price, source eMIMs	£506
Erlotinib (oral tablet)	150mg/ tablet	30	£1632	£54.4	150mg once daily	List price, source eMIMs	£381
Gemcitabine (IV powder for infusion)	200mg	1	£3.7	£3.7	1g/m2 3 x per 4 weeks	1g/m2 once weekly for 3 weeks, followed by a rest week; then repeat 4-week cycle, source of price eMIT (costed as powder as vials were slightly more expensive)	£30
	1g	1	£8	£8			
Paclitaxel (IV solution for infusion)	100mg	1	£9.8	£9.8	175mg/m2 every 3 weeks	175 mg/m2 administered over 3 hours with a 3-week interval between courses, price from eMIT[80]	£12
	150mg	1	£12.6	£12.6			
	30mg	1	£3.7	£3.7			
Nivolumab (IV solution for infusion)	40mg	1	£439	£439	3mg/kg every 2 weeks	3mg/kg by iv inf over 60 mins every 2 weeks, price from eMIMS - list price (PAS applies in UK practice)	£1,097
	100mg	1	£1097	£1,097			
Bevacizumab (IV solution for infusion)	100mg	1	£242.7	£242.7	7.5 - 15mg/kg every 3 weeks for a maximum of 6 cycles	7.5mg/kg or 15mg/kg once every 3 weeks in addition to platinum-based chemotherapy for up to 6 treatment cycles, price from eMIMS - list price	£616
	400mg	1	£924.4	£924.4			
Cyclophosphamide (oral tablet)	50mg	100	£139	£1.4	100 - 300mg daily	100 – 300 mg daily (SPC), price from eMIT [80]	£10
Doxorubicin (IV solution for injection)	200mg	1	£17	£17	60-75mg/m2 every 3 to 4 weeks	60-75mg/m2 of body surface area, each treatment cycle can be repeated every 3 to 4 weeks (SPC), price from eMIT [80]	£3
	50mg	1	£4.5	£4.5			
	10mg	1	£1.3	£1.3			
Vincristine (IV solution for injection)	5mg	5	£91	£18.1	1.4 - 1.5mg/m2 weekly	Administered intravenously at weekly intervals. The recommended dose is 1.4 to 1.5 mg/m2 up to a maximum weekly dose of 2 mg (SPC), price from eMIT [80]	£24
	2mg	5	£29	£5.9			
	1mg	5	£19	£3.7			
Pemetrexed (IV powder for vial)	100mg	1	£160	£160	500 mg/m² every 21 days	eMIMS	£480
	500mg	1	£800	£800			
Carboplatin (IV vial)	600mg	1.00	£27.89	£27.89	400 mg/m² every >= 28 days	eMIT [80]	£9
	450mg	1.00	£20.39	£20.39			
	150mg	1.00	£7.49	£7.49			
	50mg	1.00	£3.25	£3.25			
	100mg	1	£8	£8		eMIT [80]	£4

Cisplatin (IV vial)	50mg	1	£6	£6	50—100mg/m2 every 3—4 weeks or 15—20mg/m2 daily for 5 days every 3—4 weeks		
	10mg	1	£2	£2			
Docetaxel (IV vial)	1	1	£3.85	£3.85	75 mg/m² every 21 days	Docetaxel dose (2L NSCLC): 75 mg/m² every 21 days. Source: eMIT [80]	£7
	7	1	£20.62	£20.62			
Abbreviations used in the table: Emit, electronic market information tool; IV, intravenous; MIMS Monthly Index of Medical Specialities; NSCLC, non-small cell lung cancer; SPC, summary of product characteristics; PAS, patient access scheme *In the base case vial sharing is not included							

Similarly to the first-line setting, treatment administration costs for oral ALK inhibitors were assumed to incur 12 minutes of a pharmacist's time every 4 weeks, at a cost of £9.20 per administration (Table 32).[77] As for non-TKI inhibitors, the company assumed the cost of a simple chemotherapy administration (£198.94), as described in NHS Reference Costs (Table 32), every 21 days.[81]

Table 32. Drug administration costs used in the cost-effectiveness model for subsequent therapies (adapted from Table 39 of the CS)

Drug	Administration type	Source	Administration cost	Weekly cost
Alectinib	12 minutes of pharmacist time every 4 weeks (hospital pharmacist band 6)	PSSRU 2016[77]	£9.20	£2.30
Crizotinib	12 minutes of pharmacist time every 4 weeks (hospital pharmacist band 6)	PSSRU 2016[77]	£9.20	£2.30
Ceritinib	12 minutes of pharmacist time every 4 weeks (hospital pharmacist band 6)	PSSRU 2016[77]	£9.20	£2.30
Non-TKI inhibitors	Parenteral Chemotherapy delivered in an outpatient setting	NHS Reference Costs 2015-16 (SB12Z)[81]	£198.94	£64.70
Abbreviations used in the table: PSSRU, Personal Social Services Research Unit				

Subsequent therapies provided during disease progression were assumed to be the same with or without CNS metastasis. To calculate the cost per cycle (weekly cost), the total cost of a second line treatment was divided by the total number of weeks spent in the PD states with and without CNS metastasis, estimated in the economic model, for each treatment arm. The resulting cost per week for each treatment arm using those parameters is summarised in Table 33.

Table 33. Total cost of second line treatment applied in the model per cycle

Parameters	Alectinib	Crizotinib
Revised base case		
Total cost of 2nd line treatment	£13,348.08	£27,486.21
Time in PD with or without NCS progression (weeks)	178.43	197.44

Cost of 2nd line treatment per cycle	**£74.81***	**£139.21***
Scenario analysis		
Total cost of 2nd line treatment	£32,281.39	£43,665.12
Time in PD with or without CNS progression (weeks)	178.43	197.44
Cost of 2nd line treatment per cycle	£189.92	£221.15
*Values taken from the economic model as the ERG found a discrepancy between company's reply to clarification questions and economic model Abbreviations used in the table: CNS, central nervous system; PD, progressed disease		

5.4.9.3 Disease management costs

Disease management cost for PFS were estimated, irrespective of treatment arm (Table 34). The same is true for patients with progressed disease (Table 35), except for the additional cost applied to patients with CNS metastasis (Table 36).

The costing of CNS metastases was revised at clarification to include corticosteroids (dexamethasone) and stereotactic radiosurgery (SRS), rather than just SRS. In addition, following consultation with the company's clinical experts, the company explored a scenario where 77% of patients receive whole-brain radiotherapy (WBRT) and 23% of patients receive SRS. The estimated cost of WBRT amounts to a total of £4,200.

The types of resource and frequency of use were derived by the company from the SLR, previous NICE TAs, ESMO Clinical Practice Guidelines, and UK clinicians' opinion.[55, 82] Unit costs were derived from NHS Reference Costs, the Electronic Market Information Tool (eMIT), and the Personal Social Services Research Unit (PSSRU).[77, 80, 81]

Table 34. Resource use and costs for PFS health state (adapted from Table 40 and Table 43 of the CS)

Resource	No. required per month	% of patient requiring resource	Unit cost	Cost per month	Resource use source	Unit cost source
Consultant-led outpatient visit / oncologist	0.75	100%	£167.08	£125.31	TA406[55]	NHS reference costs (2015-16)[81] Medical oncology (code: 370), consultant-led appointment
GP visit	1	10%	£45.68	£4.57	TA406[55]	PSSRU 2016[77] 10.8b: Per patient contact lasting 11.7 minutes, including direct care staff costs, with qualification costs
Cancer nurse	1	50%	£67.30	£33.65	TA406[55] Further input provided from clinical experts	NHS reference costs (2014-2015)[83]; Nurse cancer relate adult face-t-face (N10AF); Inflated to 2015/16 using PSSRU (2016)[77]
Full blood test	1	100%	£3.10	£3.10	TA406[55] Further input provided from clinical experts	NHS reference costs (2015-16)[81] DAPS05: direct access pathology; haematology
Biochemistry	1	100%	£1.18	£1.18	TA406[55] Further input provided from clinical experts	NHS reference costs (2015-2016)[81] DAPS04
CT scan	0.5	100%	£118.53	£59.27	TA406[55] Further input provided from clinical experts	NHS reference costs (2015-16)[81] RD22Z: Computerised Tomography Scan of one area, with pre and post contrast
MRI scan	0.2	50%	£202.70	£20.27	Clinical expert opinion	NHS reference costs (2015-16)[81] RD03Z; Magnetic Resonance Imaging Scan of One Area, with Pre- and Post-Contrast
X ray	0.3	50%	£37.30	£5.56	Clinical expert opinion	NHS reference costs (2015-16)[81] Diagnostic imaging (code: 812), unit cost (weighted average of consultant-led and non-consultant-led appointments)
ECG	1	100%	£71.44	£71.44	Clinical expert opinion	NHS reference costs (2015-16)[81] RD51A Simple Echocardiogram, 19 years and over
Total cost per month	£324.35					
Total cost per weekly cycle	£74.86					

Abbreviations used in the table: CT, computerised tomography; ECG, electrocardiogram; GP, general practitioner; MRI, magnetic resonance imaging; PSSRU, Personal Social Services Research Unit

Table 35. Resource use and costs for PD health state (irrespective of progression location) (adapted from Table 41 and Table 43 of the CS)

Resource	No. required per month	% of patient requiring resource	Unit cost	Cost per month	Resource use source	Unit cost source
Consultant-led outpatient visit / oncologist	1.25	100%	£167.08	£208.85	TA406[55] Further input provided from clinical experts	NHS reference costs (2015-16)[81] Medical oncology (code: 370), consultant-led appointment
GP visit	1	50%	£45.68	£22.84	TA406[55] Further input provided from clinical experts	PSSRU 2016[77] 10.8b: Per patient contact lasting 11.7 minutes, including direct care staff costs, with qualification costs
Cancer nurse	1.5	80%	£67.30	£80.76	TA406[55] Further input provided from clinical experts	NHS reference costs (2014-2015)[83]; Nurse cancer relate adult face-t-face (N10AF); Inflated to 2015/16 using PSSRU (2016)[77]
Full blood test	1.5	100%	£3.10	£4.65	TA406[55] Further input provided from clinical experts	NHS reference costs (2015-16)[81] DAPS05: direct access pathology; haematology
Biochemistry	1.5	100%	£1.18	£1.77	TA406[55] Further input provided from clinical experts	DAPS04 NHS reference costs (2015-2016)
CT scan	0.75	100%	£118.53	£88.90	TA406[55] Further input provided from clinical experts	NHS reference costs (2015-16)[81] RD22Z: Computerised Tomography Scan of one area, with pre and post contrast
MRI scan	0.5	80%	£202.70	£81.08	Clinical expert opinion	NHS reference costs (2015-16)[81] RD03Z; Magnetic Resonance Imaging Scan of One Area, with Pre- and Post-Contrast
X ray	0.5	60%	£37.30	£11.19	TA406[55] Further input provided from clinical experts	NHS reference costs (2015-16)[81] Diagnostic imaging (code: 812), unit cost (weighted average of consultant-led and non-consultant-led appointments)
Total cost per month	£500.04					
Total cost per week	£115.40					

Abbreviations used in the table: CT, computerised tomography; ECG, electrocardiogram; GP, general practitioner; MRI, magnetic resonance imaging; PSSRU, Personal Social Services Research Unit

Table 36. Additional resource use for PD health state: CNS metastases (adapted from Table 42 of the CS)

Product	Resource	% of patient requiring resource	Lifetime exposure limit	Average time in PD	Unit cost	Cost per lifetime exposure	Cost per month
Alectinib	Stereotactic radiotherapy	100%	6 doses	30.7 months	£3,243.60	£19,462	£632.04
Crizotinib				35.1 months			£554.53
Source		Clinical expert opinion		Based on economic model	NHS reference costs (2015-2016) [81] AA71A; Stereotactic intracranial radiosurgery for neoplasms or other neurological conditions, with CC score 4+	Lifetime exposure * unit cost	Cost per lifetime exposure / average time in PD
Total cost per week: alectinib		+ £146.32					
Total cost per week: crizotinib		+ £127.97					
Abbreviations used in the table: PD, progressive disease;							

5.4.9.4 Adverse event costs

The model includes the costs of managing all grade 3 and 4 TRAEs with an incidence of ≥3% in either arm of the ALEX trial, and all grade 5 TRAEs irrespective of incidence. The proportions of patients experiencing each TRAE in the model have been previously reported in Section 5.4.6. The unit costs of adverse event treatment are summarised in Table 37, while the resource use and total cost to manage each TRAE is summarised in Table 38.

TRAEs are assumed to occur during PFS when patients are receiving alectinib or crizotinib as first-line treatments. The company calculated the expected cost per cycle (one week) to manage TRAEs by weighting the cost to treat adverse events (Table 38) by the weekly probability for each treatment arm in ALEX (Table 17). Following this, the expected cost to manage TRAEs each cycle was £0.60 for alectinib and £4.13 for crizotinib.

Table 37. Unit costs of adverse event treatments (adapted from Table 48 of the CS)

Resource	Unit cost	Unit cost source
Blood test	£3.10	NHS reference costs (2015-16)[81] DAPS05: direct access pathology; haematology
Outpatient visit	£167.08	NHS reference costs (2015-16)[81] Medical oncology (code: 370), consultant-led appointment
ECG	£71.44	NHS reference costs (2015-16)[81] RD51A Simple Echocardiogram, 19 years and over
Cardiac Arrest	£2291.93	NHS reference costs (2014-15)[83] EB05A: Cardiac Arrest with CC Score 9+
Pneumonitis	£2783.99	NHS reference costs (2014-15)[83] DZ11T: Lobar, Atypical or Viral Pneumonia, without Interventions, with CC Score 7-9
Neutropenia	£362.66	NICE ID900[84], NICE ID811[85] and NICE ID970[86]
Abbreviations used in the table: CC, complication and comorbidity; ECG, electrocardiogram		

Table 38. Summary of resources and costs to manage ≥ grade 3 adverse events (adapted from Table 47 and Table 49 of the CS)

Adverse event	Treatment resource	Resource source	Total cost (Table 37)
Alanine Aminotransferase Increased	2 additional blood tests 2 outpatient visits	NICE TA395[62]	£340.36
Aspartate Aminotransferase Increased	2 additional blood tests 2 outpatient visits	NICE TA395[62]	£340.36
Cardiac Arrest	Hospitalisation	NHS reference costs (2014-15)[83] EB05A: Cardiac Arrest with CC Score 9+	£2291.93
QT interval prolongation	2 additional blood tests 2 ECGs	NICE TA395[62] Clinical expert opinion	£149.08
Neutropenia	Hospitalisation	NICE ID900[84], NICE ID811[85] and NICE ID970[86]	£362.66
Pneumonitis	Hospitalisation	NHS reference costs (2014-15)[83] DZ11T: Lobar, Atypical or Viral Pneumonia, without Interventions, with CC Score 7-9	£2783.99
Abbreviations used in the table: CC, complications and comorbidities; ECG, electrocardiogram;			

5.4.9.5 Other costs

Based on the Committee's view in TA406, the company applied an initial cost of £2,380 to identify ALK+ patients from a cohort of patients with NSCLC in the first model cycle.[55] As this cost is applied to both treatment arms, in the first model cycle, there is no impact on the ICER when this figure is varied.

A one-off terminal care cost was also applied to patients who die in the model. Resource used comprised hospitalisations, hospice care and Macmillan nurses, according to previous NICE guidelines and appraisals.[84-88] Unit costs were taken from NHS Reference Costs and the PSSRU.[77, 81] Based on those sources, the total cost of terminal care per patient was estimated to be £3,679.

5.4.9.6 ERG critique

Resource use estimated for the base case analysis is based on estimates reported in previous NICE TAs in NSCLC, and the company's clinical experts' input. The estimates used are based on the 2015/16 price year, with unit costs obtained from published sources such as the NHS national schedule of

reference costs[81], the PSSRU[77], the eMIT[80], and the British National Formulary (BNF)[79], which is in line with the NICE reference case[89]. The ERG validated the costs from the sources cited, and checked that prices are correctly inflated when necessary. When NHS Reference Costs 2014/15 were referenced in the CS, the same currency code and national average unit cost was reported in NHS Reference Costs 2015/16; hence, costs reflect a 2015/16 cost year.

The ERG found a few minor discrepancies between the costs applied in the model and the company's clarification responses, including the weekly cost of subsequent treatment and mean duration of subsequent treatment. As a result, the ERG has focussed on costs reported in the model. The ERG also identified one implementation error in the updated economic model regarding administration costs, described in greater detail in Section 5.4.9.6.1.

The ERG notes that the company did not state in their submission why the cost of concomitant drugs was not considered. During the clarification stage the company provided the concomitant medications received during the study for each treatment arm, which the ERG considers to be reasonably balanced across treatment arms in ALEX, (89% and 86% of patients on crizotinib and alectinib, respectively). The company also added that those medications are understood to be relatively inexpensive and their inclusion would be expected to have a negligible impact on the ICER. Furthermore, given that alectinib has a more favourable safety profile, and that alectinib patients received slightly fewer concomitant medications than crizotinib, the company concluded that the omission was conservative. The ERG agrees with the company's decision to not include concomitant costs in the analysis.

The ERG considers that the cost estimations in the model are generally correct and sound, but disagrees with the estimation of the cost of crizotinib in the model. A full pack of crizotinib provides patients with 30 days of treatments, whereas a pack of alectinib provides 28 days of treatment. As the full-pack cost and administration cost are applied up-front, every 4 cycles (i.e. every 4 weeks or 28 days), two days of crizotinib treatment are wasted in each 4-weekly administration cycle. This is different from incorporating wastage in the cost estimation, which is related with assuming that the full pack cost will be considered, regardless of patients being alive to complete the treatment provided by that respective pack, or dying during that specific cycle.

Therefore, to address this issue, the ERG amended the cost of crizotinib in the model so one full-pack is purchased every 30 days as opposed to every 28 days. The detailed results of these analysis are provided in Section 6.

The ERG's clinical experts confirmed that the drug doses and resource use assumed for patients prior to progression are generally in line with what would be expected in UK clinical practice, except for the frequency of oncologist visits which they considered to be underestimated. To address this, the ERG

ran an additional analysis that applied an oncologist visit every 4 weeks as opposed to every 5 to 6 weeks. The detailed results of these analysis are given in Section 6.

The ERG's clinical experts agreed that the only administration cost for oral therapies would be a pharmacist's time to dispense the medications, but noted that the cost applied by the company appeared to be underestimated. In the NICE submission for ceritinib, the Committee accepted the use of an administration cost of £14.26.[55] Therefore, the ERG ran an additional analysis that amended the oral administration costs from £9.20 to £14.26. Based on list prices this analysis increased the ICER from £72,544 to £72,628 using RECIST + CNS RECIST and from £70,514 to £70,594 using RECIST. The impact on the ICER is therefore negligible.

Furthermore, clinical experts advised the ERG that the estimated cost of terminal care was relatively low considering the large number of patients with CNS metastases in the ALEX trial. Instead, clinical experts considered the Nuffield Trust estimate to be more reflective of patients with ALK+ NCLC.[90] For completeness, the ERG ran an additional analysis that applied a cost of £7,383 (inflated to 2015/16 prices using the HCHS PPI) from the Nuffield Trust.[90] The impact of changing the terminal care costs in the model is negligible, decreasing the final ICER by about £100 per QALY gained.

5.4.9.6.1 Subsequent therapy costs

Based on the available trial data, not all subsequent therapies received by patients in ALEX have marketing authorisation for use in the UK, for the treatment of NSCLC. In addition, 13 patients in ALEX received developmental products (loratinib, brigatinib and entrectinib) whose acquisition costs were not available. Furthermore, the company assumed that 100% of patients in the model receive second line treatment. The ERG considers it reasonable to assume all patients receive subsequent therapies once they progress, as this seems reflective of current clinical practice with crizotinib, but notes that the data on subsequent therapies in ALEX is not robust due to its incompleteness.

The company carried out a scenario analysis assuming a distribution of subsequent therapies in line with current UK practice, as per clinical expert advice provided to the company (Table 30). The ERG does not consider the estimates used to be reflective of clinical practice in the UK as 90% of crizotinib patients are assumed to receive a subsequent TKI (compared with the 18% reported in the England audit). Therefore, the ERG ran three scenarios analyses (previously described in Section 5.4.8.2.2), to explore the uncertainty around subsequent treatments.

To further reflect UK clinical practice, the ERG assumed that the treatments available for subsequent treatment lines consisted on crizotinib and ceritinib (post alectinib) and ceritinib (post crizotinib).In order to estimate the distribution of patients allocated to crizotinib or ceritinib post alectinib, the ERG used the data available from ALEX, which shows that 2.9% of alectinib patients received ceritinib and 8.8% of patients received crizotinib. The ERG reweighted these values, to account for the entire subgroup of patients receiving a TKI post-alectinib. The final proportions used in the ERG's analysis are 25% for ceritinib and 75% for crizotinib. Results are reported in Section 6. The ERG caveats this analysis by the fact that ceritinib is currently not recommended for treatment after alectinib. Nonetheless, there was uncertainty within the ERG's clinical experts and the experts consulted for TA500 (ceritinib),[10] about whether crizotinib, a first-generation ALK-TKI, would be used as a second line treatment after a second-generation ALK-TKI, such as alectinib. Given the acknowledged differences between first- and second-generation ALK-TKIs, some clinical experts considered it counterintuitive that crizotinib would be given after failure on a superior class of therapy. Therefore, the ERG assumed that ceritinib could be a treatment option after alectinib. The results of this analysis are reported in Section 6, however, the ERG notes that removing ceritinib as a possible TKI therapy after alectinib lead to a decrease in the ERG's exploratory ICERs of £1000 per QALYs gained.

The company did not include subsequent therapy administration costs in their cost calculations. The ERG corrected this by applying weekly administration costs (Table 32) to each of the subsequent therapies modelled by the company. However, the impact on the final ICER was found to be negligible.

The administration cost applied for IV chemotherapy in the model is the unit cost for administering chemotherapy at the first attendance, for an outpatient attendance. The ERG considered this to be a potential underestimation of chemotherapy treatment, as patients will return for subsequent IV infusions (which are more expensive than initial ones), and might also need hospital admission. Therefore, the ERG used the same HGR code applied in the recent NSCLC TA500 (Table 39) and explored this as a scenario analysis.[64] The impact on the final ICER was considered to be negligible.

Table 39. IV administration costs applied in the ERG's scenario analysis

Administration type	Source	Currency code	Cost
First IV infusion	NHS Reference Costs 2015-16	Deliver simple parenteral chemotherapy at first attendance SB12Z	£236.19
Subsequent IV infusion	NHS Reference Costs 2015-16	Deliver subsequent elements of a chemotherapy cycle SB15Z	£328.10

5.4.9.6.2 Management of CNS metastases

As explained in Section 5.4.5.2, the ERG disagrees with the company's method for estimating newly progressed CNS patients. However, the ERG agrees that newly progressed CNS patients should be estimated in order to apply the marginal cost for CNS progression in the economic analysis. The ERG's alternative analysis for estimating newly progressed patients is explained in Section 5.4.5.2, and the results are reported in Section 6.

Clinical expert opinion sought by the ERG revealed that there seems to be a consensus on the use of SRS to treat CNS metastases whenever patients' clinical condition allows it. The issue remains, that only few patients are eligible for SRS as candidates cannot have more than a maximum of two metastatic sites. Therefore, how ineligible patients are managed in UK clinical practice remains unclear.

Although it seems that there is not a consensus among the clinical community, clinical expert opinion provided to the ERG explained that clinical practice seems to be moving away from WBRT and increasingly using steroids, as supported in the Mulvenna *et al.* 2016 paper.[91] While the company suggests that 23% of patients receive SRS and 77% of patients receive WBRT, the ERG's clinical expert agreed on the proportion of patients receiving SRS but considered that the remaining 77% would receive steroids, as opposed to WBRT, given its lack of proven advantage over steroids and its side effects on patients.

Therefore, the ERG considers the company's scenario analysis to be more reflective of clinical practice than the company's base case. The ERG also conducted exploratory analysis to reflect a scenario where the 77% of patients receiving WBRT would be managed with steroids. Given the company assumption that 100% of patients receive steroids (dexamethasone) for the management of their CNS metastases,

the ERG scenario analysis consists on removing the WBRT costs from the analysis. Results are reported in Section 6.

5.5 Results included in company's submission

The company presented deterministic and probabilistic results. The base case results were calculated deterministically (using mean parameter values) as well as probabilistically (assessing the simultaneous effect of parameter uncertainty). The company also carried out a series of univariate sensitivity analyses and scenario analyses to test the robustness of model results to changes in model parameters and structural assumptions. Base case results are presented in Section 5.5.1, whereas the results of deterministic and probabilistic sensitivity analyses are presented in Sections 5.5.2 and 5.5.3, respectively.

5.5.1 Base case results

The results of the company's revised base case analysis using the RECIST+CNS RECIST analysis are presented in Table 40 using list prices. According to the company's analysis, alectinib is expected to extend patients' lives by around 11.16 months compared to crizotinib. This translates to an incremental average QALY gain for alectinib of 1.15 QALYs, and an incremental cost-effectiveness ratio (ICER) of £72,544 per QALY gained. Table 41 reports the company's base case results when RECIST-only outcomes are used. The final ICER amounts to £70,514 per QALY gained, using list prices.

Table 40. Results of company's base case analysis (list prices) (reproduced from Table 1 of the company's clarification responses – updated results)

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Crizotinib	£135,955	4.25	2.61				
Alectinib	£219,643	5.17	3.77	£83,688	0.93	1.15	£72,544
Abbreviations in table: ICER, Incremental cost-effectiveness ratio; LY, life year; QALY, Quality-adjusted life year.							

Table 41. Results of company's base case analysis (list prices) using RECIST only (taken from the economic model)

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Crizotinib	£154,013	5.17	2.80				
Alectinib	£225,992	4.25	3.82	£71,978	0.93	1.02	£70,514
Abbreviations in table: ICER, Incremental cost-effectiveness ratio; LY, life year; QALY, Quality-adjusted life year.							

The breakdown of QALYs and costs (list prices) accumulated in the model according to health state are presented in Table 42 and Table 43, respectively, for the RECIST analysis.

Table 42. Disaggregated QALYs by health state (taken from the economic model)

Health state	Alectinib	Crizotinib	Incremental
PFS	2.104	1.117	0.988
PD	1.713	1.680	0.033

Total	3.82	2.80	1.02

Table 43. Disaggregated costs by health state (taken from the economic model)

Health state	Alectinib	Crizotinib	Incremental
PFS	£186,848	£94,168	£92,680
PD	£36,073	£56,651	£-20,579
Total	£225,992	£154,013	£71,978

The ICER with the alectinib PAS incorporated is reported in Table 44 for the RECIST+CNS RECIST analysis and in Table 45 for the RECIST analysis.

Table 44. Results of company's base case analysis (alectinib PAS price) using RECIST+CNS RECIST outcomes (reproduced from Table 5 of the company's clarification responses – updated results)

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Crizotinib	£131,618	4.25	2.61	–	–	–	–
Alectinib	[redacted]	5.17	3.77	[redacted]	0.93	1.15	[redacted]
Abbreviations in table: ICER, Incremental cost-effectiveness ratio; LY, life year; QALY, Quality-adjusted life year.							

Table 45. Results of company's base case analysis (alectinib PAS price) using RECIST outcomes (taken from the economic model)

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Crizotinib	£149,724	5.17	2.80	–	–	–	–
Alectinib	[redacted]	4.25	3.82	[redacted]	0.93	1.02	[redacted]
Abbreviations in table: ICER, Incremental cost-effectiveness ratio; LY, life year; QALY, Quality-adjusted life year.							

5.5.2 Deterministic sensitivity analysis

The company carried out one-way sensitivity analyses (OWSAs) to assess the impact of varying the values of parameters from their means by ±50% except for utility values which were varied by 10%. To note is that the company only reported the results for the RECIST+CNS RECIST analysis. The company also carried out scenario analyses changing assumptions surrounding the following parameters:

- alternative wastage assumptions;
- alternative plausible OS extrapolations;
- capping of OS benefit;
- alternative plausible PFS extrapolations;
- alternative utilities;
- disutility for AEs;
- alternative CNS PFS extrapolations for CNS progressions;
- alternative CNS metastases treatments;

- alternative model structures and data sources for PFS;
- subsequent therapy market shares.

The results of the OWSA and scenario analysis carried out by the company using list prices are presented in Figure 30 and Table 46, respectively. According to the scenario analysis, results were most sensitive to the PFS distribution, subsequent treatment utilities and OS distributions. As for the OWSA, the main driver of the model was the HSUV associated with CNS-progressed disease. Using the upper and lower HSUV limits of 0.62 and 0.42 causes the ICER to range from £87,309 to £62,051 per QALY gained. Other noteworthy drivers of the model were treatment-specific HSUV for PD. On the one hand, treatment type was not found to be a statistically significant predictor of patients' quality of life as reported in Section 5.4.8.1.1. However, quality of life may differ if second line treatment is influenced by first line treatment, as described previously in Section 5.4.8. For the remaining parameters, the results of the OWSA show the base case ICER is relatively stable.

Figure 30: Tornado diagram (list prices) (reproduced from Figure 3 of the company's clarification responses – updated results)

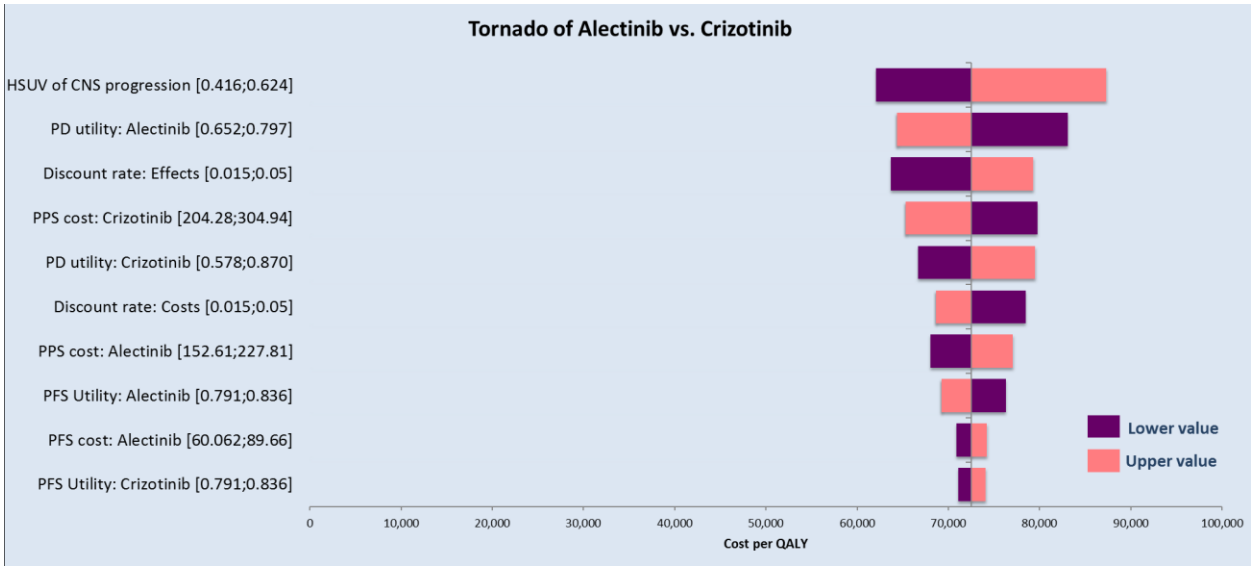


Table 46. Results of scenario analysis (list prices) (reproduced from Table 4 of the company's clarification responses – updated results)

Category	Description	Alectinib			Crizotinib			ICER
		LYs	QALYs	Costs	LYs	QALYs	Costs	
Wastage	Wastage (base case)	5.17	3.77	£219,643	4.25	2.61	£135,955	£72,544
	No wastage	5.14	3.74	£218,238	4.32	2.66	£130,944	£80,450
OS distribution	Exponential (base case)	5.17	3.77	£219,643	4.25	2.61	£135,955	£72,544
	Weibull	6.03	4.32	£223,668	3.13	2.02	£130,952	£40,238
	Log-normal	8.90	6.12	£237,942	5.08	3.05	£139,093	£32,194
	Gamma	7.82	5.47	£232,250	5.73	3.36	£142,426	£42,607
	Log logistic	7.76	5.43	£231,842	4.50	2.76	£135,902	£35,917

Capping of OS and PFS treatment effect duration	No cap (base case)	5.17	3.77	£219,643	4.25	2.61	£135,955	£72,544
	3 years	4.66	3.39	£187,198	4.25	2.61	£135,955	£66,065
	5 years	4.83	3.53	£204,416	4.25	2.61	£135,955	£75,095
	7 years	4.95	3.61	£212,495	4.25	2.61	£135,955	£76,668
	10 years	5.05	3.69	£217,286	4.25	2.61	£135,955	£75,792
PFS distribution	KM+ Exponential (base case)	5.17	3.77	£219,643	4.25	2.61	£135,955	£72,544
	Exponential	5.17	3.77	£223,070	4.25	2.61	£134,675	£76,155
	Weibull	5.17	3.83	£268,958	4.25	2.61	£130,927	£112,485
	KM+Weibull	5.17	3.83	£266,779	4.25	2.61	£131,972	£110,302
Utility scenarios	One PPS utility (base case)	5.17	3.77	£219,643	4.25	2.61	£135,955	£72,544
	One PPS utility, ALEX data only	5.17	3.77	£219,643	4.25	2.61	£135,955	£72,544
	2nd & 3rd line PPS utilities	5.17	3.24	£219,643	4.25	2.36	£135,955	£95,820
AE disutility	No (base case)	5.17	3.77	£219,643	4.25	2.61	£135,955	£72,544
	Yes	5.17	3.77	£219,643	4.25	2.61	£135,955	£72,533
CNS PFS extrapolation	Gamma (base case)	5.17	3.77	£219,643	4.25	2.61	£135,955	£72,544
	Exponential	5.17	3.59	£220,376	4.25	2.53	£136,027	£79,142
	Weibull	5.17	3.73	£219,773	4.25	2.50	£134,534	£69,122
	Log-normal	5.17	3.77	£219,641	4.25	2.54	£136,334	£67,876
	Log-logistic	5.17	3.77	£219,643	4.25	2.56	£136,272	£68,932
	KM with Gamma tail	5.17	3.75	£219,712	4.25	2.61	£135,960	£73,673
% of patients receiving SRS + corticosteroids at CNS progression	100% SRS (base case)	5.17	3.77	£219,643	4.25	2.61	£135,955	£72,544
	23.26%, and 76.74%	5.17	3.77	£213,432	4.25	2.61	£126,173	£75,640
Survival model	RECIST + CNS RECIST (base case)	5.17	3.77	£219,643	4.25	2.61	£135,955	£72,544
	Original modelling strategy (post corrections)	5.17	3.74	£219,941	4.25	2.71	£149,539	£68,508
	RECIST only	5.17	3.82	£225,992	4.25	2.80	£154,013	£70,514
Subsequent treatments *	ALEX trial (base case)	5.17	3.77	£219,643	4.25	2.61	£135,955	£72,544
	Clinical practice	5.17	3.77	£234,346	4.25	2.61	£149,575	£73,483

Abbreviations used in the table: AE, adverse event; CNS, central nervous system; ICER, incremental cost-effectiveness ratio, KM, Kaplan-Meier; LYs, life years; OS, overall survival; PFS, progression-free survival; PPS, post-progression survival; QALYs, quality-adjusted life years; SRS, stereotactic radiosurgery

*Omitted from the company's clarification responses, results produced from the company's model

The results of the OWSA and scenario analysis carried out by the company using the alectinib PAS price are presented in Figure 31 and Table 46, respectively. According to the scenario analysis, results

were most sensitive to the PFS distribution and survival model using RECIST criteria. As for the OWSA, the main driver of the model was the cost of post-progression survival. Using the upper and lower costs of £274 and £183 for crizotinib causes the ICER to range from [redacted] to [redacted] per QALY gained. As for alectinib, using the upper and lower costs of £228 and £153 causes the ICER to range from [redacted] to [redacted]. Similar to the OWSA using list prices, results were sensitive to the HSUV associated with CNS-progressed disease, although to a lesser extent.

Figure 31. Tornado diagram (alectinib PAS price) (reproduced from Figure 8 of the company's clarification responses – updated results)

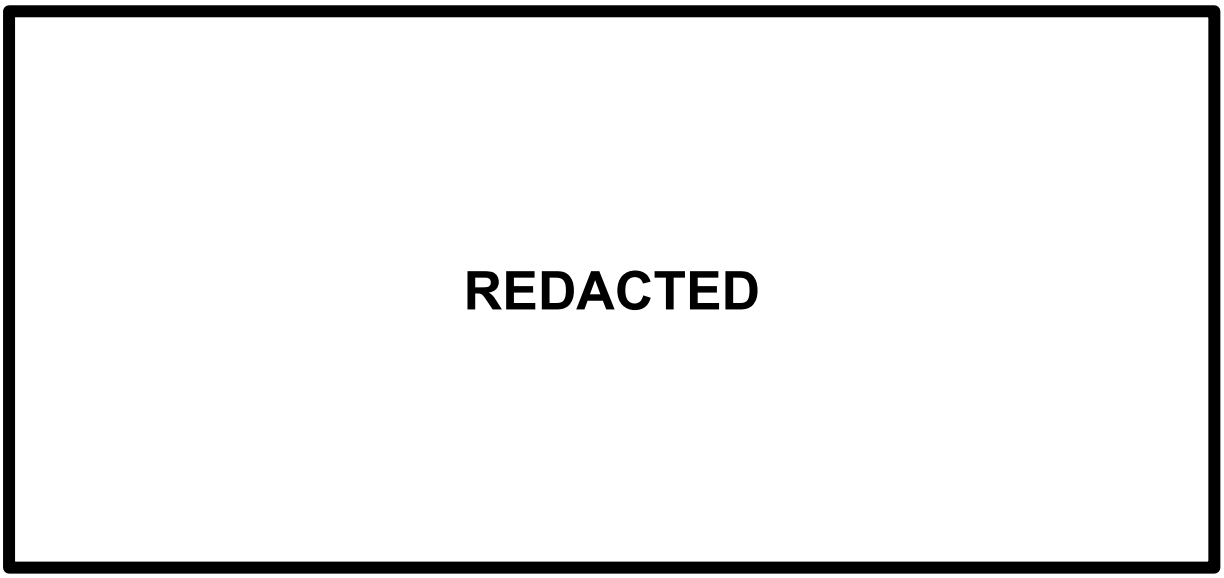


Table 47. Results of scenario analysis (alectinib PAS price) (reproduced from Table 4 of the company's clarification responses – updated results)

Category	Description	Alectinib			Crizotinib			ICER
		LYs	QALYs	Costs	LYs	QALYs	Costs	
Wastage	Wastage (base case)	5.17	3.77	[redacted]	4.25	2.61	£131,618	[redacted]
	No wastage	5.14	3.74	[redacted]	4.32	2.66	£126,603	[redacted]
OS distribution	Exponential (base case)	5.17	3.77	[redacted]	4.25	2.61	£131,618	[redacted]
	Weibull	6.03	4.32	[redacted]	3.13	2.02	£126,270	[redacted]
	Log-normal	8.90	6.12	[redacted]	5.08	3.05	£135,136	[redacted]
	Gamma	7.82	5.47	[redacted]	5.73	3.36	£138,624	[redacted]
	Log logistic	7.76	5.43	[redacted]	4.50	2.76	£131,852	[redacted]
Capping of OS and PFS treatment effect duration	No cap (base case)	5.17	3.77	[redacted]	4.25	2.61	£131,618	[redacted]
	3 years	4.66	3.39	[redacted]	4.25	2.61	£131,618	[redacted]
	5 years	4.83	3.53	[redacted]	4.25	2.61	£131,618	[redacted]
	7 years	4.95	3.61	[redacted]	4.25	2.61	£131,618	[redacted]
	10 years	5.05	3.69	[redacted]	4.25	2.61	£131,618	[redacted]
PFS distribution	KM+ Exponential (base case)	5.17	3.77	[redacted]	4.25	2.61	£131,618	[redacted]

	Exponential	5.17	3.77	[redacted]	4.25	2.61	£130,334	[redacted]
	Weibull	5.17	3.83	[redacted]	4.25	2.61	£126,581	[redacted]
	KM+Weibull	5.17	3.83	[redacted]	4.25	2.61	£127,629	[redacted]
Utility scenarios	One PPS utility (base case)	5.17	3.77	[redacted]	4.25	2.61	£131,618	[redacted]
	One PPS utility, ALEX data only	5.17	3.77	[redacted]	4.25	2.61	£131,618	[redacted]
	2nd & 3rd line PPS utilities	5.17	3.24	[redacted]	4.25	2.36	£131,618	[redacted]
AE disutility	No (base case)	5.17	3.77	[redacted]	4.25	2.61	£131,618	[redacted]
	Yes	5.17	3.77	[redacted]	4.25	2.61	£131,618	[redacted]
CNS PFS extrapolation	Gamma (base case)	5.17	3.77	[redacted]	4.25	2.61	£131,618	[redacted]
	Exponential	5.17	3.59	[redacted]	4.25	2.53	£131,688	[redacted]
	Weibull	5.17	3.73	[redacted]	4.25	2.50	£130,193	[redacted]
	Log-normal	5.17	3.77	[redacted]	4.25	2.54	£131,996	[redacted]
	Log-logistic	5.17	3.77	[redacted]	4.25	2.56	£131,935	[redacted]
	KM with Gamma tail	5.17	3.75	[redacted]	4.25	2.61	£131,623	[redacted]
% of patients receiving SRS + corticosteroids at CNS progression	100% SRS (base case)	5.17	3.77	[redacted]	4.25	2.61	£131,618	[redacted]
	23.26%, and 76.74%	5.17	3.77	[redacted]	4.25	2.61	£121,835	[redacted]
Survival model	RECIST + CNS RECIST (base case)	5.17	3.77	[redacted]	4.25	2.61	£131,618	[redacted]
	Original modelling strategy (post corrections)	5.17	3.77	[redacted]	4.25	2.61	£131,618	[redacted]
	RECIST only	5.17	3.74	[redacted]	4.25	2.71	£149,724	[redacted]
Subsequent treatments *	ALEX trial (base case)	5.17	3.77	[redacted]	4.25	2.61	£131,618	[redacted]
	Clinical practice	5.17	3.77	[redacted]	4.25	2.61	£149,575	[redacted]

Abbreviations used in the table: AE, adverse event; CNS, central nervous system; ICER, incremental cost-effectiveness ratio KM, Kaplan-Meier; LYs, life years; OS, overall survival; PFS, progression-free survival; PPS, post-progression survival; QALYs, quality-adjusted life years; SRS, stereotactic radiosurgery

*Omitted from the company's clarification responses, results produced from the model by the ERG

5.5.3 Probabilistic sensitivity analysis

The company performed a probabilistic sensitivity analysis (PSA) to assess the joint parameter uncertainty around the base case results. The results are based on 1,000 PSA iterations. The mean probabilistic ICER is presented in Table 48 using list prices and in Table 49 using the PAS price for alectinib. The ERG notes that results were only reported for the RECIST+CNS RECIST analysis.

Administration costs, terminal care costs and the costs of ALK testing were varied using a lognormal distribution, while supportive care costs and adverse event costs were varied using a Normal distribution. Utilities were varied using a beta distribution. Clinical inputs (parametric survival curves) were also varied in PSA using a decomposition of the variance–covariance matrix. Remaining model parameters including adverse event rates, subsequent treatment distributions, acquisition costs and general population parameters were kept constant. The ERG considers the parameters and distributions respective distributions chosen for PSA to be generally sound, but questions why a Normal distribution was applied to some cost inputs.

Table 48. Results of company's PSA (list prices) (adapted from Table 2 of the company's clarification responses – updated results)

Therapy	Total costs	Total QALYs	ICER
Crizotinib	£132,761	2.61	
Alectinib	£216,573	3.77	£72,651
Abbreviations in table: ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year.			

Table 49. Results of company's PSA (PAS prices) (adapted from Table 6 of the company's clarification responses – updated results)

Therapy	Total costs	Total QALYs	ICER
Crizotinib	£128,631	2.62	
Alectinib	[redacted]	3.79	[redacted]
Abbreviations in table: ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year.			

The scatterplots and cost-effectiveness acceptability curves (CEACs) are presented in Figure 32 and Figure 33 using list prices and Figure 34 and Figure 35 using PAS prices for alectinib.

The probability of alectinib being cost-effective compared to crizotinib at a willingness-to-pay (WTP) threshold of £30,000 per QALY is 0% using list prices. However, when the PAS discount is applied to alectinib, the ERG found the probability to increase to [redacted]%.

Figure 32. Distribution of cost-effectiveness simulation on the cost-effectiveness plane for alectinib vs crizotinib (list prices)

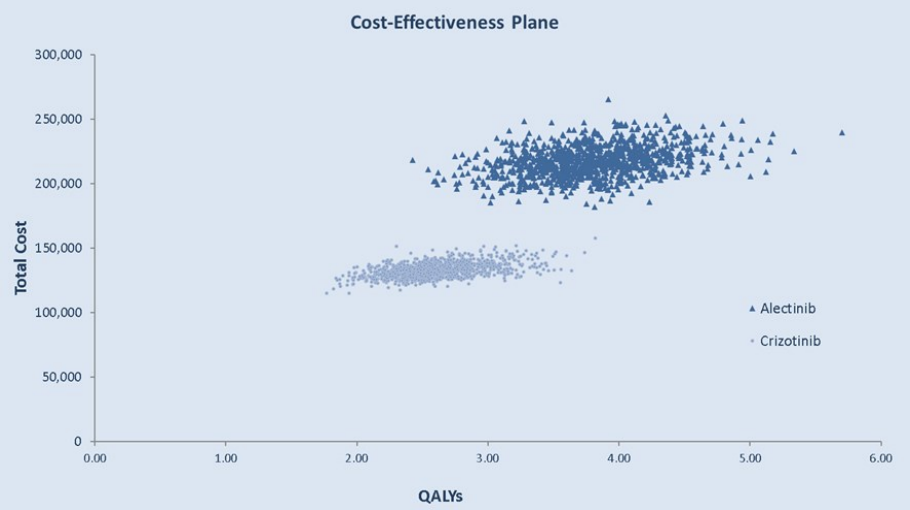


Figure 33.Cost-effectiveness acceptability curves (list prices)

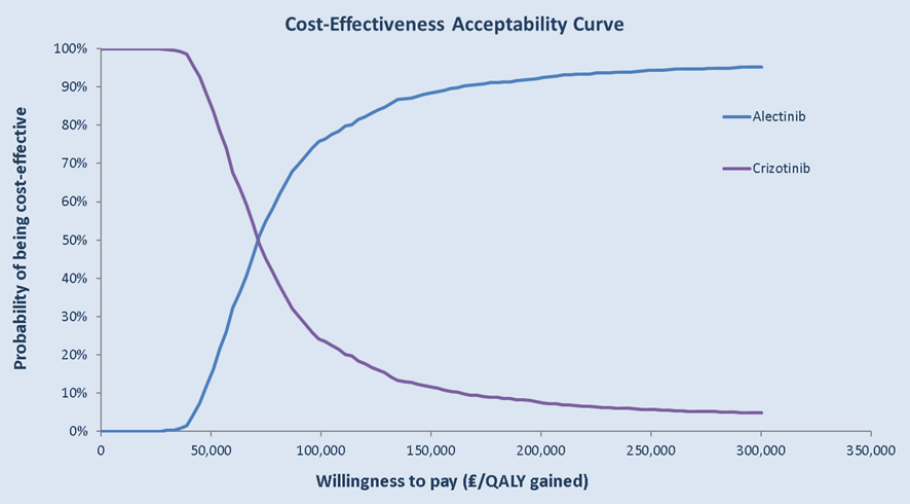
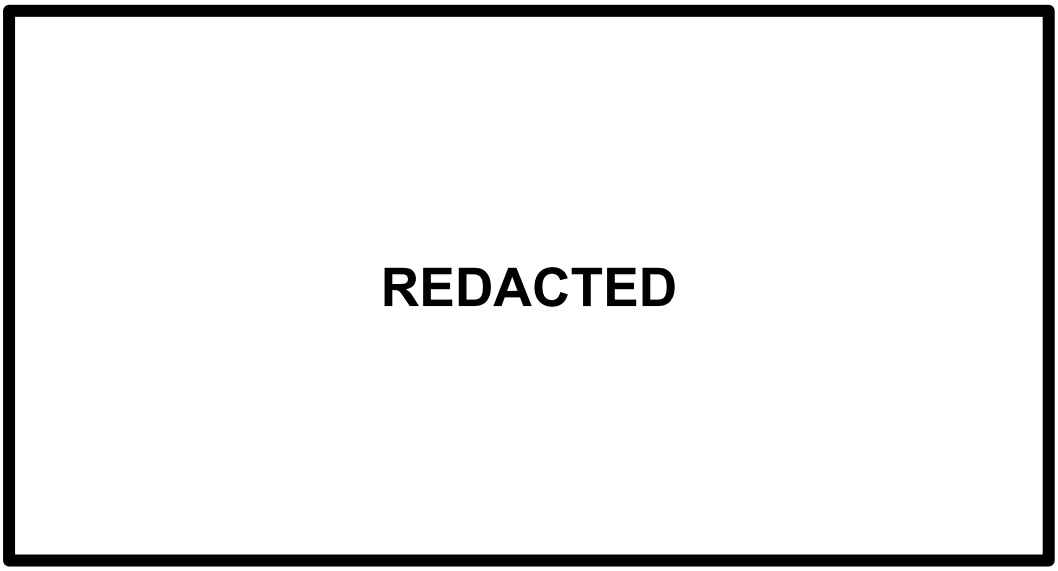


Figure 34. Distribution of cost-effectiveness simulation on the cost-effectiveness plane for alectinib vs crizotinib (alectinib PAS)

REDACTED

Figure 35. Cost-effectiveness acceptability curves (alectinib PAS price)



6 ADDITIONAL WORK UNDERTAKEN BY THE ERG

6.1 Model corrections

The ERG described the errors found in the company's analysis throughout Section 5 of the report. These are summarised here, together with the combined impact of the corrections on the final ICER. The ERG made the following corrections:

1. The company's analysis of newly progressed CNS patients used the number of CNS events captured by the RECIST+CNS RECIST. The ERG found a discrepancy between the company's model and the results reported in the company's reply to clarification question B1, as the number of CNS events in the crizotinib arm were 68 and not 63. The ERG replaced the 63 by 68 in the company's analysis;

2. The ERG disagrees with the estimation of the cost of crizotinib in the model. A full pack of crizotinib provides patients with 30 days of treatments, whereas a pack of alectinib provides 28 days of treatment. As the full-pack cost and administration cost are applied up-front, every 4 cycles (i.e. every 4 weeks or 28 days), two days of crizotinib treatment are wasted in each 4-weekly administration cycle. Therefore, to address this issue, the ERG amended the cost of crizotinib in the model so one full-pack is purchased every 30 days as opposed to every 28 days.

Results are provided in Table 50 and Table 51 for list prices, for the company's corrected base case and the company's analysis using RECIST outcomes, respectively. Table 52 and Table 53 report the equivalent analyses, when the alectinib PAS is applied.

Table 50. Results of company's base case analysis corrected by the ERG

Therapy	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Crizotinib	£132,686	2.61	–	–	–
Alectinib	£219,643	3.77	£86,958	1.15	£75,378

Table 51. Results of company's base case analysis corrected by the ERG using RECIST

Therapy	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Crizotinib	£149,354	2.80	–	–	–
Alectinib	£225,992	3.82	£76,638	1.02	£75,079

Table 52. Results of company's base case analysis corrected by the ERG (PAS for alectinib)

Therapy	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Crizotinib	£128,348	2.61	–	–	–
Alectinib	[redacted]	3.77	[redacted]	1.15	[redacted]

Table 53. Results of company's base case analysis corrected by the ERG using RECIST (PAS for alectinib)

Therapy	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Crizotinib	£145,064	2.80	–	–	–
Alectinib	[redacted]	3.82	[redacted]	1.02	[redacted]

6.2 ERG scenario analysis

The scenario analyses undertaken by the ERG are explained throughout Section 5 of the report. The exploratory analyses undertaken by the ERG uses RECIST outcomes for PFS and CNS PFS. The analyses consist on the following:

1. The ERG disagrees with the method used by the company to cap the CNS PFS curve by taking the minimum risk each model cycle for OS, CNS PFS and background survival, to determine the proportion of patients in the CNS PFS curve. Alternatively, the ERG capped the CNS PFS curve by the OS curve;

2. The ERG disagrees with the method used for the estimation of newly progressed patients in the model as it uses a fixed proportion of CNS events (captured by the RECIST+CNS RECIST measure) throughout the analysis. A more robust approach would have been to estimate the number of newly progressed patients every cycle, instead of relying on a fixed proportion. Therefore, the ERG replaced the company's method (Equation 2) with the following formula: $(CNS\ PD_{t+1} - CNS\ PD_t) + (1 - OS_{t+1}/OS_t) * (CNS\ PD_t)$;

3. The ERG replaced the exponential curves used to estimate OS for alectinib and crizotinib by the KM+exponential tail curves;

4. The ERG's clinical experts advised that the frequency of oncologist visits should be every 4 weeks as opposed to every 5 to 6 weeks. The ERG replaced this in the economic model.

5. The ERG ran three scenario analyses to reflect the uncertainty around the changes in clinical practice if alectinib is recommended. Furthermore, the ERG removed the third line of treatment from the company's analysis as this line of treatment was not incorporated as an option for the cost analysis in the company's model (only second line treatment was included). These scenarios consist on the following:

    a. Assuming 64% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib;

b. Assuming patients on alectinib are equally likely to receive a subsequent TKI as crizotinib patients (31.4% of patients assumed for both);

c. Assuming 19.1% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib;

6. The ERG ran the three scenarios analyses described in 5, to estimate the costs of each alternative scenario. To further reflect UK clinical practice, the ERG assumed that the TKI treatments available for subsequent treatment lines consisted on crizotinib (75% of total TKI treatments) and ceritinib (25% of total TKI treatments) (post alectinib) and ceritinib (post crizotinib);

7. The ERG conducted exploratory analysis to reflect a scenario where 77% of patients receive steroids rather than WBRT to manage their CNS metastases;

8. Given that CNS-related utility value is one of the key drivers of the economic results, the ERG ran a scenario where the utility associated with CNS progression was varied by a range of values. The base case utility value (0.52) was increased by 1%, 2%, 3%, 4% and 5%.

Results from the ERG analysis are reported in Table 54. From a methodological point of view, changing the OS modelling approach from an exponential to a KM+exponential curve has a considerable impact on the company's corrected ICER (£75,079 to £80,146).

The other key model drivers are related to the clinical assumptions incorporated in the economic analysis. The two main drivers are the assumptions related with subsequent therapies in the model, namely the proportion of patients receiving a TKI and a non-TKI after treatment with alectinib or crizotinib. This has implications for the incremental costs, and to a greater extent, for QALY gain related with alectinib. The other key driver of the analysis is the modelling of CNS metastases, in terms of its impact on patients' quality of life and treatment costs (Figure 36).

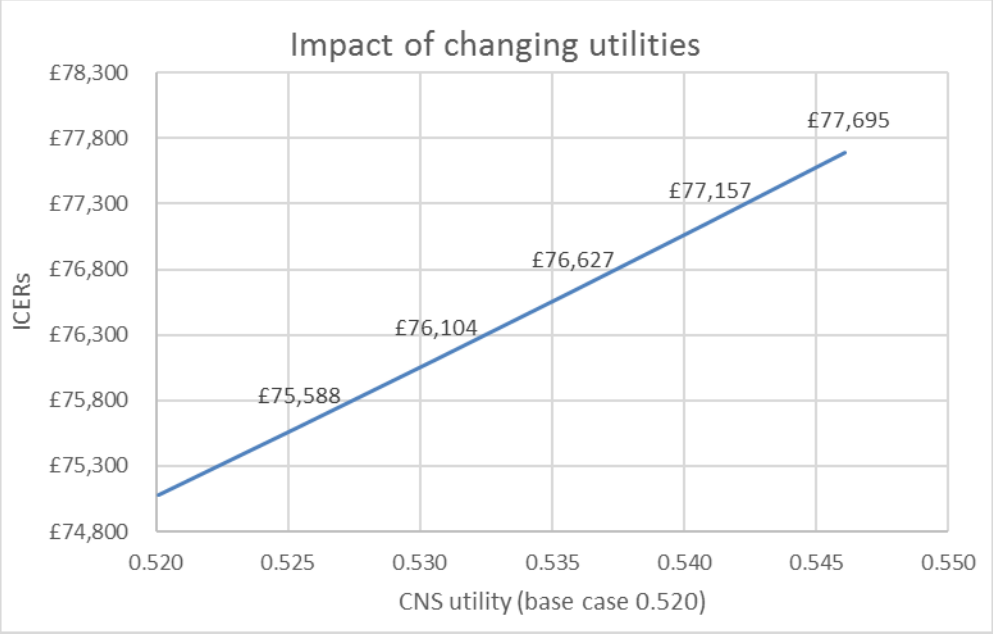
The impact of varying the combined costs and QALYs related with subsequent treatments on the final ICER is reported in the next subsection.

Table 54. Results of the ERG's scenario analysis

Analysis from list	Results per patient	Alectinib (1)	Crizotinib (2)	Incremental value (1-2)
0	**Company's corrected base using RECIST outcomes**			
	Total costs (£)	£225,992	£149,354	£76,638
	QALYs	3.82	2.80	1.02
	ICER		**£75,079**	
1	**Capping the CNS PFS curve by the OS curve**			
	Total costs (£)	£225,805	£149,110	£76,695
	QALYs	3.86	2.84	1.02
	ICER		**£75,219**	
2	**Using different method to estimate newly progressed patients**			
	Total costs (£)	£216,959	£140,949	£76,010
	QALYs	3.82	2.80	1.02
	ICER		**£74,463**	
3	**Replacing the exponential curves used to estimate OS for alectinib and crizotinib by the KM+exponential tail curves**			
	Total costs (£)	£225,841	£149,912	£75,929
	QALYs	3.79	2.84	0.95
	ICER		**£80,146**	
4	**Changing the frequency of oncologist visits to every 4 weeks as opposed to every 5 to 6 weeks**			
	Total costs (£)	£227,309	£150,048	£77,261
	QALYs	3.82	2.80	1.02
	ICER		**£75,689**	
5 a)	**Assuming 64% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib**			
	Total costs (£)	£225,992	£149,354	£76,638
	QALYs	3.83	3.01	0.82
	ICER		**£93,856**	
5 b)	**Assuming 31.4% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib**			
	Total costs (£)	£225,992	£149,354	£76,638
	QALYs	3.78	3.01	0.76
	ICER		**£100,220**	
5 c)	**Assuming 19.1% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib**			
	Total costs (£)	£225,992	£149,354	£76,638
	QALYs	3.76	3.01	0.75
	ICER		**£102,851**	
6 a)	**Assuming 64% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib**			
	Total costs (£)	£241,685	£139,839	£101,846
	QALYs	3.82	2.80	1.02

Analysis from list	Results per patient	Alectinib (1)	Crizotinib (2)	Incremental value (1-2)
	ICER		**£99,774**	
6 b)	**Assuming 31.4% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib**			
	Total costs (£)	£228,927	£139,839	£89,088
	QALYs	3.82	2.80	1.02
	ICER		**£87,275**	
6 c)	**Assuming 19.1% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib**			
	Total costs (£)	£224,113	£139,839	£84,274
	QALYs	3.82	2.80	1.02
	ICER		**£82,560**	
7	**Assuming patients receive steroids rather than WBRT to manage their CNS metastases**			
	Total costs (£)	£218,134	£137,108	£81,026
	QALYs	3.82	2.80	1.02
	ICER		**£79,378**	
Abbreviations used in the table: CSR, clinical study report; ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; QALY, quality-adjusted life year; RDI, relative dose intensity; TRAE, treatment-related adverse event.				

Figure 36. Scenario analysis 8



6.3 ERG base case ICER

In this section, the ERG reports three ICERs, reflecting three different scenarios in terms of subsequent therapies received after alectinib. The ERG caveats the analyses presented with the high degree of uncertainty embedded in the ALEX's data regarding patients' subsequent therapies. Related to this, is the estimated survival from ALEX, which as evidence suggests, can be highly impacted by the availability of subsequent treatment with ALKs. Although it is not possible to draw final conclusions from the naïve comparison undertaken by the ERG comparing the ALEX and the PROFILE 1014 data,

it could be argued that if ALEX data were to be adjusted to real-life data, the survival predictions for crizotinib would be more conservative (with the potential impact on alectinib being unknown). The ERG considers that ALEX does not provide robust evidence to substantiate a long-term OS benefit of alectinib compared with crizotinib. Furthermore, comparative OS data from ALEX may not be a reasonable reflection of what would be seen in UK clinical practice because treatment beyond PD may differ for alectinib and crizotinib in practice, and subsequent therapies available to patients in ALEX do not reflect the UK pathway for ALK+ advanced NSCLC.

The assumptions incorporated in the ICERs presented in Table 55 include the scenario analyses numbered and described in Section 6.2. The exception is the company's scenario analysis discussed in Section 5.4.9.6.1, which assumes that only 23% of patients receive SRS, while 77% of patients receive WBRT.

The ERG produced three different ICERs, ranging from £129,195 to £140,467, per QALY gained. The lowest ICER corresponds to the scenario where a lower proportion of alectinib patients (19%) compared with crizotinib patients (31%) receive subsequent TKIs. Conversely, the highest ICER corresponds to the scenario where more alectinib patients (64%) receive subsequent TKIs, compared to crizotinib patients. When the same proportion of patients is assumed to receive subsequent TKIs, ICER amounts to £132,510, per QALY gained. The three ERG's exploratory ICERs amount to [redacted], [redacted] and [redacted] when the alectinib PAS is applied (Table 56).

Table 55. ERG's alternative base case ICERs

	Results per patient	Alectinib (1)	Crizotinib (2)	Incremental value (1-2)
0	**Company's corrected base using RECIST outcomes**			
	Total costs (£)	£225,992	£149,354	£76,638
	QALYs	3.82	2.80	1.02
	ICER			**£75,079**
1	**Capping the CNS PFS curve by the OS curve**			
	Total costs (£)	£225,805	£149,110	£76,695
	QALYs	3.86	2.84	1.02
	ICER (compared with base case)			£75,219
	ICER with all changes incorporated			**£75,219**
2	**Using different method to estimate newly progressed patients**			
	Total costs (£)	£216,959	£140,949	£76,010
	QALYs	3.82	2.80	1.02
	ICER (compared with base case)			£74,463
	ICER with all changes incorporated			**£74,858**
3	**Replacing the exponential curves used to estimate OS for alectinib and crizotinib by the KM+exponential tail curves**			

	Total costs (£)	£225,841	£149,912	£75,929
	QALYs	3.79	2.84	0.95
	ICER (compared with base case)			£80,146
	ICER with all changes incorporated			**£77,948**
4	**Changing the frequency of oncologist visits to every 4 weeks as opposed to every 5 to 6 weeks**			
	Total costs (£)	£227,309	£150,048	£77,261
	QALYs	3.82	2.80	1.02
	ICER (compared with base case)			£75,689
	ICER with all changes incorporated			**£78,593**
Company's SA	**Company's scenario analysis assuming that 23% of patients receive SRS and 77% of patients receive WBRT**			
	Total costs (£)	£219,830	£139,751	£80,079
	QALYs	3.82	2.80	1.02
	ICER (compared with base case)			£78,450
	ICER with all changes incorporated			**£82,839**
5a+6a	**Assuming 64% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib**			
	Total costs (£)	£241,685	£139,839	£101,846
	QALYs	3.83	3.01	0.82
	ICER (compared with base case)			£124,727
	ICER with all changes incorporated			**£140,467**
5b+6b	**Assuming 31.4% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib**			
	Total costs (£)	£228,927	£139,839	£89,088
	QALYs	3.78	3.01	0.76
	ICER (compared with base case)			£116,501
	ICER with all changes incorporated			**£132,510**
5c+6c	**Assuming 19.1% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib**			
	Total costs (£)	£224,113	£139,839	£84,274
	QALYs	3.76	3.01	0.75
	ICER (compared with base case)			£113,099
	ICER with all changes incorporated			**£129,195**
	Abbreviation used in table: ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; QALYs, quality-adjusted life years; RDI, relative dose intensity.			

Table 56. ERG's alternative base case ICERs with alectinib PAS

	Results per patient	**Alectinib (1)**	**Crizotinib (2)**	**Incremental value (1-2)**
0	**Company's corrected base using RECIST outcomes**			
	Total costs (£)	[redacted]	£145,064	[redacted]
	QALYs	3.82	2.80	1.02
	ICER			[redacted]

1	**Capping the CNS PFS curve by the OS curve**			
	Total costs (£)	[redacted]	£144,821	[redacted]
	QALYs	3.86	2.84	1.02
	ICER (compared with base case)			[redacted]
	ICER with all changes incorporated			[redacted]
2	**Using different method to estimate newly progressed patients**			
	Total costs (£)	[redacted]	£136,660	[redacted]
	QALYs	3.82	2.80	1.02
	ICER (compared with base case)			[redacted]
	ICER with all changes incorporated			[redacted]
3	**Replacing the exponential curves used to estimate OS for alectinib and crizotinib by the KM+exponential tail curves**			
	Total costs (£)	[redacted]	£145,618	[redacted]
	QALYs	3.79	2.84	0.95
	ICER (compared with base case)			[redacted]
	ICER with all changes incorporated			[redacted]
4	**Changing the frequency of oncologist visits to every 4 weeks as opposed to every 5 to 6 weeks**			
	Total costs (£)	[redacted]	£145,758	[redacted]
	QALYs	3.82	2.80	1.02
	ICER (compared with base case)			[redacted]
	ICER with all changes incorporated			[redacted]
Company's SA	**Company's scenario analysis assuming that 23% of patients receive SRS and 77% of patients receive WBRT**			
	Total costs (£)	[redacted]	£135,461	[redacted]
	QALYs	3.82	2.80	1.02
	ICER (compared with base case)			[redacted]
	ICER with all changes incorporated			[redacted]
5a+6a	**Assuming 64% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib**			
	Total costs (£)	[redacted]	£139,839	[redacted]
	QALYs	3.83	3.01	0.82
	ICER (compared with base case)			[redacted]
	ICER with all changes incorporated			[redacted]
5b+6b	**Assuming 31.4% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib**			
	Total costs (£)	[redacted]	£139,839	[redacted]
	QALYs	3.78	3.01	0.76
	ICER (compared with base case)			[redacted]
	ICER with all changes incorporated			[redacted]
5c+6c	**Assuming 19.1% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib**			
	Total costs (£)	[redacted]	£139,839	[redacted]

	QALYs	3.76	3.01	0.75
	ICER (compared with base case)			[redacted]
	ICER with all changes incorporated			[redacted]
	Abbreviation used in table: ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; QALYs, quality-adjusted life years; RDI, relative dose intensity.			

7 END OF LIFE

The company submission (CS) did not state whether the company are requesting that alectinib for anaplastic lymphoma kinase positive (ALK+) advanced non-small-cell lung cancer (NSCLC) be considered in the end of life setting. The company did not put forward a rationale for end of life considerations outlined by the National Institute for Health and Care Excellence (NICE), so the Evidence Review Group's (ERG's) assessment alone is presented in Table 57. In brief, alectinib is indicated for a small patient population, but data from ALEX do not suggest that the life expectancy of patients with first-line ALK+ advanced NSCLC is less than 24 months, and the study has not demonstrated a survival benefit of alectinib over crizotinib.

Table 57. End of life considerations

NICE criterion	ERG assessment
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	The ERG's clinical experts stated that most patients diagnosed with ALK+ advanced NSCLC are expected to live for 2 to 3 years from first-line therapy. After a median follow-up of 18.6 months and 17.6 months in the alectinib and crizotinib groups of ALEX, respectively, 23% of the alectinib group and 26.5% of the crizotinib group have died. The ALEX data suggest median survival will be longer than 24 months. Real world evidence suggests OS of patients with ALK+ advanced NSCLC in the UK may shorter than has been shown in clinical trials (e.g. due to generally healthier trial populations and access to subsequent therapies not available in the UK), but the evidence is not specific to a first-line population.[48]
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	OS from ALEX is immature and has not demonstrated a statistically significant difference between alectinib and crizotinib.
The treatment is licensed or otherwise indicated, for small patient populations	While NSCLC affects a relatively large patient population, the percentage with ALK rearrangement is only 5%. The company estimate that [redacted] patients will be eligible for 1L alectinib in 2018.

Abbreviations: 1L, first line; ALK+, anaplastic lymphoma kinase positive; NHS, National Health Service; NSCLC, non-small-cell lung cancer; OS, overall survival; UK, United Kingdom.

8 OVERALL CONCLUSIONS

Clinical

Alectinib (Alecensa®; Roche) has a European marketing authorisation that covers adults with untreated anaplastic lymphoma kinase positive (ALK+) advanced non-small-cell lung cancer (NSCLC). Results from the randomised controlled trial (RCT), ALEX, indicate substantial benefits of alectinib on progression free survival (PFS) and time to progression in the central nervous system (CNS PFS) compared with current standard therapy, crizotinib. One-year survival and response rates were similar between the two treatments, and overall survival (OS) and duration of response (DOR) were immature at the most recent data cut. [redacted].

There was a consistent benefit of alectinib for PFS across all predefined subgroups, except those based on very few patients. Evidence from exploratory analyses of the ALEX data suggest the PFS benefit of alectinib may be most pronounced compared with crizotinib for those with CNS metastases at baseline, and alectinib led to more frequent and longer CNS response than crizotinib for those patients. Results from safety assessments and patient-reported outcomes in ALEX give some indication that alectinib may have some tolerability benefits over crizotinib, but time to symptom deterioration and global health status is not significantly different between the two treatments.

Evidence underpinning the company submission (CS) was based solely on ALEX, which closely matches the decision problem outlined in the final scope issued by the National Institute for Health and Care Excellence (NICE).[1] The ERG agrees that an indirect comparison was not required to provide estimates of comparative effectiveness. ALEX was open-label but was otherwise judged to be largely free from internal biases. The ERG thus considers outcomes assigned by independent review committee (IRC) more reliable than those assessed by study investigators.

The company conducted alternative analyses of time to CNS progression (CNS PFS) after an error was identified after a question asked by the ERG during the clarification process to provide more robust comparative clinical effectiveness results. The company mostly reported methods with sufficient transparency to enable the ERG to critique and validate the findings, and conduct its own analyses. The ERG considers the analyses of PFS and CNS PFS based on standard RECIST criteria more clinically applicable than those incorporating events assessed with the CNS RECIST also used in ALEX.

The ERG had some concerns that the long-term effects of alectinib compared with crizotinib have not been captured adequately in ALEX to assess the clinical plausibility of extrapolations required for the evaluation of cost-effectiveness. Outcomes observed in ALEX may not be reflected in UK clinical practice due to differences in patient baseline characteristics, access to subsequent therapies and treatment beyond disease progression. Exploratory analyses requested by the ERG at the clarification

phase did not suggest that these factors would have an appreciable impact on comparative effectiveness in ALEX. However, the incomplete capture of subsequent therapies in ALEX leaves uncertainty around the applicability of OS to UK clinical practice, particularly because there was concern within the ERG's clinical experts about the availability of effective NICE-approved therapies to use second-line after alectinib.

Economic

The ERG's main concerns are focused on the subsequent treatment received in ALEX and consequently, in the model; and in the CNS data used and its respective modelling. It also remains unclear to the ERG if clinicians will use alectinib beyond disease progression in the UK, or what further treatments will be considered for patients who progress on alectinib. Even though the marketing authorisation for alectinib does not allow for treatment beyond progression, treating patients with (the same) ALK inhibitor beyond disease progression seems established practice in the UK as long as the clinician considers the patient to be benefiting from treatment. This also relates to the availability of subsequent therapies, although if alectinib is recommended by NICE, there will be no available guidance to support the use of alectinib as a second-line treatment. At the moment, the only TKI treatment available after alectinib is crizotinib. However, there was uncertainty within the ERG's clinical experts and the experts consulted for TA500 (ceritinib)[10] about whether crizotinib, a first-generation ALK-TKI, would be used as a second line treatment after a second-generation ALK-TKI such as alectinib. Given the acknowledged differences between first- and second-generation ALK-TKIs, some clinical experts considered it counterintuitive that crizotinib would be given after failure on a superior class of therapy.

The ERG considers it important to emphasise that any analysis of subsequent therapies in ALEX and their impact on trial outcomes is very incomplete and flawed, as subsequent therapies were not systematically captured in ALEX. Of all patients who discontinued study treatment, only 41% of these have data regarding subsequent treatment. Therefore, while the ERG agrees with matching the clinical effectiveness data to its respective costs and benefits (i.e. modelling the clinical trial subsequent therapies with its respective costs and QALYs), this analysis is not possible with the limited data available from ALEX, and any attempt will introduce a high degree of uncertainty to the analysis. Given that modelling the trial therapies relies heavily on assumptions, the ERG finds it more valuable to link these assumptions to the anticipated use of the drugs in UK clinical practice, rather than on the anticipated use of drugs in the ALEX trial.

The ERG finds the company's estimates of subsequent therapies in ALEX unlikely to be reflective of clinical practice in the UK (to note is that these estimates are based on assumptions rather than on actual trial data). Furthermore, the ERG disagrees with the company's assumptions made with regards to the

proportion of patients receiving subsequent treatments in the UK, included in the company's scenario analysis for costs.

The ERG has some reservations with regards to CNS data and its incorporation in the economic model. The details of the updated model including the CNS data analysis were described in a short document provided by the company after clarification; therefore, the ERG based its critique on the latter and on inspection of the economic model. The limited information available in the document shed some light on CNS data collection in the trial but is not entirely transparent and so the ERG is still unclear on a few aspects of the company's analysis. The ERG had to make assumptions with regards to the data, which are discussed in the report, however, it is important to caveat the ERG's assumptions. If the latter are not correct, then the company's model is flawed as the manipulation of the data in the economic analysis is likely to be incorrect. The ERG remains unclear on the validity of the incorporation of clinical data into the economic model. It is vital that the company clarifies the following issues:

1. All RECIST-assessed primary CNS events were simultaneously systemic progressions;
2. How were secondary CNS events captured in the CNS PFS KM curves (i.e. systematically or not systematically)?
3. How can OS and CNS PFS curves (and whether these are KM or extrapolated curves) cross when primary non-CNS events were censored from the CNS PFS curves?

Overall, it is likely that survival outcomes in ALEX, and in the model, are overestimated compared with the ALK+ NSCLC population in the UK. The ERG's clinical experts suggested most people with ALK+ advanced NSCLC are expected to live between 1 to 3 years from initiation of treatment with crizotinib. The experts' experience is substantiated by a recent audit of crizotinib for ALK+ advanced NSCLC at 20 UK centres since it was added to the Cancer Drugs Fund in 2012, although not limited to its use as a first line therapy.[69] Median OS for the 99 patients in the audit was 13.5 months, which compares to approximately 80% of crizotinib patients being alive at 12 months in ALEX and in PROFILE 1014. The more mature PROFILE 1014 data shows a 4-year survival of 56.6%, which again is a very different estimate to the clinical experts' predictions.

The company considered that a naïve comparison of the ALEX and the PROFILE 1014 studies is inappropriate as patients in PROFILE 1014 are considered to be healthier and therefore, perform better. However, the ERG finds these populations comparable, to some degree. Comparing the crizotinib groups in ALEX and PROFILE 1014, the ERG notes the difference in the proportion of patients with brain metastases at baseline, and prior treatment for brain metastases, which may support the company's assertion, but considers other characteristics (i.e. age, ECOG performance status, stage of disease and smoking history) comparable between the two trials. The analysis performed in TA406 to adjust

PROFILE 1014 data to real-life data, resulted in a median OS for crizotinib of 21.7 months and a mean adjusted OS of 29 months. This compares to the approximately 68% of patients still alive in the unadjusted OS curve for PROFILE 1014 at 22 months (note that median OS was not reached in the unadjusted OS curve). Although it is not possible to draw final conclusions from this naïve comparison, it could be argued that if ALEX data were to be adjusted to real-life data, the survival predictions for crizotinib would be more conservative.

The ERG considers that ALEX does not provide robust evidence to substantiate a long-term OS benefit of alectinib compared with crizotinib. Furthermore, comparative OS data from ALEX may not be a reasonable reflection of what would be seen in UK clinical practice because treatment beyond PD may differ for alectinib and crizotinib in practice, and subsequent therapies available to patients in ALEX do not reflect the UK pathway for ALK+ advanced NSCLC.

Overall, the ERG agrees with modelling treatment arms independently in the economic analysis. The modelling approach for PFS data (and the ERG's preferred approach for the OS data) relies on using the KM data for the initial 18 months of the economic model, and then apply the exponential tail of the curve fitted to the entire dataset. There are some limitations to this approach:

a. The exponential tail of the curve was still derived from fitting an exponential distribution to the KM curve, which proved to be a relatively bad fit, for both OS and PFS data. Hence, the portion of the curve used after 18 months is still based on a badly fitting curve;

b. The fact that at 18 months (where the exponential tails are used in the model), the hazard ratio between the alectinib and crizotinib curves becomes proportional. This is because the underlying hazard in each curve will remain constant throughout the rest of the model. There is no clinical justification for this and, in fact, the company's assessment of PH indicated that the PH assumption is unlikely to hold for PFS or for OS data;

c. The ERG considers that the choice of the cut-off point (18 months) for the KM data used by the company is quite arbitrary. This should have been better substantiated, and some sensitivity analysis should have been undertaken by the company to reflect the impact of changing this parameter in the analysis. The company reports that censoring increases after this point. However, the same could be argued for other cut-off, and more importantly, the alectinib and crizotinib curves do not necessarily have the same "appropriate" cut-off points.

The ERG has two main concerns regarding the company's modelling approach including the utility value applied to patients with CNS metastases, and the quality of life of patients on subsequent therapies. The HSUV associated with CNS progression were taken from Roughly *et al.* 2014[71], which is a conference abstract, therefore providing a limited description of methods and results.[71] Consequently, the ERG could not investigate in detail the data used, and it was not possible to compare patient demographics with the population in ALEX, as advised by the NICE Technical Support Unit (DSU document 12).[76]

The ERG considers that the impact of subsequent therapies on patients' quality of life is a key driver in the model. As the ERG does not consider the company's estimates of subsequent therapies to be reflective of clinical practice, the ERG ran three scenario analyses to reflect the uncertainty around the changes in clinical practice if alectinib is recommended. These scenarios include the possibility of alectinib patients being more, less, and equally likely than crizotinib patients to receive subsequent treatment with a TKI. All patients not receiving a TKI as subsequent treatment were assumed to receive a non-TKI (i.e. 100% of patients receive subsequent treatment in the ERG's analysis). These analyses are caveated by the fact that CNS impact on patients' quality of life has not been included, and by the fact that the sources for utility values and treatment duration related with subsequent therapies are taken from various literature sources. The ERG ran the same analyses to consider the impact of subsequent therapies on costs,

8.1 Implications for research

Crizotinib is the current standard of care for patients with untreated ALK+ advanced NSCLC in England. ALEX provides high quality head-to-head evidence that alectinib has appreciable benefits for PFS and progression in the CNS over crizotinib and may have a more tolerable side effect profile. The best available evidence suggests alectinib and crizotinib may be comparable for OS, response and quality of life. More mature data [redacted] may resolve the current uncertainty in comparative effectiveness of alectinib and crizotinib for key outcomes, and provide more information about whether the CNS protective effect of alectinib translates to improved OS.

The ERG highlights the importance of conducting additional research to identify the impact of CNS metastases on patients' quality of life, to reduce the current uncertainty.

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10 APPENDICES

10.1 Methods of the company's treatment effectiveness systematic literature review (SLR)

Table 58. Example search strategy (reproduced from Table 1, CS Appendix D1.1)

No.	Query	Results
#1	'non small cell lung cancer'/exp OR 'lung metastasis'/exp OR 'brain metastasis'/exp OR 'central nervous system metastasis'/exp OR ((lung OR poumon) NEAR/3 (neoplasm* OR cancer* OR carcinoma* OR adenocarcinoma* OR angiosarcoma* OR chrondosarcoma* OR sarcoma* OR teratoma* OR blastoma* OR microcytic* OR carcinogenesis OR tumour* OR tumor* OR metasta* OR métastasé OR métastatique OR avancé OR 'progression localisée')):ab,ti OR nsclc*:ab,ti OR mnsclc*:ab,ti OR 'm nsclc':ab,ti OR ansclc*:ab,ti OR 'a nsclc':ab,ti OR msqnsclc*:ab,ti OR 'msq nsclc':ab,ti OR nonsqnsclc:ab,ti OR 'non sqnsclc':ab,ti OR 'non sq nsclc':ab,ti OR sqclc*:ab,ti OR 'ns nsclc':ab,ti OR nsnsclc*:ab,ti OR 'n s nsclc':ab,ti OR 'la nsclc':ab,ti OR lansclc*:ab,ti OR cpnpc*:ab,ti OR (lac NEAR/3 (lung OR adenocarcinoma)):ab,ti OR ((scc NEAR/3 'squamous cell carcinoma'):ab,ti AND lung:ab,ti) OR (non NEAR/3 small NEAR/3 cell NEAR/3 lung NEAR/3 (cancer* OR carcinoma*)):ab,ti OR (('non small' OR nonsmall) NEAR/3 lung NEAR/3 cell NEAR/3 (cancer* OR carcinoma*)):ab,ti OR (('non small' OR nonsmall) NEAR/3 cell NEAR/3 lung NEAR/3 (cancer* OR carcinoma*)):ab,ti OR (bronchial NEAR/3 ('non small' OR nonsmall) NEAR/3 cell NEAR/3 (cancer* OR carcinoma*)):ab,ti OR ('non small cell' NEAR/3 (lung OR bronchial OR pulmonary OR bronchopulmonary OR bronchus) NEAR/3 (cancer* OR carcinoma*)):ab,ti OR ('non small' NEAR/3 cell NEAR/3 (cancer* OR carcinoma*) NEAR/3 lung*):ab,ti OR (pulmonary NEAR/3 'non small cell' NEAR/3 (cancer* OR carcinoma*)):ab,ti OR (large NEAR/3 cell NEAR/3 lung NEAR/3 (cancer* OR carcinoma*)):ab,ti OR ((squamous OR nonsquamous OR 'non squamous') NEAR/5 (cell OR 'non small cell') NEAR/3 lung NEAR/3 (cancer* OR carcinoma*)):ab,ti OR (bronchus NEAR/3 squamous NEAR/3 cell NEAR/3 (cancer* OR carcinoma*)):ab,ti OR (lung NEAR/3 epidermoid NEAR/3 (cancer* OR carcinoma*)):ab,ti OR (lung NEAR/3 squamous NEAR/3 cell NEAR/3 (cancer* OR carcinoma*)):ab,ti OR (lung:ab,ti OR poumon:ab,ti AND (nsclc*:ab,ti OR cpnpc*:ab,ti OR 'non small':ab,ti OR nonsmall:ab,ti OR large:ab,ti OR squamous:ab,ti OR 'non squamous':ab,ti OR nonsquamous:ab,ti OR 'non à petites cellules':ab,ti)) OR ((adenocancer OR adenocarcinoma) NEAR/3 (lung OR pulmonary)):ab,ti OR (((cancer OR tumeur) NEAR/3 (poumon OR bronchique)):ab,ti AND ('non à petites cellules':ab,ti OR 'non-lié à de petites cellules':ab,ti)) OR ((brain OR cns OR 'central nervous system' OR cerebral) NEAR/3 (metastasis OR metastases OR metastatic)):ab,ti	333209
#2	'anaplastic lymphoma kinase'/exp OR alk:ab,ti OR alkfusion:ab,ti OR eml4alk*:ab,ti OR (anaplastic NEAR/3 lymphoma NEAR/3 kinase*):ab,ti OR (alk*:ab,ti AND (anaplastic:ab,ti OR lymphoma:ab,ti OR kinase:ab,ti))	22200
#3	l1196m:ab,ti OR c1156y:ab,ti OR l1152*:ab,ti OR 1151tins:ab,ti OR g1202r:ab,ti OR v118l:ab,ti OR i1171t:ab,ti OR s1206y:ab,ti OR f1174c:ab,ti OR d1203n:ab,ti OR g1269a:ab,ti OR g1123s*:ab,ti OR ((crizotinib* OR ceritinib* OR alectinib* OR 'alk tki' OR alktki OR alki) NEAR/3 (experienced OR treated OR pretreated OR 'pre treated' OR 'previously treated' OR 'treated previously' OR resistan* OR refractory OR naïve)):ab,ti	783
#4	#2 OR #3	22257
#5	anaplastic lymphoma kinase inhibitor'/exp OR 'alk tki':ab,ti OR alktki:ab,ti OR (alk NEAR/3 (inhibitor OR inhibitors)):ab,ti OR ((anaplastic NEAR/3 lymphoma NEAR/3 kinase):ab,ti AND (inhibitor:ab,ti OR inhibitors:ab,ti)) OR alectinib*:ab,ti OR 'af 802':ab,ti OR af802:ab,ti OR 'ch 5424802':ab,ti OR ch5424802:ab,ti OR ro5424802:ab,ti OR rg7853:ab,ti OR alecensa:ab,ti OR crizotinib*:ab,ti OR 'pf 02341066':ab,ti OR pf02341066:ab,ti OR 'pf 1066':ab,ti OR pf1066:ab,ti OR 'pf 2341066':ab,ti OR pf2341066:ab,ti OR xalkori:ab,ti OR ceritinib*:ab,ti OR 'ldk 378':ab,ti OR ldk378:ab,ti OR 'nvp ldk 378':ab,ti OR 'nvp ldk378':ab,ti OR 'nvp ldk378nx':ab,ti OR zykadia:ab,ti OR entrectinib*:ab,ti OR 'nms e 628':ab,ti OR 'nms e628':ab,ti OR 'rxdx 101':ab,ti OR rxdx101:ab,ti OR brigatinib*:ab,ti OR 'ap 26113':ab,ti OR ap26113:ab,ti OR lorlatinib*:ab,ti OR 'pf 06463922':ab,ti OR pf06463922:ab,ti OR 'tsr 011':ab,ti OR tsr011:ab,ti OR 'cep 37440':ab,ti OR cep37440:ab,ti OR 'x 396':ab,ti OR x396:ab,ti OR 'x 276':ab,ti OR x276:ab,ti OR 'asp 3026':ab,ti OR asp3026:ab,ti OR 'nvp tae 684':ab,ti OR 'nvp tae684':ab,ti OR 'tae 684':ab,ti OR tae684:ab,ti OR 'cep 28122':ab,ti OR cep28122:ab,ti OR 'cep 14083':ab,ti OR cep14083:ab,ti OR 'cep 14513':ab,ti OR cep14513:ab,ti OR 'gsk 1838705a':ab,ti OR gsk1838705a:ab,ti	5751
#6	'heat shock protein 90 inhibitor'/exp OR 'heat shock protein 90'/exp OR 'hsp 90 inhibitor':ab,ti OR 'hsp90 inhibitor':ab,ti OR luminespib*:ab,ti OR 'auy 922':ab,ti OR auy922:ab,ti OR 'nvp auy 922':ab,ti OR 'nvp auy922':ab,ti OR 'ver 52296':ab,ti OR ver52296:ab,ti OR ganetespib*:ab,ti OR 'sta 9090':ab,ti OR sta9090:ab,ti OR onalespib*:ab,ti OR 'at 13387':ab,ti OR at13387:ab,ti OR ribociclib*:ab,ti OR 'lee 011':ab,ti OR lee011:ab,ti OR 'ipi 504':ab,ti OR ipi504:ab,ti OR retaspimycin:ab,ti OR tanespimycin*:ab,ti OR 'kos 953':ab,ti OR kos953:ab,ti OR 'nsc 330507':ab,ti OR nsc330507:ab,ti OR geldanamycin*:ab,ti OR 'nsc 122750':ab,ti OR nsc122750:ab,ti OR	15999

	gamendazole*:ab,ti OR gambogic*:ab,ti OR 'beta guttiferin':ab,ti OR 'guttic acid':ab,ti OR celastrol*:ab,ti OR tripterin:ab,ti OR 'biib 028':ab,ti OR biib028:ab,ti OR alvespimycin:ab,ti OR 'bms 826476':ab,ti OR bms826476:ab,ti OR 'kos 1022':ab,ti OR kos1022:ab,ti OR 'nsc 707545':ab,ti OR nsc707545:ab,ti OR debio0932:ab,ti OR 'debio 0932':ab,ti	
#7	'protein kinase b'/exp OR ((akt OR 'c akt') NEAR/3 (kinase OR protein OR proteins)):ab,ti	67167
#8	'gold standard'/exp OR ((gold OR golden) NEAR/3 standard):ab,ti OR 'best supportive care':ab,ti OR 'standard of care':ab,ti OR (bsc NEAR/3 (best OR supportive OR care)):ab,ti OR (soc NEAR/3 (standard OR care)):ab,ti	118767
#9	'placebo'/exp OR placebo*:ab,ti	386174
#10	'docetaxel'/exp OR 'paclitaxel'/exp OR daxotel:ab,ti OR dexotel:ab,ti OR docefrez:ab,ti OR docetaxel*:ab,ti OR 'lit 976':ab,ti OR lit976:ab,ti OR deacetyltaxol:ab,ti OR 'nsc 628503':ab,ti OR nsc628503:ab,ti OR oncodocel:ab,ti OR 'rp 56976':ab,ti OR rp56976:ab,ti OR taxoter:ab,ti OR taxotere*:ab,ti OR texot:ab,ti OR taxespira:ab,ti OR 'abi 007':ab,ti OR abi007:ab,ti OR abraxane:ab,ti OR anzatax:ab,ti OR asotax:ab,ti OR biotax:ab,ti OR 'bms 181339':ab,ti OR bms181339:ab,ti OR bristaxol:ab,ti OR britaxol:ab,ti OR coroxane:ab,ti OR formoxol:ab,ti OR genexol:ab,ti OR 'genexol pm':ab,ti OR hunxol:ab,ti OR ifaxol:ab,ti OR infinnium:ab,ti OR intaxel:ab,ti OR 'mbt 0206':ab,ti OR mbt0206:ab,ti OR medixel:ab,ti OR mitotax:ab,ti OR 'nab paclitaxel':ab,ti OR 'nsc 125973':ab,ti OR nsc125973:ab,ti OR oncogel:ab,ti OR onxol:ab,ti OR pacitaxel:ab,ti OR paclitaxel*:ab,ti OR 'paclitaxel nab':ab,ti OR pacxel:ab,ti OR padexol:ab,ti OR parexel:ab,ti OR paxceed:ab,ti OR paxene:ab,ti OR paxus:ab,ti OR praxel:ab,ti OR taxocris:ab,ti OR taxol:ab,ti OR taxus:ab,ti OR taycovit:ab,ti OR yewtaxan:ab,ti	114807
#11	'pemetrexed'/exp OR 'carboplatin'/exp OR 'cisplatin'/exp OR 'gemcitabine'/exp OR 'navelbine'/exp OR pemetrexed*:ab,ti OR alimta*:ab,ti OR ciambra:ab,ti OR elimta:ab,ti OR 'ly 231514':ab,ti OR ly231514:ab,ti OR blastocarb:ab,ti OR boplatex:ab,ti OR carboplat:ab,ti OR carboplatin*:ab,ti OR carbosin:ab,ti OR 'carbosin lundbeck':ab,ti OR carbotec:ab,ti OR carplan:ab,ti OR cbdca:ab,ti OR cycloplatin:ab,ti OR 'delta west carboplatin':ab,ti OR erbakar:ab,ti OR ercar:ab,ti OR ifacap:ab,ti OR 'jm 8':ab,ti OR kemocarb:ab,ti OR 'nsc 241240':ab,ti OR oncocarbin:ab,ti OR paraplatin*:ab,ti OR platinum*:ab,ti OR abiplatin:ab,ti OR biocisplatinum:ab,ti OR biocysplatinum:ab,ti OR blastolem:ab,ti OR briplatin:ab,ti OR 'cddp ti':ab,ti OR 'cis ddp':ab,ti OR 'cis diamine dichloroplatinum':ab,ti OR 'cis diaminechloroplatinum':ab,ti OR 'cis diaminedichloroplatinum':ab,ti OR 'cis diammine dichloroplatinum':ab,ti OR 'cis diamminedichloroplatinum':ab,ti OR 'cis dichloridiammineplatinum':ab,ti OR 'cis dichloroadiamine platinum':ab,ti OR 'cis dichlorodiamine platinum':ab,ti OR 'cis dichlorodiammineplatinum':ab,ti OR 'cis platinous diamino dichloride':ab,ti OR 'cis platinum':ab,ti OR (cis* NEAR/3 platinum*):ab,ti OR cisplatin*:ab,ti OR cisplatyl:ab,ti OR citoplatino:ab,ti OR cytoplatin:ab,ti OR cytosplat:ab,ti OR 'diamine dichloroplatinum':ab,ti OR diaminodichloroplatinum:ab,ti OR diamminedichloroplatinum:ab,ti OR 'dichlorodiamine platinum':ab,ti OR dichlorodiammineplatinum:ab,ti OR docistin:ab,ti OR elvecis:ab,ti OR kemoplat:ab,ti OR lederplatin:ab,ti OR lipoplatin:ab,ti OR 'liposomal cisplatin':ab,ti OR 'mpi 5010':ab,ti OR mpi5010:ab,ti OR neoplatin:ab,ti OR niyaplat:ab,ti OR 'nk 801':ab,ti OR noveldexis:ab,ti OR 'nsc 119875':ab,ti OR platamine:ab,ti OR 'platamine rtu':ab,ti OR platiblastin:ab,ti OR platidiam:ab,ti OR platimine:ab,ti OR platinex:ab,ti OR platinil:ab,ti OR platinol*:ab,ti OR platinoxan:ab,ti OR platiran:ab,ti OR platistil:ab,ti OR platistin:ab,ti OR platosin:ab,ti OR randa:ab,ti OR romcis:ab,ti OR sicatem:ab,ti OR 'spi 077':ab,ti OR tecnoplatin:ab,ti OR gemcitabine*:ab,ti OR gemzar*:ab,ti OR difluorodeoxycytidine:ab,ti OR gemcite:ab,ti OR 'ly 188011':ab,ti OR ly188011:ab,ti OR vinorelbine*:ab,ti OR noranhydrovinblastine:ab,ti OR anhydrovinblastine:ab,ti OR 'anx 530':ab,ti OR anx530:ab,ti OR eunades:ab,ti OR exelbine:ab,ti OR 'kw 2307':ab,ti OR kw2307:ab,ti OR navelbin:ab,ti OR navirel:ab,ti OR vinbine:ab,ti OR vinelbine:ab,ti	231814
#12	'programmed death 1 ligand 1'/exp OR 'nivolumab'/exp OR 'pembrolizumab'/exp OR 'avelumab'/exp OR 'atezolizumab'/exp OR 'durvalumab'/exp OR 'ticilimumab'/exp OR 'pd l1':ab,ti OR pdl1:ab,ti OR 'pd 1':ab,ti OR pd1:ab,ti OR nivolumab*:ab,ti OR 'bms 936558':ab,ti OR bms936558:ab,ti OR 'mdx 1106':ab,ti OR mdx1106:ab,ti OR 'ono 4538':ab,ti OR ono4538:ab,ti OR opdivo:ab,ti OR pembrolizumab*:ab,ti OR keytruda:ab,ti OR lambrolizumab:ab,ti OR 'mk 3475':ab,ti OR mk3475:ab,ti OR avelumab*:ab,ti OR 'msb 0010718c':ab,ti OR msb0010718c:ab,ti OR atezolizumab*:ab,ti OR 'mpdl 3280a':ab,ti OR mpdl3280a:ab,ti OR 'rg 7446':ab,ti OR rg7446:ab,ti OR durvalumab*:ab,ti OR medi4736:ab,ti OR 'medi 4736':ab,ti OR ticilimumab*:ab,ti OR tremelimumab*:ab,ti OR 'cp 675 206':ab,ti OR 'cp 675, 206':ab,ti OR 'cp 675206':ab,ti OR 'cp675 206':ab,ti OR 'cp675, 206':ab,ti OR cp675206:ab,ti17470	17470
#13	'rabusertib'/exp OR 'prexasertib'/exp OR rabusertib*:ab,ti OR ly2603618:ab,ti OR 'ly 2603618':ab,ti OR prexasertib*:ab,ti OR 'ly 2606368':ab,ti OR ly2606368:ab,ti OR (('chk 1' OR chk1) NEAR/3 inhibitor*):ab,ti	680
#14	'somatomedin c receptor'/exp OR 'figitumumab'/exp OR figitumumab*:ab,ti OR 'cp 751871':ab,ti OR cp751871:ab,ti OR 'insulin like growth factor':ab,ti OR 'igf type 1':ab,ti OR 'igf 1r':ab,ti OR igf1r:ab,ti OR 'igf 1 receptor':ab,ti	48419
#15	'epidermal growth factor receptor kinase inhibitor'/exp OR afatinib:ab,ti OR canertinib:ab,ti OR dacomitinib:ab,ti OR erlotinib:ab,ti OR gefitinib:ab,ti OR genistein:ab,ti OR icotinib:ab,ti OR lapatinib:ab,ti OR naquotinib:ab,ti OR nazartinib:ab,ti OR neratinib:ab,ti OR olmutinib:ab,ti OR	61728

	osimertinib:ab,ti OR pelitinib:ab,ti OR poziotinib:ab,ti OR rociletinib:ab,ti OR sapitinib:ab,ti OR tarloxotinib:ab,ti OR varlitinib:ab,ti OR (('egf receptor' OR 'epidermal growth factor receptor') NEAR/3 inhibit*):ab,ti	
#16	'bevacizumab'/exp OR bevacizumab*:ab,ti OR altuzan:ab,ti OR avastin:ab,ti OR 'nsc 704865':ab,ti OR nsc704865:ab,ti	43708
#17	'antineoplastic agent'/exp OR 'immunotherapy'/exp OR 'drug therapy'/exp OR 'protein tyrosine kinase inhibitor'/exp	3448065
#18	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17	3866381
#19	'systematic review'/exp OR 'meta analysis'/exp OR metaanalysis:ab,ti OR 'meta analysis':ab,ti OR 'systematic review':ab,ti OR 'adjusted indirect comparison':ab,ti OR (systematic* NEAR/3 review*):ab,ti OR ((mixed OR indirect) NEAR/3 treatment* NEAR/3 comparison*):ab,ti OR (simulated NEAR/3 (treatment* OR tx) NEAR/3 comparison*):ab,ti OR (match* NEAR/4 adjust* NEAR/3 (indirect OR comparison*)):ab,ti OR (nma NEAR/3 (network OR metaanalysis OR 'meta analysis')):ab,ti OR (itc NEAR/3 (indirect OR treatment* OR comparison*)):ab,ti OR (mtc NEAR/3 (mixed OR treatment* OR comparison*)):ab,ti OR (maic NEAR/4 (match* OR adjust* OR indirect OR comparison*)):ab,ti OR (stc NEAR/3 (simulated OR treatment* OR comparison*)):ab,ti OR (nma NEAR/3 (fp OR 'fractional polynomial')):ab,ti AND [2012-2017]/py	143380
#20	#19 AND 'conference abstract'/it	29641
#21	#19 NOT #20	113739
#22	'controlled clinical trial'/exp OR randomized:ab,ti OR randomised:ab,ti OR randomly:ab,ti OR placebo:ab,ti OR trial:ab,ti OR 'randomized controlled trial':de OR 'controlled clinical trial':de	1548897
#23	'case study'/exp OR (('single arm' OR 'single agent') NEAR/3 (trial OR study)):ab,ti OR (historical* NEAR/3 control*):ab,ti OR ('case series':ab,ti AND prospective*:ab,ti)	66025
#24	'phase 2 clinical trial'/exp OR 'phase 3 clinical trial'/exp OR 'phase 4 clinical trial'/exp OR 'open study'/exp OR 'postmarketing surveillance'/exp OR bayesian:ab,ti OR 'expanded access':ab,ti OR ((postmarketing OR 'post marketing') NEAR/2 surveillance):ab,ti OR (('2 arm' OR '3 arm' OR '4 arm' OR 'non inferiority' OR superiority OR 'proof of concept' OR 'proof of principle' OR 'proof of correlation' OR 'phase 1 2' OR 'phase1 2' OR 'phase i ii' OR 'phasei ii' OR 'phase ii' OR 'phaseii' OR 'phase 2' OR 'phase2' OR 'ph ii' OR phii* OR 'ph 2' OR ph2* OR 'phase 2 3' OR 'phase2 3' OR 'phase ii iii' OR 'phaseii iii' OR 'phase iii' OR phaseiii* OR 'phase 3' OR phase3* OR 'ph 3' OR ph3* OR 'ph iii' OR phiii* OR 'phase iv' OR phaseiv* OR 'phase 4' OR phase4* OR 'ph 4' OR ph4* OR 'ph iv' OR phiv* OR pivotal OR efficacy OR adaptive) NEAR/5 (trial OR study OR design)):ab,ti OR (extension NEAR/3 (trial OR study OR phase)):ab,ti OR (control* NEAR/3 ('clinical trial' OR 'clinical study')):ab,ti	329469
#25	#22 OR #23 OR #24	1749894
#26	'phase 1':ti OR 'phase i':ti OR 'phase 1a':ti OR 'phase 1b':ti OR 'phase ia':ti OR 'phase ib':ti OR phase1:ti OR phasei:ti NOT ('phase 1 2':ti OR 'phase 1b 2':ti OR 'phase 1b 2a':ti OR 'phase i ii':ti OR 'phase ib ii':ti OR 'phase ib iia':ti OR 'phase i iia':ti OR 'phase1 2':ti OR 'phase1b 2':ti OR 'phase1b 2a':ti OR 'phase 1 2a':ti OR 'phasei ii':ti OR 'phaseib ii':ti OR 'phaseib iia':ti OR 'phasei iia':ti OR 'phase 1 and 2':ti OR 'phase i and ii':ti)	19334
#27	#25 NOT #26	1737354
#28	#21 OR #27	1809557
#29	#1 AND #4 AND #18 AND #28	1024
#30	#29 AND ('chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it)	26
#31	#29 NOT #30	998

Table 59. Study eligibility criteria (reproduced from Table 6, CS Appendix D1.1)

Characteristic	Inclusion criteria
Population	Adults patients (18+ years) with ALK+ mNSCLC diagnosed by any method+ from either biopsy tumour tissue or CTCs Oligometastatic populations also eligible Studies enrolling ALK+ NSCLC patients specifically with brain/CNS metastases are also eligible. Population must be ALK+, either as single or as multiple mutation population (e.g. ALK+ and KRAS) # Population can be any combination of chemotherapy-naïve or –experienced or ALK-TKI-naïve or -experienced in any treatment line within the advanced/metastatic setting Further subgroups of interest are patients with brain metastases, or Asian / non-Asian patients
Mixed populations	For mixed lung cancer type (NSCLC/SCLC), at least 80%§ must be NSCLC For mixed stage of disease, at least 80%§ must be advanced (stage IIIB) and/or metastatic (stage IV) For non-mutation specific populations, the ALK-positive subgroup data must be reported separately or at least 80%§ of patients must have ALK-positive NSCLC
Interventions/ comparators	At least 1 arm is a licensed or investigational pharmacological treatment (chemotherapy or targeted therapy) for ALK+ mNSCLC ± compared to another such pharmacological treatment, SoC (including BSC) or PLA Licensed or investigational doses/formulations are eligible ALK-TKIs in combination with another agent, e.g. EGFR inhibitors or IGF-1R inhibitors or Hsp90 inhibitor are also eligible Treatments of interest include: ALK-TKIs: ALEC, CRZ, CER, entrectinib, brigatinib, lorlatinib, TSR 011, cep 37440, X-396, X276, ASP3026, NVPTAE684, CEP28122, CEP14083, CEP14513, GSK 1838705, RXDX101, AP26113, PF-06463922 Hsp90 inhibitors: ganetespib, IPI-504, luminespib, onalespib, ribociclib, retaspimycin, tanespimycin, geldanamycin, gamendazole, alvespimycin, bib 028, celastrol, gambogic acid, debio0932 Protein kinase B (Akt kinase / c Akt protein) inhibitors Standard of care / best supportive care Placebo Taxanes: docetaxel, paclitaxel Pemetrexed, gemcitabine, cisplatin, carboplatin, vinorelbine Immunotherapies: nivolumab, pembrolizumab, avelumab, atezolizumab, durvalumab, ticilimumab/tremelimumab Checkpoint inhibitors: rabusertib, prexasertib Insulin-like growth factor receptor antibodies: figitumumab EGFR inhibitors: afatinib, canertinib, dacomitinib, erlotinib, gefitinib, genistein, icotinib, lapatinib, naquotinib, nazartinib, neratinib, olmutinib, osimertinib, pelitinib, poziotinib, rociletinib, sapitinib, tarloxotinib, varlitinib Bevacizumab Chemotherapy trials not reporting subgroup results by ALK status will be excluded
Outcomes	At least 1 prespecified outcome reported, as a 1ry or 2ry outcome, out of: Efficacy – PFS, TTP, OS, response (objective response, complete response, partial response), DOR, duration of benefit after stopping treatment, CNS response PROs HRQoL SAEs Grade III/IV/V AEs (grouped) Pre-specified AEs of interest: gastrointestinal (e.g. diarrhoea, vomiting, nausea), oedema, raised ALT, raised AST, bilirubin elevation (hepatotoxicity), myalgia, CPK elevation, hyperglycaemia, thrombocytopenia, neutropenia, leukopenia, cardiotoxicity, corrected QT interval prolongation, fatigue, lipase elevation, amylase elevation, pancreatitis, interstitial lung disease, pneumonitis Duration of treatment and duration of treatment beyond progression

	Tolerability: Dose reductions and interruptions, Discontinuation (any reason), Discontinuation (due to AEs) All time-points will be included in the SLR itself. Decisions will be taken at meta-analysis feasibility stage as to the appropriateness (or not) for inclusion in the NMA
Study design	**For inclusion in the NMA:** Prospective parallel design RCTs (phase 2-4¶) with active or PLA controls Studies allowing for cross-over can be included provided study is a parallel randomised, design **For inclusion in the qualitative review:** Other controlled clinical trials (interventional, prospective, non-randomised) Single-arm studies and prospective case series
Date limits	SRs/NMAs are limited by the searches from 2012 onwards. Individual studies are not limited
Child abstract	Child abstract with unique data
Publication type	Errata Original articles
Language	Any foreign language paper with an English abstract will be included at 1st pass if sufficient information is present in the English abstract to ensure the eligibility criteria are met.

Abbreviations: AE, Adverse Event; BSC, best supportive care; CNS, Central Nervous System; CTC, Circulating Tumour Cells; DOR, duration of response; HRQoL, Health-Related Quality of Life; NMA, Network Meta-Analysis; NSCLC, Non-Small Cell Lung Cancer; OS, Overall Survival; PFS, Progression-Free Survival; PLA, placebo; PRO, Patient Reported Outcome; RCT, Randomised Controlled Trial; SCLC, Small Cell Lung Cancer; SoC, Standard of Care; SLR, Systematic Review; TTP, Time to Progression.

+ The diagnosis does not have to be by the FDA-approved test of FISH. It can be by any method, including IHC. In terms of the initial diagnosis and ongoing monitoring of patients during treatment, circulating tumour cells or biopsy material may be used. Traditionally this would be done via tumour tissue from biopsy.

Shames et al. 2013(Shames et al., 2013) have identified that >67% of NSCLC patients are positive for >1 biomarker and >33% of patients are positive for at least 3 biomarkers. Prevalence of biomarkers in adenocarcinoma was EGFR mutation (13%), KRAS mutation (29%), TTF1 IHC (83%), p63 IHC (7%), MET IHC (50%), PDL1 IHC (45%), PTEN loss IHC (11%), NaPi2B IHC (76%), EGFR IHC (FLEX cut-off, 11%).

§ 80% will be used as an initial standard, though arbitrary, cut-off, for mixed populations. During screening, dependent upon the data identified, the 80% cut-off may be revised and the rationale documented.

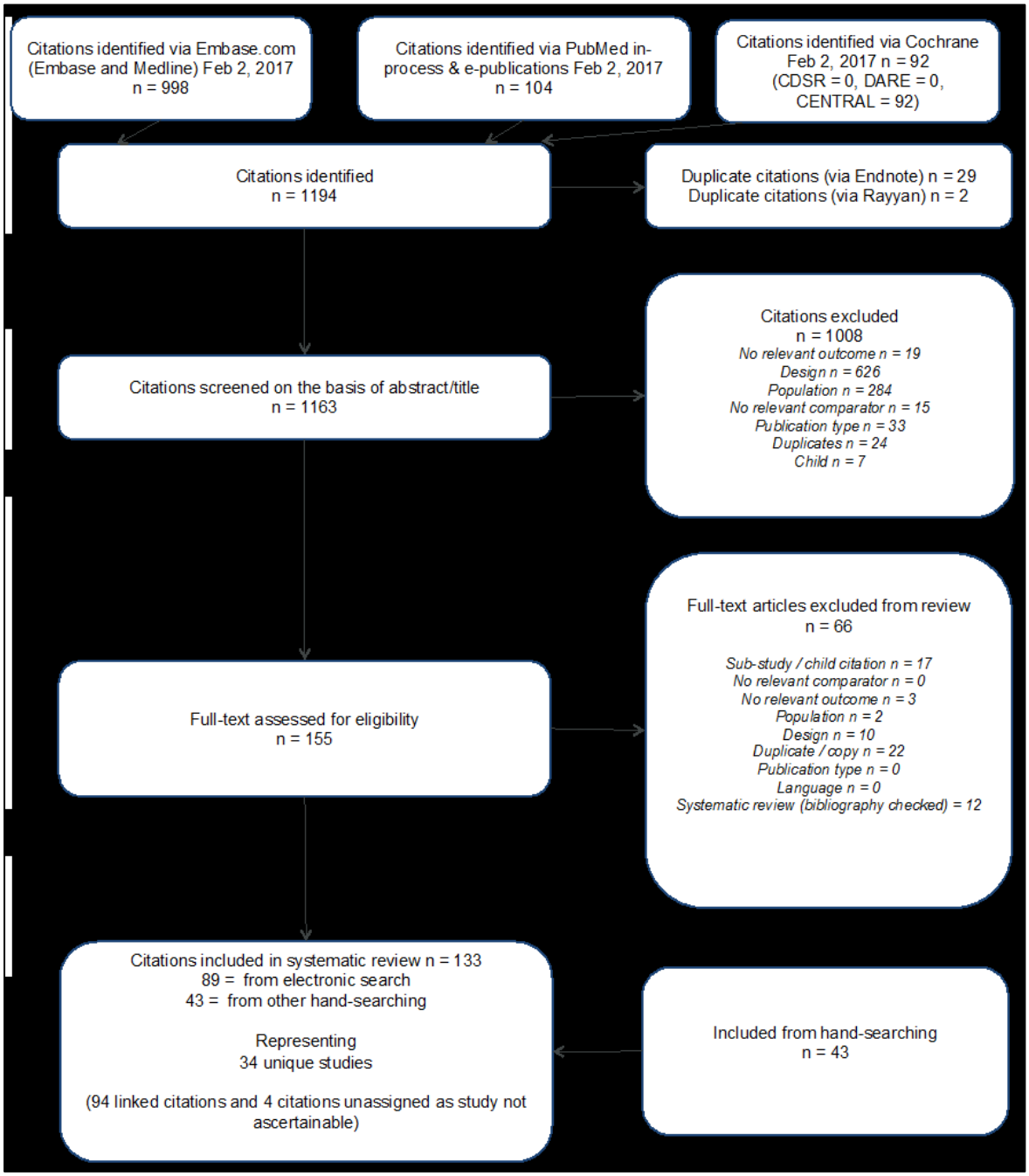
¶ The search strings will also capture phase 1/2 studies. These will be included if the phase 2 data is reported, and the phase 2 data will be extracted only.

++ Treatments of interest are any pharmacological agents, for example, immunotherapies, chemotherapies, Hsp90 inhibitors, ALK inhibitors, protein kinase B inhibitors, checkpoint kinase inhibitors and chemotherapy treatments used in practice(DiBonaventura et al., 2016a; DiBonaventura et al., 2016b) (e.g. erlotinib, docetaxel, cisplatin/pemetrexed, bevacizumab)

2007 was the date when the EML4-ALK fusion gene was first identified.(Soda et al., 2007) However as there were very few publications prior to 2007 in the search string dataset it was unnecessary to apply a date limitation.

§§ epidemica's language capabilities included English, Czech, French, German, Hungarian, Italian, Polish, Portuguese and Spanish. No articles were excluded on the basis of language.

Figure 37. PRISMA flow diagram for study identification and selection (reproduced from Figure 1, CS Appendix D1.1)



10.2 Results of the company's treatment effectiveness systematic literature review (SLR)

Table 60. Summary of included studies (compiled from Tables 10, 15, 16 and 17, CS Appendix D1.1)

Study ID/Ref ID	Registration	Design	Location	N ALK+ (% of population)	Treatment 1	Treatment 2	Population
Included in company submission (for validation or comparison with ALEX)							
ALEX/Peters 2017[25]	NCT02075840	RCT III OL	International	303 (100%)	Alectinib 600x2	Crizotinib 250x2	A
J-ALEX/Kim 2016c[26]	JapicCTI-132316	RCT III OL	Japan	207 (100%)	Alectinib 300x2	Crizotinib 250x2	A/B (64%/36%)
PROFILE 1014/Solomon 2014[37]	NCT01154140	RCT III OL	International	343 (100%)	Crizotinib 250x2	Pemetrexed + cisplatin or carboplatin	A
PROFILE 1029/Lu 2016[39]	NCT01639001	RCT III OL	International	207 (100%)	Crizotinib 250x2	Pemetrexed + cisplatin or carboplatin	A
ASCEND-4/Soria 2017[38]	NCT01828099	RCT III OL	International	376 (100%)	Ceritinib 750	Pemetrexed +/- cisplatin or carboplatin	A
ALUR/Roche 2016[40]	NCT02604342	RCT III OL	International	107 (100%)	Alectinib 600x2	Pemetrexed or docetaxel	D
ASCEND-5/Scagliotti 2016[45]	NCT01828112	RCT III OL	International	231 (100%)	Ceritinib 750	Pemetrexed or docetaxel	D
PROFILE 1007/Shaw 2013a[46]	NCT00932893	RCT III OL	International	347 (100%)	Crizotinib 250x2	Pemetrexed or docetaxel	B
Listed as included in the systematic literature review, but not mentioned in main submission							
JP28927/Hida 2016[41]	JapicCTI-132186	RCT OL	Japan	35 (100%)	Alectinib 300x2 (150 mg capsules)	Alectinib 300x2 (20/40 mg capsules)	Mixed
ALTA/Kim 2016[93]	NCT02094573	RCT II OL	International	222 (100%)	Brigatinib 90	Brigatinib 90-180	C/D
ONALESPIB/Lee 2016[94]	NCT01712217	RCTI/II OL	International	228 (100%)	Crizotinib 250x2	Crizotinib + onalespib	C
EURTAC/Rosell 2012[95]	NCT00446225	RCT III OL	France/Italy/Spain	15 (16%)	Erlotinib	Docetaxel or gemcitabine + cisplatin or carboplatin	A
CALGB30406/Stinchcombe 2013[96]	NCT00126581	RCT III OL	USA	8 (7%)	Erlotinib	Erlotinib + carboplatin + Paclitaxel	A
Zhang 2013[97]	NR	RCT	China	29 (12%)	Pemetrexed + Cisplatin	Gemcitabine + cisplatin	A
Zhao 2015[98]	NA	RCT	China	NR	Crizotinib 250x2	Unclear	B (probably)
Cui 2015[99]	NR	NR	China	72 (100%)	Crizotinib 250x2	-	A/B

CAUY922A220/Felip 2012[100]	NCT01124864	P II	International	22 (18%)	Luminespib	-	B/D
ASCEND-3/Felip 2015b[101]	NCT01685138	P II	International	124 (100%)	Ceritinib 750	-	A/B
AP26113-11-101/Gettinger 2016b[102]	NCT01449461	P I/II	Spain/USA	79 (58%)	Brigatinib 90-180	-	Mixed
LOGK1401/Iwama 2017[42]	UMIN000015094/ UMIN000017806	P II	Japan	18 (100%)	Alectinib 300x2	-	A/mixed (72%/28%)
Kawano 2013[103]	UMIN000002847	P II	Japan	6 (15%)	Pemetrexed	Cisplatin	A
X396-CLI-101/Lovly 2016[104]	NCT01625234	P I/II	USA	57 (100%)	Ensartinib	-	Mixed
ALEC case series/Metro 2016[43]	NCT02075840/ NCT01801111	Case series	Italy	11 (100%)	Alectinib 600x2	-	Mixed
TSR-001-PR-20-5006[105]	NCT02048488	P I/II	International	72 planned	Belizatinib	-	NR/pretreated
PROFILE 1005/Riely 2011[106]	NCT00932451	P II	International	439 (100%)	Crizotinib 250x2	-	B
IPI-504-03/Sequist 2010a[107]	NCT00431015	P II	USA	3 (4%)	RET IPI-504 220	-	B
GAN 9090-06/Socinski 2013[108]	NCT01031225	P II	USA	4 (4%)	Ganetespib	-	A/B
AF-001JP/Tamura 2017[44]	JapicCTI-101264	P I/II	Japan	46 (100%)	Alectinib 300x2	-	B

Abbreviations: ID, identifier; N ALK+, number with anaplastic lymphoma kinase mutation; NR, not reported; OL, open-label; P I, phase one study; P II, phase two study; RCT, randomised controlled trial; USA, United States of America. Population A: naïve to crizotinib and chemotherapy; Population B: naïve to crizotinib but not chemotherapy; Population C: naïve to chemotherapy but not to crizotinib; Population D: prior crizotinib and chemotherapy.
Note: Where specified for clarity, doses are in mg

Table 61. Patient characteristics of Population A RCTs identified in the company's SLR (adapted from Table 18, CS Appendix D1.1)

	ALEX[25]		**PROFILE 1014[37]**		**PROFILE 1029[39]**		**ASCEND-4[38]**	
	Alectinib	**Crizotinib**	**Crizotinib**	**PEM+CIS/CARB**	**Crizotinib**	**PEM+CIS/CARB**	**Ceritinib**	**PEM+CIS/CARB + MAIN PEM**
N, randomised	152	151	172	171	104	103	189	187
Age, Median (range)	58 (25-88)	54 (18-91)	52 (22-76)	54 (19-78)	Mean 48.2	Mean 48.9	55 (22-81)	54 (22-80)
Male, n (%)	68 (45)	64 (42)	68 (40)	63 (37)	50 (48.1)	43 (41.7)	87 (46.0)	73 (39.0)
Race, n (%)								
Asian	69 (45)	69 (46)	77 (45)	80 (47)	104 (100)	103 (100)	76 (40)	82 (44)
Other	83 (55)	82 (54)	95 (55)	91 (53)	-	-	113 (60)	105 (56)
ECOG/WHO PS, n (%)								
0–1	142 (93)	141 (93)	161 (94)	163 (95)	99 (95)	98 (95)	176 (93)	175 (93)
2	10 (7)	10 (7)	10 (6)	8 (5)	5 (5)	5 (5)	13 (7)	11 (6)+
Stage at baseline, n %								
IIIB/locally advanced	4 (3)	6 (4)	4 (2)	3 (2)	NR	NR	9 (5)	5 (3)
IV/metastatic	148 (97)	145 (96)	168 (98)	168 (98)	NR	NR	180 (95)	182 (97)
Histology/cytology, n (%)								
Adenocarcinoma	16 (90)	142 (94)	161 (94)	161 (94)	NR	NR	180 (95)	183 (98)
Other	16 (10)	9 (6)	11 (6)	10 (6)	NR	NR	9 (5)	4 (2)
Smoking history, n (%)								
Active smoker	12 (8)	5 (3)	10 (6)	5 (3)	NR	NR	15 (8)	15 (8)
Non-smoker	92 (61)	98 (65)	106 (62)	112 (65)	NR	NR	108 (57)	122 (35)
Past smoker	48 (32)	48 (32)	56 (33)	54 (32)	NR	NR	66 (35)	50 (27)
Brain/CNS metastasis, n (%)	64 (42)	58 (38)	45 (26)	47 (27)	21 (20)	32 (31)	59 (31)	62 (33)
Prior brain radiation, n (%)	26 (17)	21 (14)	NR#	NR#	NR	NR	24 (13)	26 (14)

Abbreviations: CARB, carboplatin; CIS, cisplatin; CNS, Central Nervous System; ECOG PS, Eastern Cooperative Oncology Group Performance Score; MAIN, maintenance; NR, not reported; PEM, pemetrexed; RCTs, randomised controlled trials; SLR, systematic literature review; WHO, World Health Organization; + Does not sum to 100% due to missing observations; # 39 (23%) of patients in the CRZ arm and 40 (23%) in the chemotherapy arm received prior treatment for brain metastases, details of prior radiotherapy reported during the trial were limited so the numbers of patients receiving radiotherapy are not available.

Table 62. Company's Cochrane risk of bias assessment of ALEX (Peters 2017[25]; adapted from Table 7, clarification response)

Risk of bias domain	Rating	Justification
Random sequence generation	●	Randomisation was stratified using a block-stratified randomisation procedure, suggesting randomisation sequence generated adequately
Allocation concealment	●	Randomisation was performed centrally via interactive voice or web-based response system
Participant + personnel blinding	●	Study was open-label. IRC corroborated INV assessments, and IRC assessments of secondary endpoints PFS and TTP outcomes were made blind, so these are unlikely to have been affected. IDMC meetings were conducted blind to the sponsor. The primary outcome was PFS assessed by INV, and this could have been affected potentially by the lack of blinding, however. Discontinuation from treatment (any reason) was higher in the CRZ control arm (105/151, 69.5%) than in the ALEC arm (68/152, 44.7%), as was withdrawal by subjects (11/151, 7.3% with CRZ vs. 3/152, 2% with ALEC)
Outcome assessor blinding	●	The primary outcome was PFS assessed by INV, and this could have been affected by the lack of blinding, as could ORR (also assessed by INV), hence high risk of bias. Secondary endpoints (PFS, Time to CNS progression) were assessed by blinded IRC so these are associated with a low risk of bias. OS would also be associated with a low risk of bias.
Incomplete outcome data	●	No missing outcome data for primary and key secondary outcomes
Selective reporting	●	All primary and key secondary outcomes reported (data in confidence). Of the secondary outcomes listed in clinicaltrials.gov data regarding pharmacokinetic endpoints and HRQoL (time to deterioration in QLQ-C30 or in QLQ-LC13, QLQ-C30 scores, QLQ-LC13 scores) have not yet been reported.
Other bias	●	Baseline characteristics well balanced and there were no protocol violations. All patients randomised were treated as planned. Mean dose intensity was 92.4% with CRZ and 95.6% with ALEC 38% and 42% had BM at BL (IRC assessed), and 38% and 40% (INV assessed) for CRZ and ALEC, respectively. These %s, although balanced within the study, are higher than in PROFILE 1014, PROFILE 1029 and ASCEND-4, which could influence inter-study comparisons. Whether it could affect the comparison of relative effects is not known.

Abbreviations: AEs, adverse events; ALEC, alectinib; BL, baseline; BMs, brain metastases; CHEMO, chemotherapy; CRZ, crizotinib; HRQoL, health-related quality of life; INV, investigator-assessed; IRR, independent radiology review; ORR, objective response rate; OS, overall survival; PEM, pemetrexed; PFS, progression-free survival; QLQ-C30, quality of life questionnaire core 30; QLQ-LC13, quality of life questionnaire lung cancer module; TTP, time to progression.

Table 63. Company's Cochrane risk of bias assessment of PROFILE 1014 (Solomon 2014[37]; adapted from Table 7, clarification response)

Risk of bias domain	Rating	
Random sequence generation	●	Randomisation was stratified, suggesting randomisation sequence generated adequately
Allocation concealment	●	Method of concealment not described
Participant + personnel blinding	●	Study was open-label, but all scans were assessed by central IRR by radiologists unaware of group assignments. Lack of blinding does not appear to have resulted in larger number of withdrawals in the comparator arm.
Outcome assessor blinding	●	Outcome assessed by central IRR by radiologists unaware of group assignments

Incomplete outcome data	●	No missing outcome data
Selective reporting	●	Study protocol not available but all pre-specified outcomes are reported in publications and/or registry
Other bias	●	When the study was designed the standard comparator was considered PEM+platinum-based chemotherapy. The comparator arm was based on this strategy. Since then there is evidence that adding PEM maintenance therapy after the maximum of 6 cycles of CHEMO can have additional benefit. There was no maintenance therapy in this study and the treatment duration for CRZ was, therefore, much longer (median 10.9 mths) than that of CHEMO (median 4.1 mths). Only one outcome (rate of AEs associated with cardiac failure) was adjusted for treatment duration differences. The choice of platinum chemotherapy was made by the investigator. 23% of patients in each arm had brain metastases at BL (all treated with brain radiotherapy and neurologically stable and BIRC assessed)
Abbreviations: AEs, adverse events; BL, baseline; BMs, brain metastases; CHEMO, chemotherapy; CRZ, crizotinib; IRR, independent radiology review; PEM, pemetrexed.		

Table 64. Company's Cochrane risk of bias assessment of PROFILE 1029 (Lu 2016[39]; adapted from Table 7, clarification response)

Risk of bias domain	**Rating**	
Random sequence generation	●	Randomisation was stratified, suggesting randomisation sequence generated adequately
Allocation concealment	●	Method of concealment not described
Participant + personnel blinding	●	Study was open-label. Scans were assessed by IRR but not reported in registry or abstract (no full paper yet published) whether assessment was performed at a central lab or whether radiologists were blind to treatment assignment
Outcome assessor blinding	●	Study was open-label. Scans were assessed by IRR but not reported in registry or abstract (no full paper yet published) whether assessment was performed at a central lab or whether radiologists were blind to treatment assignment
Incomplete outcome data	●	Withdrawals due to AEs or lack of efficacy has not been reported, nor has treatment dose changes or interruptions.
Selective reporting	●	Study protocol not available but all pre-specified outcomes are reported in publications and/or registry
Other bias	●	When the study was designed the standard comparator was considered PEM+platinum-based chemotherapy. The comparator arm was based on this strategy. Since then there is evidence that adding PEM maintenance therapy after the maximum of 6 cycles of CHEMO can have additional benefit. There was no maintenance therapy in this study and the treatment duration for each arm was not reported. All pts with BMs at BL had BMs that were treated with brain radiotherapy and neurologically stable in order to be eligible. 20% and 31% in CRZ and CHEMO arms respectively had brain metastases at BL, an imbalance that could favour CRZ
Abbreviations: AEs, adverse events; BL, baseline; BMs, brain metastases; CHEMO, chemotherapy; CRZ, crizotinib; IRR, independent radiology review		

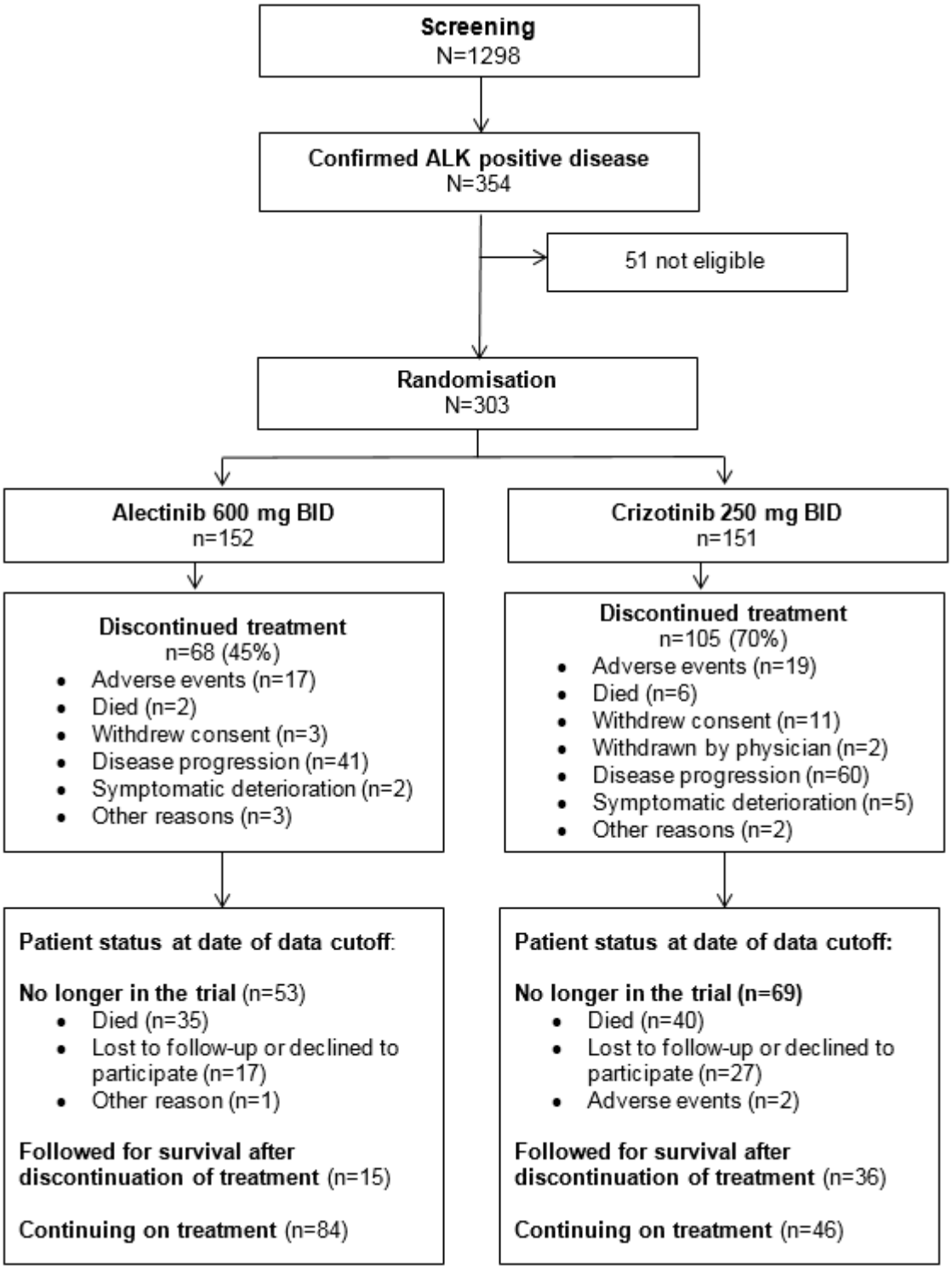
Table 65. Company's Cochrane risk of bias assessment of ASCEND-4 (Soria 2017[38]; adapted from Table 7, clarification response)

Risk of bias domain	Rating	Justification
Random sequence generation	●	Randomisation was stratified, suggesting randomisation sequence generated adequately
Allocation concealment	●	Randomisation assigned by interactive response technology
Participant + personnel blinding	●	Study was open-label - patients and investigators were not masked to treatment - but most study sponsor personnel were blind to treatment assignment. As response outcomes were assessed by BIRC, it is unlikely that the open-label nature of the study would have influenced outcome assessment. However, it may have influenced withdrawals potentially: withdrawal due to lack of efficacy was higher in the CHEMO arm (94/187, 50%) than in the ceritinib arm (51/189, 27%) and withdrawals for any reason were also higher with CHEMO (157/187, 84%) than with ceritinib (94/189, 50%).
Outcome assessor blinding	●	As response outcomes were assessed by BIRC, it is unlikely that the open-label nature of the study would have influenced outcome assessment.
Incomplete outcome data	●	No missing outcome data
Selective reporting	●	Grouped Serious Adverse Event data were not reported. Full paper does indicate that serious adverse drug reactions were similar in both treatment groups but no data are given
Other bias	●	Relative dose intensity of ceritinib was 78.4% vs. 93.8-99.2%, which may make the comparative assessment more conservative. The CHEMO comparative arm allowed maintenance therapy with PEM, meaning that the comparative assessment would be more conservative compared to use of a CHEMO regimen consisting of a maximum of 6 cycles. Withdrawal due to lack of efficacy was higher in the CHEMO arm (94/187, 50%) than in the ceritinib arm (51/189, 27%) and withdrawals for any reason were also higher with CHEMO (157/187, 84%) than with ceritinib (94/189, 50%). Assessment of intracranial response may differ from other studies as RECIST 1.1 was modified to be more rigorous: "a maximum of five target lesions in the brain could be selected (if the minimum size of the longest diameter was 10mm) at baseline and evaluated at each subsequent timepoint" 31% and 33% of pts in CER or CHEMO arms respectively had brain metastases. BM (INV-assessed) were neurologically stable, symptomatic or non-symptomatic, and with/without previous brain radiation (59% of patients with BM did not have prior brain radiotherapy, in contrast to PROFILE 1014 where patients with BM had treated BM).

Abbreviations: BIRC, blinded independent central review; BMs, brain metastases; CER, ceritinib; CHEMO, chemotherapy; AEs, adverse events; PEM, pemetrexed; RECIST, response evaluation criteria in solid tumous.

10.3 Participant flow

Figure 38. Patient disposition and reasons for discontinuation in ALEX (reproduced from Figure 2, CS Appendix D1.2)



10.4 Baseline characteristics

Table 66. Patient demographics and baseline characteristics of the ALEX population (adapted from Table 5, CS pg 23 and Table 6 and 7 of the CSR[35])

		Alectinib (n = 152)	Crizotinib (n = 151)
Age, years	Mean (SD)	56.3 (12.0)	53.8 (13.5)
	Median	58.0 (25–88)	54.0 (18–91)
Male, n (%)		68 (45)	64 (42)
Race, n (%)	Asian	69 (45)	69 (46)
	Non-Asian	83 (55)	82 (54)
ECOG PS, n (%)	0	43 (28.3)	54 (35.8)
	1	99 (65.1)	87 (57.6)
	2	10 (6.6)	10 (6.6)
Smoking status, n (%)	Active smoker	12 (8)	4 (3)
	Former smoker	48 (32)	48 (32)
	Non-smoker	92 (61)	98 (65)
Current stage of disease, n (%)	IIIB	4 (3)	6 (4)
	IV	148 (97)	145 (96)
Histologic type, n (%)	Adenocarcinoma	137 (90)	142 (94)
	Undifferentiated or other*	15 (10)	9 (6)
Prior treatment for NSCLC, %			
	Adjuvant or neoadjuvant chemo	8.6	11.3
	Radiotherapy	26	27
	Surgery	36	32
Presence of CNS metastases by IRC, n (%)		64(42)	58 (38)
Prior treatment for CNS metastases, n (% of full population)		27 (17.8)	22 (14.6)
Number of lesions per patient	Median (range)	2 (1–5)	2 (1–5)
	1 – 3	177 (77.5)	114 (75.0)
	>3	34 (22.5)	38 (25.0)
Number of sites/patient, median (range)		2 (1–5)	2 (1–5)
At least 1 RECIST target lesion in			
	Lung, pleura or pleural effusion	123 (81.5)	125 (82.2)
	Lymph nodes	71 (47.0)	77 (50.7)
	Bone (including bone marrow)	2 (1.3)	0 (0.0)
	CNS	13 (8.6)	18 (11.8)
	Liver	5 (23.2)	27 (17.8)
	Adrenal	12 (7.9)	7 (4.6)
	Skin	0 (0.0)	1 (0.7)
	Other	14 (9.3)	23 (15.1)

Abbreviations: CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance score; ERG, evidence review group; IRC, independent review committee; n, number of patients; NSCLC, non-small-cell lung cancer; RECIST; Response Evaluation Criteria in Solid Tumours; SD, standard deviation.
*footnote not provided in the company submission. Other histologic types reported in Peters 2017[25] were large-cell carcinoma, mixed with predominantly adenocarcinoma component, and squamous-cell carcinoma.
Note: ECOG PS was reported as 0-1 and 2 in the CS but the ERG requested breakdown by 0, 1 and 2 at the clarification stage.

10.5 Subsequent therapies in ALEX

Table 67. Subsequent therapies captured in ALEX for 41%* of patients who have permanently discontinued study treatment (adapted from Table 3, clarification response)

	Alectinib		**Crizotinib**	
Treatment **Number of patients (%)**	**2nd line** **(n = 68)**	**3rd line +** **(n = 68)**	**2nd line** **(n = 105)**	**3rd line +** **(n = 105)**
Any subsequent anti-cancer therapy	31 (45.6)	9 (13.2)	40 (38.1)	4 (3.8)
Any TKI	13 (19.1)	5 (7.4)	33 (31.4)	3 (2.9%
ceritinib	2 (2.9)	2 (2.9)	13 (12.4)	1 (1.0)
alectinib	0 (0.0)	0 (0.0)	8 (7.6)	2 (1.9)
crizotinib	6 (8.8)	3 (4.4)	2 (1.9)	0 (0.0)
lorlatinib	4 (5.9)	1 (1.5)	2 (1.9)	0 (0.0)
brigatinib	1 (1.5)	0 (0.0)	4 (3.8)	0 (0.0)
gefitinib	0 (0.0)	0 (0.0)	2 (1.9)	0 (0.0)
entrectinib	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
erolinib	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
Any platinum compound	16 (23.5%)	3 (4.4%)	6 (5.7%)	0 (0.0%)
carboplatin	7 (10.3)	0 (0.0)	5 (4.8)	0 (0.0)
cisplatin	9 (13.2)	3 (4.4)	1 (1.0)	0 (0.0)
Any antimetabolite	14 (20.6)	3 (4.4)	6 (5.7)	0 (0.0)
pemetrexed	8 (11.8)	2 (2.9)	5 (4.8)	0 (0.0)
pemetrexed diosodium	4 (5.9)	1 (1.5)	0 (0.0)	0 (0.0)
Gemicitabine	2 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)
gemcitabine hydrochloride	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
Any taxane	3 (4.4)	0 (0.0)	0 (0.0)	1 (1.0)
paclitaxel	3 (4.4)	0 (0.0)	0 (0.0)	0 (0.0)
docetaxel	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Any immunostimulant (nivolumab)	0 (0.0)	2 (2.9)	0 (0.0)	0 (0.0)
Angiogenesis inhibitor (bevacizumab)	2 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)
Any alkylating agent (cyclophosphamide)	3 (4.4)	1 (1.5)	1 (1.0)	0 (0.0)
Any antineoplastic agent NOS	0 (0.0)	1 (1.5)	1 (1.0)	0 (0.0)
antineoplastic agent NOS	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
FAZ053 (anti PD-L1)	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)
Any cytotoxic antibiotic (doxorubicin)	1 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)
Any vinca alkaloid (vincristine)	1 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: NOS, not otherwise specified; PD-L1, programmed death-ligand; TKI, tyrosine kinase inhibitor
*Subsequent therapies are not known for the remaining 59% of patients who have permanently discontinued study treatment.

10.6 Subgroup and exploratory analyses

Table 68. Concordance analysis between the INV and IRC assessed progressive disease (ITT population; adapted from CSR, Table 14, pg 93)

	Alectinib (n = 152)	**Crizotinib (n = 151)**
Number of patients evaluable for concordance	[redacted]	[redacted]
Concordance between PD occurrence	[redacted]	[redacted]
PD per INV and IRC	[redacted]	[redacted]
no PD per INV and IRC	[redacted]	[redacted]
Discordance between PD occurrence	[redacted]	[redacted]
PD per INV and no PD per IRC	[redacted]	[redacted]
No PD per INV and PD per IRC	[redacted]	[redacted]
Concordance between PD occurrence and timing of PD	[redacted]	[redacted]
PD per INV and PD per IRC, dates within 14 days	[redacted]	[redacted]
No PD per INV and no PD per IRC	[redacted]	[redacted]
Discordance between PD occurrence and timing of PD	[redacted]	[redacted]
PD per INV and no PD per IRC	[redacted]	[redacted]
No PD per INV and PD per IRC	[redacted]	[redacted]
PD per INV and PD per IRC, dates differ by > 14 days	[redacted]	[redacted]

Abbreviations: INV, investigator; IRC, independent review committee; ITT, intent to treat population; PD, progressive disease.

Figure 39. Overall survival (OS) subgroup analysis for alectinib (**A**) and crizotinib (**B**): patients in ALEX who received a subsequent TKI (red) vs patients who received a subsequent non-TKI (blue; adapted from the company's clarification response, figures 3 and 4)

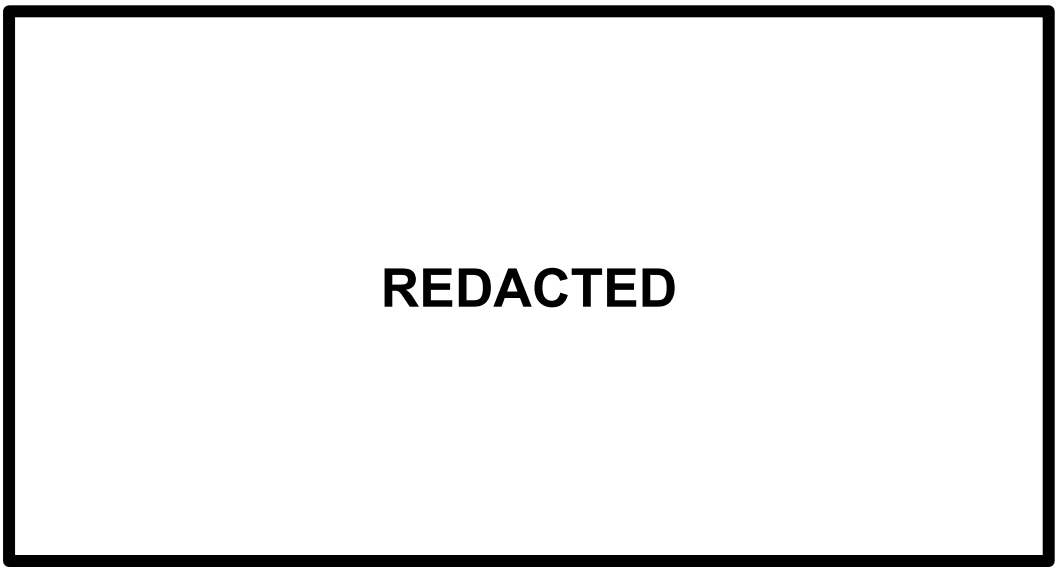


Figure 40. Overall survival (OS) subgroup analysis for alectinib (A) and crizotinib (B): patients in ALEX who had CNS metastases at baseline (red) vs those who did not (blue; adapted from the company's clarification response, figures 5 and 6)

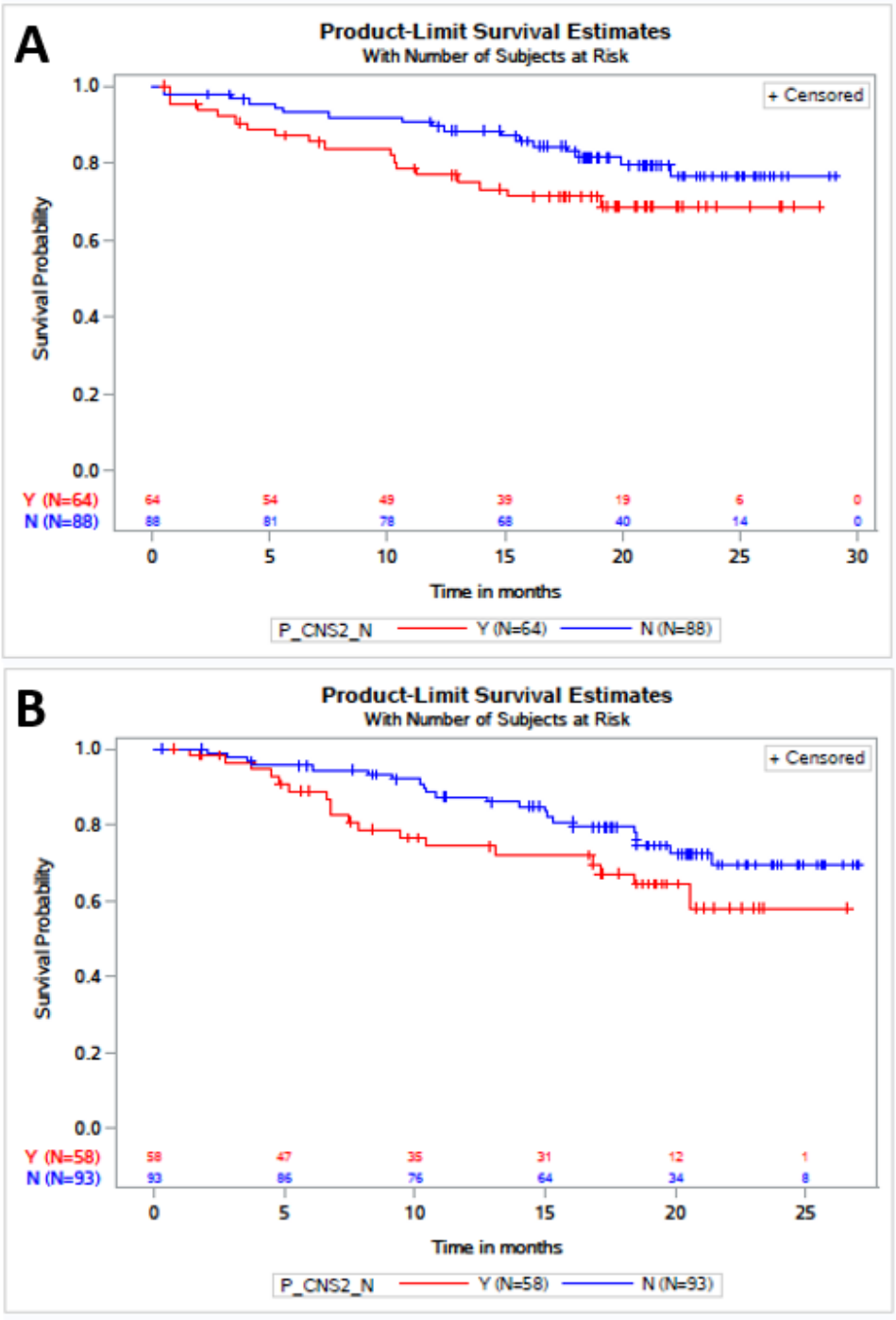
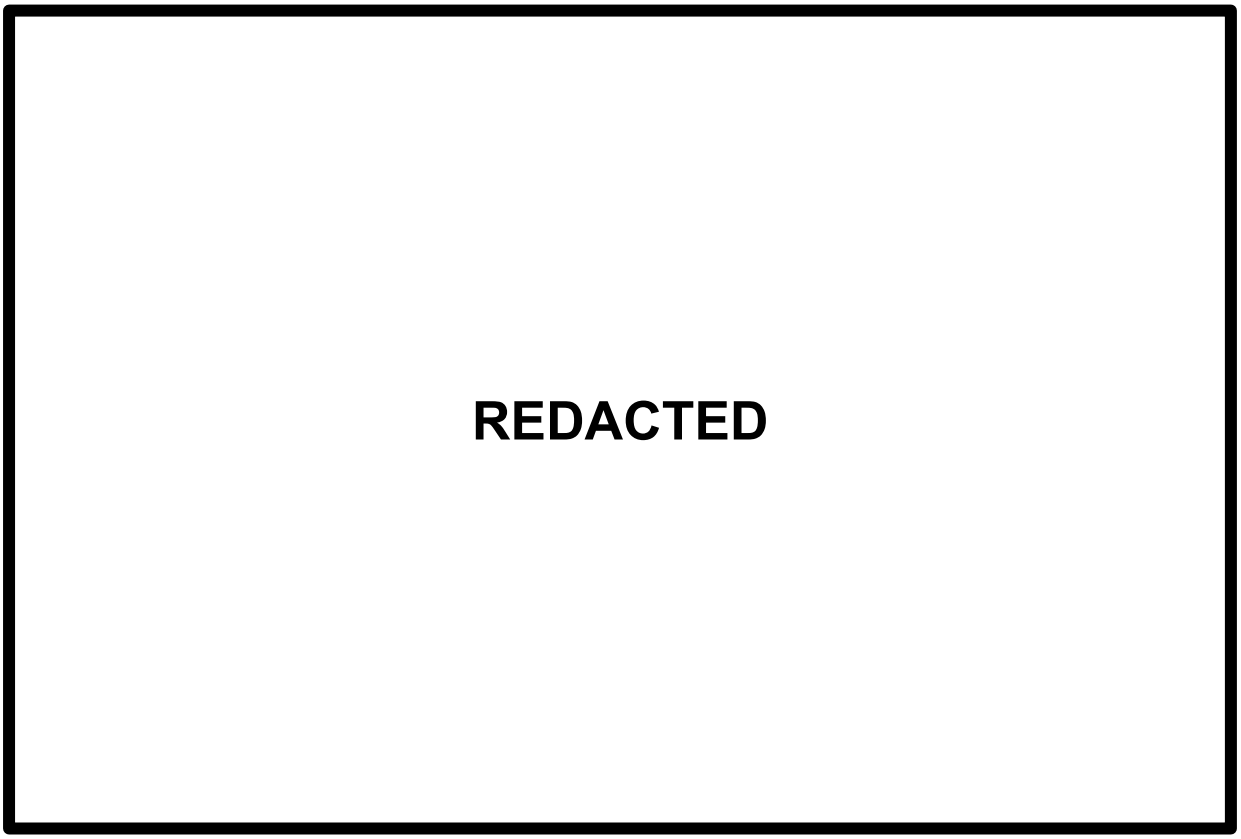


Figure 41. 6- and 12-month landmark analyses of adapted CNS PFS (IRC RECIST-only) as a predictor of OS in ALEX (reproduced from response to CQ A6)



10.7 Cost effectiveness appendices

Table 69: Summary of NICE TA406 (adapted from Table 14 of the CS and Table 35, Appendix G of the CS)

Study	Summary of model structure	Population	Utilities	Resources	Costs	Currency (cost reference year)	ICER (per QALY gained)
NICE TA406[55]	State transition model (semi-Markov)	Locally advanced or metastatic ALK+ NSCLC	Utilities: • PF, crizotinib: redacted • PF, pemetrexed + platinum: redacted • Treatment beyond progression with crizotinib: redacted • PD, docetaxel: 0.66 • PD, BSC: 0.47 Disutilities associated with AEs: • Elevated transaminases: 0.00 • Neutropenia: 0.09 • Anaemia: 0.07 • Leukopenia: 0.09 • Thrombocytopenia: 0.09	• Drug acquisition and administration • Monitoring • ALK testing • Outpatient visits • Oncologist visits • GP visits • Cancer nurse • Complete blood count • Biochemistry • CT scans and X-rays • Palliative care • Treating AEs	Drug costs/cycle: • Crizotinib: £4,689 • Pemetrexed: £1,440 (with wastage) • Cisplatin: £47 (with wastage) • Carboplatin: £34 (with wastage) Other costs: • AEs (one-off cost, chemotherapy arm only): £163 • FISH test: £120 per test	GBP (2016)	crizotinib vs. pemetrexed plus platinum chemotherapy: £47,291 with PAS

Abbreviations used in the table: AEs, adverse event; ALK, anaplastic lymphoma kinase; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; NSCLC, non-small cell lung cancer; QALY, quality adjusted life year; PAS, patient access scheme; PD, progressed disease; PFS, progression free survival

Table 70: Update to Table 25 in CS: Study summary and reported utility data of the relevant study identified in the systematic review

Study	Population details	Method of deriving HSUVs	Countries	Mean HSUVs		
				Pre-progression	Post-progression	Other
Solomon 2014 (PROFILE 1014)[37]	Locally advanced, recurrent, or metastatic ALK+ NSCLC (N=343)	Instrument: EQ-5D Valuation: NR Elicitation: NR Scale: NR	Australia, Austria, Belgium, Brazil, Canada, Chile, China, Finland, France, Germany, Hong Kong, India, Ireland Italy, Japan, South Korea, Luxembourg, Mexico, Netherlands, Norway, Peru, Portugal, Russia, Singapore, South Africa, Spain, Switzerland, Taiwan, Ukraine, UK, US	Baseline (SD): Crizotinib, 0.72 (0.30) Chemotherapy, 0.71 (0.26) During treatment (SE): Crizotinib, 0.73 (0.02) Chemotherapy, NR	NA	NA
Felip, 2015 (PROFILE 1014)[60]	Advanced non-squamous ALK+ NSCLC (N=343)	Instrument: EQ-5D (3L version) Valuation: NR (calculated using a standard algorithm) Elicitation: NR Scale: 0-1	NR	Baseline (SD): Crizotinib, 0.72 (0.30) Chemotherapy, 0.71 (0.26) During treatment (SD): Crizotinib, 0.81 (NR) Chemotherapy, 0.72 (NR)	NA	NA
Blackhall 2014 (PROFILE 1007) [61]	Locally advanced or metastatic ALK+ NSCLC (N=347)	Instrument: EQ-5D (version not clear) Valuation: NR Elicitation: NR Scale: NR	Australia, Brazil, Bulgaria, Canada, China, France, Germany, Greece, Hong Kong, Hungary, Ireland, Italy, Japan, South Korea, Netherlands, Poland, Russia, Spain, Sweden, Taiwan, UK, US	Baseline (SD): Crizotinib, 0.73 (0.24) Chemotherapy, 0.70 (0.26) Pemetrexed, 0.73 (0.24) Docetaxel, 0.67 (0.29) During treatment (SE): Crizotinib, 0.82 (0.01) Chemotherapy, 0.73 (0.02) Pemetrexed, 0.74 (0.02) Docetaxel, 0.66 (0.04)	NA	NA

Abbreviations used in the table: ALK+, anaplastic lymphoma kinase-positive; HSUV, health state utility value; NA, not available; NR, not reported; NSCLC, non-small cell lung cancer; SD, standard deviation; SE, standard error; UK, United Kingdom; US, United States.

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Alectinib for untreated anaplastic lymphoma kinase positive advanced non-small- cell lung cancer [ID925]

You are asked to check the ERG report from BMJ Group to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on 12 February 2018** using the below proforma 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.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Contradictory statements throughout report

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
<u>Contradictory statements regarding anticipated subsequent therapies</u> Throughout the report, there are contradictory statements on the anticipated subsequent therapies available for crizotinib and alectinib, as well as the anticipated proportions of patients assigned to each treatment regimen. The views presented	Edit to one standard, evidence supported recommendation of anticipated subsequent therapies available for both crizotinib and alectinib, as well as the anticipated proportions of patients assigned to each treatment regimen. Roche recommend utilising the previously NICE	Contradictory statements are confusing and can mislead the reader. The ERG utilise ceritinib as an	Not a factual error. The effect of including ceritinib as a subsequent

<table>
<tr>
<td>often oppose the clinical expert opinion sought by the ERG, NICE recommendations in the appraisal of ceritinib (1), and marketing authorisation restrictions for second line indications.

The ERG have heard from clinical experts, and the committee in the appraisal of ceritinib, that:

1) Not all patients are fit for second line treatment
2) It would be counterintuitive that crizotinib would be given after failure on a superior class of therapy
3) Concern over availability of appropriate 2L therapies for use after second-generation ALK-TKIs such as alectinib: “the only option after ceritinib [or alectinib] is chemotherapy, whereas people on crizotinib can switch to ceritinib”
4) Ceritinib is approved, and currently the preferred treatment for use after 1L crizotinib in England

However, in the ERG base case and scenario analyses, they have assumed the following:

1) 100% of first line patients receive subsequent treatment
2) 100% of alectinib treated patients would receive subsequent TKIs: 75% crizotinib, 25% ceritinib
3) 31.4% crizotinib treated patients would receive subsequent TKIs (quoting Yip et al, a flawed source - see Issue 2)

Two tables have been included below highlighting all the pages and statements made within the report which either support greater, or less ALK inhibitor usage in subsequent therapy lines after alectinib and crizotinib, respectively.</td>
<td>Committee D endorsed assumptions from the ceritinib 1L appraisal (1), where direct trial evidence was adapted to UK clinical practice (and available licenses), assuming 60% of patients in both treatment arms would receive a subsequent therapy:

Table 40 Base case: Trial-based distribution and total cost of second-line treatments, according to first-line treatment arm
<table><tr><th>Second-line treatment</th><th>Ceritinib (%)</th><th>Crizotinib (%)</th></tr><tr><td>Ceritinib</td><td>1.9</td><td>10.8</td></tr><tr><td>Crizotinib</td><td>9.4</td><td>1.5</td></tr><tr><td>Docetaxel</td><td>3.8</td><td>4.6</td></tr><tr><td>Pemetrexed</td><td>0.0</td><td>0.0</td></tr><tr><td>Platinum doublet</td><td>45.0</td><td>43.1</td></tr><tr><td>pemetrexed +</td><td>45.0</td><td>43.1</td></tr><tr><td>cisplatin, or</td><td>22.5</td><td>20.0</td></tr><tr><td>carboplatin</td><td>22.5</td><td>23.1</td></tr><tr><td>No active treatment</td><td>40.0</td><td>40.0</td></tr><tr><td>Total PD treatment cost, £</td><td>8,135.41</td><td>8,645.67</td></tr></table>
When accounting for patients who have died within the subsequent therapies analysis for ALEX, the resulting “missing” information due to either data collection, or patients not receiving subsequent therapies is 32 alectinib patients (47%) and 48 crizotinib patients (46%): not dissimilar to the 40% of patients not receiving subsequent therapy in the ceritinib appraisal. Therefore, it could be speculated a large proportion of this group are not, in fact “missing data”, and rather have just not received subsequent therapy.

As such, the resulting distributions using these assumptions for the ALEX trial, accounting for licensed and available therapies, derived from only first subsequent lines of therapy (as found in Table 3 of response to clarification questions) are:
<table><tr><th>Second-line treatment</th><th>Alectinib (%)</th><th>Crizotinib (%)</th></tr></table></td>
<td>appropriate treatment after alectinib, however, there is no license available in this indication, thus it would not be appropriate for such a treatment to be included in the treatment pathway post-alectinib.

Finally, as NICE committee D have expressed a preference regarding the distribution of subsequent therapies, a level of alignment is required between appraisals.</td>
<td>therapy for alectinib was tested, and this scenario is described in the ERG’s report. Removing ceritinib and including crizotinib as the only licensed option decreases the ICER by around £1000.</td>
</tr>
</table>

Greater ALK usage post-alectinib		Less ALK usage post-alectinib	
Pg.	Quote	Pg.	Quote
25	“Furthermore, clinical expert opinion provided to the ERG indicates that (although there is no clinical consensus on how to treat progressed patients after alectinib), it would appear plausible that alectinib patients would be fitter than crizotinib patients, and therefore more likely to tolerate subsequent treatment with a TKI.”	40, 102, 150, 172	“Given the acknowledged differences between first- and second-generation ALK-TKIs, some clinical experts considered it counterintuitive that crizotinib would be given after failure on a superior class of therapy. However, the recommendation associated with ceritinib, the only second-generation ALK-TKI available for use at 2L (TA395) specifies prior crizotinib use, so it is not a NICE-recommended option after 1L alectinib.”
25, 136	“As clinical experts anticipate that alectinib will have a protective effect on the CNS compared with crizotinib, it is	73, 101	“Subsequent treatment options may be more limited in the UK than in ALEX. The ERG’s clinical experts

Ceritinib	0.0	30.0
Alectinib	0.0	0.0
Crizotinib	10.5882	4.615
Docetaxel	0.0	0.0
Pemetrexed	21.1765	11.538
Platinum doublet	28.2353	13.846
Cisplatin	12.3529	11.538
Carboplatin	15.8824	2.308
No active treatment	40.0	40.0

	likely that a higher percentage of alectinib patients receive a subsequent TKI."		expressed concern about the availability of appropriate 2L therapies for use after second-generation ALK-TKIs such as alectinib, whereas ceritinib is approved for use after 1L crizotinib in England" "This is because the only option after ceritinib is chemotherapy, whereas people on crizotinib can switch to ceritinib."			
31, 32, 150, 163	"To further reflect UK clinical practice, the ERG assumed that the treatments available for subsequent treatment lines consisted on crizotinib and ceritinib (post-alectinib) and ceritinib (post-crizotinib). In order to estimate the distribution of patients allocated to crizotinib or ceritinib	150	"ceritinib is currently not recommended for treatment after alectinib"			

	post alectinib, the ERG used the data available from ALEX, which shows that 2.9% of alectinib patients received ceritinib and 8.8% of patients received crizotinib. The ERG reweighted these values, to account for the entire subgroup of patients receiving a TKI post-alectinib. The final proportions used in the ERG's analysis are 25% for ceritinib and 75% for crizotinib."		

Greater ALK usage post-crizotinib		Less ALK usage post-crizotinib	
Pg	Quote	Pg	Quote
40, 73, 101	"At second line (2L), the ERG's clinical experts agreed that ceritinib is the currently preferred treatment following first-line crizotinib, which was	25,29	"With regards to crizotinib, the England audit data (Yip et al, 2017) available suggests that 18% of patients who received crizotinib, received a

	recommended by NICE TA395 in 2016" "the only option after ceritinib is chemotherapy, whereas people on crizotinib can switch to ceritinib."		second-line TKI"			
150	"The ERG considers it reasonable to assume all patients receive subsequent therapies once they progress, as this seems reflective of current clinical practice with crizotinib"	25, 136	"The clinical experts added that, the reason why a relatively low percentage of patients receive a TKI treatment after crizotinib in the UK is related to the development of CNS metastases, which leave the patients too ill to receive a further TKI, and so chemotherapy is the only viable option."			
<u>Contradictory statements regarding OS benefit of alectinib</u> The ERG appear to misrepresent feedback received from their clinical experts regarding the OS benefit of alectinib. Page 72: "The ERG's clinical experts did not consider the divergence of the curves at 18 months in Figure 3 demonstrated an OS				Retract sentence on page 77	Contradictory statements are confusing and can mislead the reader.	Not a factual error. Pg 72 highlights that ALEX has not shown a statistically significant difference

benefit for alectinib over crizotinib, but do expect that the benefits of alectinib shown in ALEX for PFS and CNS metastases (Section 4.3.2) will translate to an OS benefit in clinical practice" Page 77: "Given the reservations of the ERG's clinical experts about the clinical plausibility of OS observed in ALEX in the UK setting"			between treatments but that experts expect alectinib to have a benefit in practice, whereas pg 77 refers to the length of OS in ALEX (for both treatments) likely overestimating what will happen in UK clinical practice.
<u>Contradictory statements regarding the CNS impact of alectinib:</u> The ERG acknowledge the importance of capturing CNS impact in the cost effectiveness analysis of alectinib, but fail to implement it in their base case and scenario analyses. Page 17: "On the advice of clinical experts, the ERG considered it important to capture this proposed benefit, given the important effects of CNS progression on prognosis and patients' quality of life." Page 50, page 61: "After consultation with clinical experts, the ERG considered that it was important to reflect CNS activity in the review of cost effectiveness. CNS progressions are a common site of progression in ALK+ NSCLC with distinct clinical and cost	Incorporate CNS impact on patient quality of life in to the ERG base case	Contradictory statements are confusing and can mislead the reader.	Not a factual error. The quoted sections refer to the inclusion of CNS PFS data (which was not included in the scope) and not to indirect data about the impact of CNS progression on quality of life.

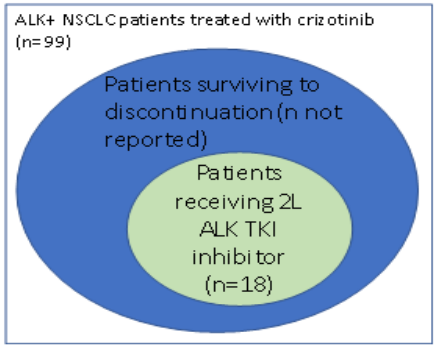
implications, and the company propose the activity of alectinib in the CNS is an important benefit that is not reflected fully by PFS." Page 52: "the ERG consider it appropriate to reflect CNS progression in the review of cost-effectiveness." Page 85: "The ERG's clinical experts highlighted that patients with ALK+ NSCLC frequently experience progression in the CNS, which can have an important impact on OS and quality of life. A subgroup analysis of OS by presence of CNS metastases at baseline was not outlined in the NICE final scope1 but the ERG considered it to be a valuable analysis considering the purported activity of alectinib in the CNS." Page 30, Page 137, Page 175: "This analysis *[the ERG base case and scenario analyses]* is caveated by the fact that CNS impact on patients' quality of life has not been included in the analysis"			
<u>Statements regarding crizotinib treatment beyond progression:</u> The ERG report appears to oppose recommendations and conclusions made by NICE in the appraisal of ceritinib (1) on this topic, references in the same report. Page 23: "treating patients with (the same) ALK inhibitor beyond disease progression seems established practice in the UK" Page 24:	Reconciliation required.	Contradictory statements are confusing and can mislead the reader.	Not a factual error.

"If crizotinib was given for a shorter period of time in ALEX than it would in clinical practice, there might be a negative bias in the observed outcomes from ALEX against crizotinib." Page 98: "there seems to be a reasonable evidence base suggesting that the majority of patients will receive crizotinib beyond treatment progression in clinical practice" Page 102: "there seems to be a reasonable evidence base suggesting that the majority of patients (over 75% of patients in ASCEND-4 and PROFILE 1014) will receive crizotinib beyond treatment progression in clinical practice" Page 24, Page 101: "The Committee concluded that in current practice, treatment with ceritinib, and to a lesser extent crizotinib, continues beyond disease progression." Page 101: "It was added that people taking ceritinib are more likely to continue treatment beyond disease progression than people taking crizotinib. This is because the only option after ceritinib is chemotherapy, whereas people on crizotinib can switch to ceritinib."			

Issue 2 ERG error in interpretation of England Audit data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG appear to utilise an old,	Retract all mentions of 18% in reference to	The abstract from Yip et al. (2) states the	The ERG accepts that

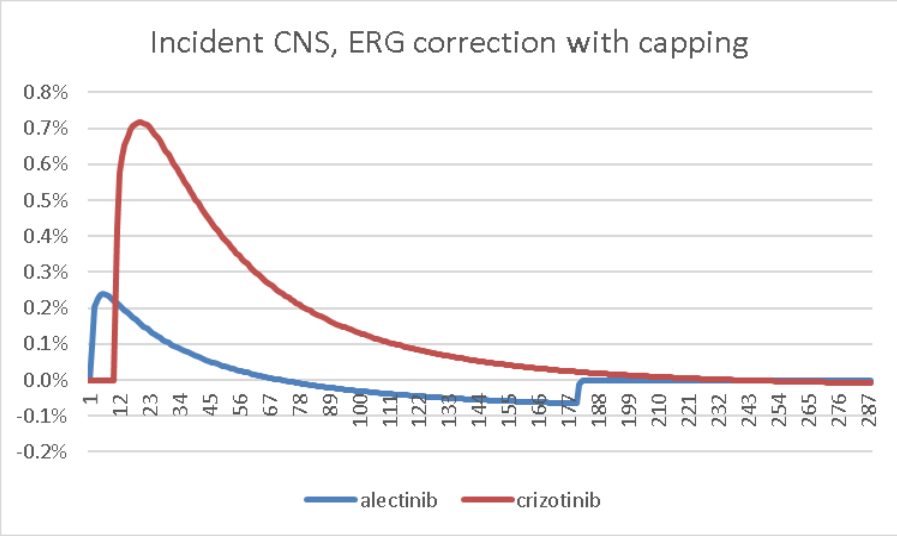
incomplete data set which is not relevant to the decision problem (all lines of therapy included), misinterpreting the result to justify: 1) Lack of validity of subsequent therapies in ALEX 2) Lack of validity of expert opinion obtained by Roche 3) An arbitrary figure of subsequent TKI usage for crizotinib in the ERG base case	the audit data. Retract all influence of this figure on the model	following: "18 patients received a second generation ALK TKI on progression post crizotinib." There is no indication within the abstract that this number takes into account the number of patients that died whilst being treated with crizotinib, and that the interpretation is therefore approximately the percentage of crizotinib patients that receive ALK TKIs at second line from the patients who progress. Instead, this number represents the number of patients from an original cohort of 99 which survived through progression, discontinuation of crizotinib, and long enough to receive a second-line ALK TKI inhibitor. The remaining pool of patients which would be considered for eligibility for second-line treatment with an ALK TKI inhibitor can only be 99 if all 99 patients within the cohort survived beyond discontinuation of crizotinib. To illustrate, in the below figure the ratio of the area within the green and blue circles respectively represents the proportion of discontinued patients receiving a 2L ALK TKI inhibitor (i.e. the appropriate number to apply in the model). Note that the number of patients surviving to discontinuation was not provided. The ratio of the green circle to the white square is the number 18/99 reported by Yip et al.	post-crizotinib TKI use is likely to be higher than the estimates reported in the Yip audit since ceritinib was approved, as highlighted by the company. The ERG stresses that the figure of 18% is not used directly in the ERG's base case or scenario analyses. The audit is the best available source of evidence of current practice in England, and of TKI use after crizotinib. The Yip results were substantiated by one of NICE's clinical expert statements: "The Yip data clearly shows that UK practice is substandard and associated with unnecessary early death. The most likely reason for low usage of next generation ALKi is that many patients "drop off" with rapid deterioration most likely due to
Page 25: "With regards to crizotinib, the England audit data (Yip et al, 2017) available suggests that 18% of patients who received crizotinib, received a second-line TKI."			
Page 29: "Given the England audit data suggests 18% of patients receive a second-line TKI after crizotinib"			

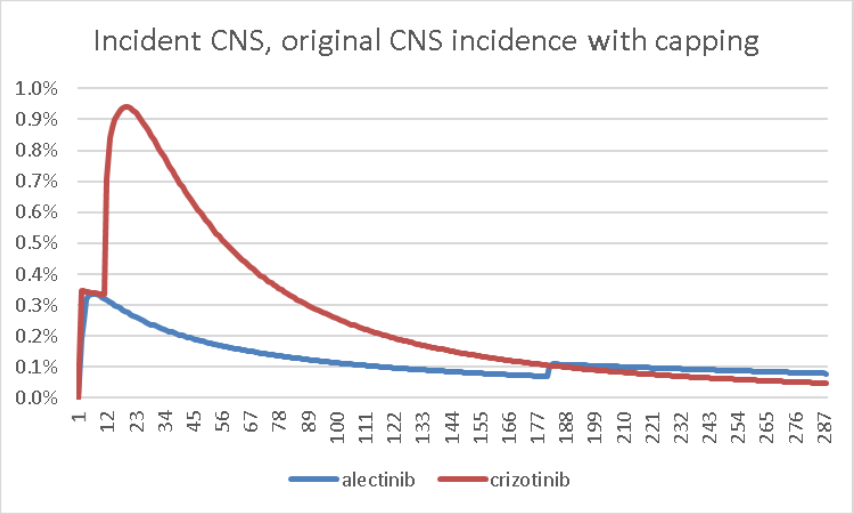
		 Further, it's imperative to note: this abstract explores the period January 2013-August 2016. Considering ceritinib only received a NICE recommendation in June 2016, 18% subsequent TKI usage is further invalidated, as there was no routine access to a second-line ALK inhibitor for 30 out of 32 months of this analysis. These issues are in addition to the issue already identified by the ERG, that the report includes patients receiving crizotinib at all lines of therapy and not just first-line.	progressive brain mets." The ERG has amended the wording on the following pages to reflect that 18% is considered a minimum estimate for the reasons outlined above: page 25, 29, 31, 81, 131, 132 and 146
Page 31: "The ERG does not consider the estimates used to be reflective of clinical practice in the UK as 90% of crizotinib patients are assumed to receive a subsequent TKI (compared with the 18% reported in the England audit)."			
Page 84: "If it is assumed that none of the patients in the missing subset received 2L therapy after 1L crizotinib, the percentage (33/105; 31.4%) remains higher than the 18% of patients who received a second-generation TKI after crizotinib in the audit of crizotinib use in England"			
Page 135: "With regards to crizotinib, the England audit data48 available suggests that 18% of patients who received crizotinib, received a second-line TKI"			
Page 137: "Given the England audit data suggests 18% of patients receive			

a second-line TKI after crizotinib, the ERG assumed that the 31.4% (Table 14) receiving a TKI after crizotinib in ALEX could be a reasonable approximation to the UK clinical practice"			
Page 150: "The ERG does not consider the estimates used to be reflective of clinical practice in the UK as 90% of crizotinib patients are assumed to receive a subsequent TKI (compared with the 18% reported in the England audit)."			

Issue 3 ERG correction of CNS metastases incidence generates implausible results

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 26, 31, 113: "The ERG disagrees with the method used for the estimation of newly progressed patients in the model as it uses a fixed proportion of CNS events (captured by the RECIST+CNS RECIST measure)	Retract statement and analyses	The ERG have incorrectly implemented their correction to the proportion of patients entering the CNS metastasis state, resulting in negative incidence of CNS metastasis in the alectinib arm. The below figure shows the incidence of CNS progression by cycle in the corrected base case model, in which the CPFS curve is capped by OS. Note that there is a 100 cycle (week) stretch in which there is a negative incidence of CNS progression within the alectinib arm. This is impossible.	The ERG thanks the company for identifying the problem resulting from the interaction of the ERG's two scenario analyses (capping the CPFS curve by the OS curve and estimating newly progressed

throughout the analysis. A more robust approach would have been to estimate the number of newly progressed patients every cycle, instead of relying on a fixed proportion.”		 On the other hand, the implementation of (non-death) CNS incidence implemented in the model submitted following clarification questions did not have this issue (see below). This is not sensitive to whether the CPFS and OS hazards are maximised each cycle, or the CPFS curve is capped by the OS curve. The fact that the correction proposed by the ERG suggests that alectinib reverses CNS metastasis is the reason that ERG scenario 2 has a lower ICER than the corrected base-case ICER	patients). The ERG agrees with the clinical implausibility of having a negative incidence in the CPFS curve. The ERG notes that capping the newly progressed curve estimated in the ERG model by zero, would solve this issue, as the newly progression estimation is not incorrect. Nonetheless, due to the interaction of the newly progressed curve and the capping method used (discussed in issue 4 and issue 5), the ERG removed its scenario analysis from the model.

		 Although the assumption of a fixed proportion of CNS progression events being deaths is a simplifying one, the implementation of it in this instance is such that impossibilities do not occur. The correction assumes that the rate of death is constant across all health states which is much less plausible (this issue, and the relaxation of the assumption that the hazard of the CPFS curve cannot be lower than the hazard of the OS curve, is what is causing the negative incidences). As the selection of method to implement in this case has very little bearing on the base-case results, we recommend that the original method be used.	
Page 162, CE model: Scenario 2 (Table 55) As described above, scenario not clinically valid	Correct the "all changes" version of this result if this is to be kept. We would recommend removing the scenario entirely given the clinically implausible result	In scenario 2, the ICER of £78,858 is only generated when only capping of OS curve is added in conjunction with Scenario 1, not when all changes are made. The same results are not generated when making the other changes proposed. This is inconsistent with the definition of all changes used for the other scenarios. Further, as this generates negative incidence of CNS progression, this instance of the scenario should be removed, as it is not clinically valid	All ERG scenario results have been updated as a result of the issue aforementioned.

	(negative incidence of CNS progression)		

Issue 4 Incorrect descriptions of the economic model

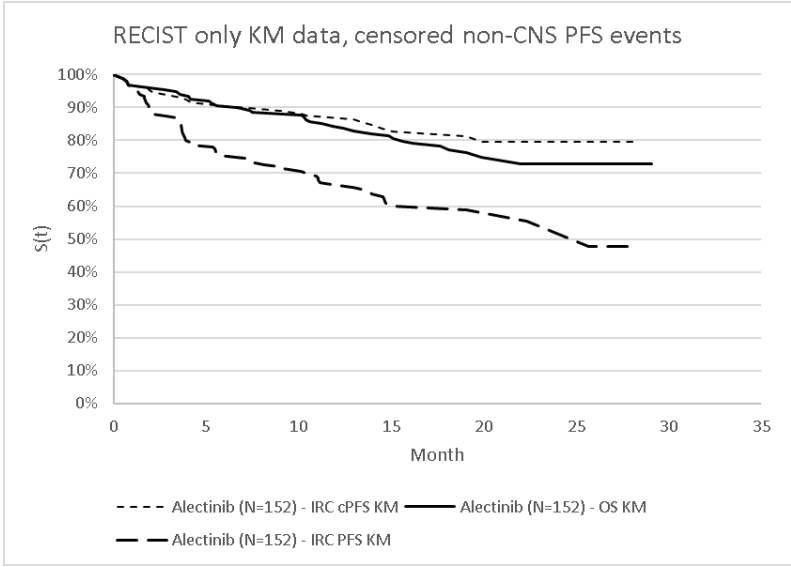
Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 26: "The ERG disagrees with the method used by the company to cap the CNS PFS data. Given that the company took the minimum risk each cycle to determine the proportion of patients in the CNS PFS curve, the risk of death (taken from the OS curve) was used from month 20 (approximately) to estimate the CNS PFS curve in the model for alectinib, and from month 50 (approximately) to estimate the CNS PFS curve for crizotinib. Nonetheless, the OS and CNS PFS curves for alectinib do not cross until 42 months. A similar situation is observed for the crizotinib model, where the OS and CNS PFS curves do not cross until 163 months. The ERG does not see a reason why the risk of events in the CNS PFS curve should not be higher than the risk of events in the OS curve. In fact, the CNS PFS curve includes death and	Refine the description of the hazard maximisation	The model is described as selecting the minimum (one cycle) risk of experiencing an event, when the reverse is true. The model selects the minimum risk of not experiencing the event in question, which is mathematically equivalent to the maximum risk of experiencing the event in question. That is: [redacted] Where the risk of an event: $R_t = 1 - \frac{S_t}{S_{t-1}}$ This re-calculation of hazards has often been used in NICE oncology HTAs where the best fitting or most clinically plausible survival fits to Kaplan-Meier data have extrapolations which will eventually cross. The RECIST only and RECIST+CNS RECIST curves in this model are defined by the first event to occur (i.e. the PFS curve is defined as first event of: any progression, CNS progression, death; whilst the CPFS curve is the first event of: CNS progression, death). Consequently, whenever the gradient of a preceding curve (e.g. the CPFS curve with respect to the OS curve) has a gradient closer to zero than the subsequent (e.g. OS) curve, the probability of death amongst the whole population (OS) is, at that instant, higher than the probability of death OR CNS metastasis (the	The ERG agrees with the company that the approach taken maximises the risk of the events, instead of minimising these. This has been corrected in the ERG report.

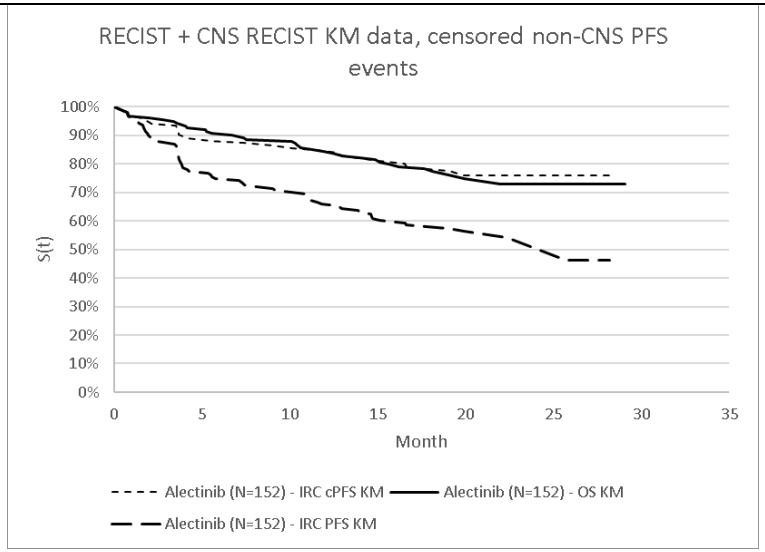
progression events, and therefore the risk of events in the curve should, on average, be higher than the risk of events in the OS curve. Alternatively, the company should have capped the CNS PFS curve by the OS curve when these cross, as the OS curve cannot be below the CNS PFS curve (yielding a negative proportion of patients in the model). The ERG replaced the company's approach by capping the CNS PFS curve by the OS curve."		CPFS curve) within the progressed without CNS progression and progression-free population. This is counterintuitive and clinically implausible.	

Issue 5 Incorrect interpretation of evidence

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Throughout the document CNS PFS and time to CNS progression are used interchangeably, this is incorrect as these are 2 different endpoints. The instances where time to CNS progression is used incorrectly as follows: "time to CNS progression (CNS PFS) " - page 17 "Time to CNS progression (also referred to as CNS PFS)" - page 48 "Time to CNS progression (CNS PFS) " - page 48 "The ERG noted inconsistencies between the analysis of time to CNS progression and PFS in the submitted evidence, and asked the company to clarify how events were counted in each analysis. The company confirmed that time to CNS progression" - page 48	Replace time to CNS progression with "CNS progression-free survival" in all instances barring the one on page 65 where IRC CNS PFS needs replacing with IRC time to CNS progression Amend the description of CNS RECIST, as the RECIST criteria were being considered on a different scan specifically of the brain by a separate IRC made up of experts in intracranial lesions. Recommended wording: "The company confirmed that CNS progression-free survival had been represented erroneously as a function of PFS in the CNS, because CNS progression could be captured by either one of two procedures in ALEX: one IRC assessment for systemic progression for the main PFS outcome (based on RECIST v 1.1), and a separate IRC assessment, by a separate IRC made up of specialists in	CNS progression free survival and time to CNS progression are two different endpoints (the former classes death as an event and does not censor for non CNS progressions, the latter as reported in the original submission comes from the competing risk analysis reported in the CSR). Description of the two assessments within the report is currently unclear. The report is currently unclear as it does not differentiate between the time to CNS progression secondary endpoint reported in the ALEX study CSR, page 93, and the endpoint used in the model following clarification questions	The ERG has amended the pages to better differentiate time to CNS progression and CNS PFS. The difference between the analyses is described fully throughout the rest of the report.

"Time to CNS progression (CNS PFS)" - page 59 "IRC CNS PFS, which was not listed in the NICE final scope,1 was originally analysed with the log-rank test including death and non-CNS progression as competing risks, to compare time to CNS progression only in patients who had not experienced prior non-CNS progression or died." - page 65; here the mistake is referring to time to CNS progression as IRC CNS PFS "time to CNS progression (CNS PFS)" - Page 87 "time to CNS progression (CNS PFS) " - page 167	intracranial CNS lesions, based on the results of scans specifically of the brain (also based on RECIST v 1.1)."		
Page 26, 31, 111, 158: “The ERG does not see a reason why the risk of events in the CNS PFS curve should not be higher than the risk of events in the OS curve. In fact, the CNS PFS curve includes death and progression events, and therefore the risk of events in the curve should, on average, be higher than the risk of events in the OS curve.”	This statement should be retracted, and this scenario should be removed from the model	This is a contradictory and incorrect statement. The risk of events in the model is maximised between the OS and CPFS curve, not minimised (i.e. the "risk of surviving" is minimised). Secondly, if the CNS PFS curve includes death and progression events, its hazard at any point in time should therefore be the same or higher than that of the OS curve. Simply capping the CPFS curve by the OS curve allows the instantaneous hazard in the CPFS curve (or rather in the context of this model, the 1-cycle risk of death OR CNS progression) to fall below that of the OS curve (the 1-cycle risk of just death). This is not clinically plausible. In the correction, hazards are allowed to cross at an early point in the model (approximately month 40), creating	The ERG removed the statement from the report, as requested by the company. The ERG removed the scenario analysis, as requested by the company.

		survival curves which are clinically implausible from that point onwards. Further, in interaction with the correction on the modelled incidence of non-death CNS progression, this correction allows negative incidence of CNS progression, which is impossible.	
Page 66, Page 110: "The ERG is equally concerned with the company's statement which reports that when primary non-CNS events were censored in the CNS PFS curve, that lead to the OS and the CNS curves crossing. The ERG is unclear if the company means the KM curves from ALEX or the extrapolated curves used in the economic analysis. If the former is true, that is extremely worrying, as OS and CNS PFS KM curves should never cross if the data are robustly estimated. If the company means the latter, then the ERG does not consider this to be a valid justification for not censoring secondary events, as OS and CNS PFS estimated curves still cross in the company's model (this is further discussed in Section 5.4.5.2.2)"	Retract statement	The KM's crossed because non-CNS events were censored, as can occur due to the effect of censoring rules. This is because non-CNS progressed patients have different levels of mortality than CNS progressed patients, so censoring pushes the CPFS curve up above the OS curve. When these events are not censored, the curves can no longer cross because CNS progress after death is impossible.  	The explanation provided in this proforma was not available in the clarification responses, so this is not a factual inaccuracy.
Page 68, Page 79, Page 93: "Further uncertainty was	The statement regarding lack of understanding should be retracted, given a clear		As above, this is not a factual inaccuracy given the

introduced because neither CNS PFS analysis (RECIST+CNS RECIST and RECIST-only) censored patients who experienced non-CNS PD (i.e. PD not involving the CNS), meaning some CNS events in the analysis were secondary to systemic PD. The company justified this approach because censoring non-CNS PD caused the curves to cross the OS curve. The ERG does not understand why this would be the case (see Section 5.4.5.2) and considers the inclusion of secondary CNS progression a potential confounding factor in the CNS PFS analyses, particularly because, "after the first progression event, further progression events have not been systematically captured"" Table 9	explanation is available	 As reported in the answer to clarification question A9, "A total of 11 patients (5 in alectinib, 6 in crizotinib) had a CNS progression after having a systemic progression by IRC." These patients had mortality such that when their non-CNS events were censored, the CPFS curve of the whole population crosses the OS curve in the alectinib arm. Therefore, non-CNS progression events were not censored to ensure that the CPFS curve did not cross the OS curve.	information that was available at the time, and the fact that secondary progression events were not captured systematically remains an issue to be highlighted.
Page 78: "the ERG understands CNS RECIST to be a more sensitive measure of intracranial lesions that may not meet criteria for PD by RECIST"	"the ERG understands CNS RECIST to be an adaptation on RECIST: whereas RECIST is a more general assessment of investigator-chosen sites, conducted by the investigator or an IRC; CNS-RECIST is a	RECIST and CNS RECIST are assessed using the same critera. The difference between the two is the clinician assessing the scan, and the location of the scan. CNS RECIST refers to RECIST criteria being applied by expert radiologists to a scan of the brain, whilst RECIST refers to RECIST criteria being applied by clinicians to a scan which can have any location in the body.	The ERG has corrected the factual inaccuracy on page 78 from RECIST to RECIST+CNS

	specific intracranial assessment, conducted by a separate panel of radiologists, specifically to explore progression in this one site"	Additionally (page 78): the paragraph incorrectly states adapted PFS was RECIST only.	RECIST
Page 78: "The ERG understands that any given patient could be represented differently in IRC PFS (RECIST) and adapted PFS analysis (RECIST+CNS RECIST) because patients could have more than one 'type' of progression event captured over the course of ALEX. The ERG considered that, if CNS progression was likely to meet CNS RECIST criteria before RECIST criteria, there would be inconsistency between IRC PFS (RECIST) and adapted PFS (RECIST) where both happened during ALEX. There is no inconsistency in scenarios where the first event captured was death or a PD by RECIST, which would be counted as the primary event in the company's and the ERG's preferred option."	"The ERG understands that any given patient could be represented differently in IRC PFS (RECIST) and adapted PFS analysis (RECIST+CNS RECIST) because patients could have more than one 'type' of progression event captured over the course of ALEX. The ERG considered that, if CNS progression *was assessed via CNS RECIST before RECIST*, there would be a difference between IRC PFS (RECIST) and adapted PFS (RECIST+CNS RECIST). There is no *difference between these 2 measures* in scenarios where the first event captured was death or a PD by RECIST, which would be counted as the primary event in the company's and the ERG's preferred option."		The ERG does not consider the wording factually inaccurate.
Page 105: "secondly, in the company's	Retract last sentence	The PFS curve was defined as the first of: non-CNS progression, CNS progression, death. As this includes CNS progression events, when a CNS progression event occurs, both the PFS and	Not a factual error.

statement that patients in the CNS PFS curve (the curve capturing the proportion of patients free from CNS progression) were followed until the first CNS progression, death or follow-up, regardless of whether a non-CNS progression event was observed. This implies that non-CNS progression events were not censored in the CNS PFS KM curve (represented by the beige circle and curve in Figure 15). These same events would, of course, be accounted for in the PFS curve (represented by the yellow circle and curve in Figure 15). What was unclear to the ERG from the company's reply was how CNS events were accounted for in the PFS curve, considering the fact that CNS events did not necessarily include systemic progressions in ALEX, but could equally be accounted as such"		CPFS curves move down. As all the curves are defined as the first of a set of events to take place, censoring is not required in the PFS curve.	
Page 105: "What was unclear to the ERG from the company's reply was how CNS events were accounted for in the PFS curve, considering the fact that CNS events did not necessarily	Retract statement	For the CPFS curve using RECIST + CNS RECIST, the definition of an event was the first of a CNS progression event in either the RECIST or CNS-RECIST measures. The PFS curve was the first of progression, CNS progression or death, from either the RECIST assessed progression or CNS RECIST assessed progression.	Not a factual error.

include systemic progressions in ALEX, but could equally be accounted as such. In order for the company's manipulation of the clinical data to be correct, in particular for the two equations: non-CNS PD = P(CNS PFS) – P(PFS); and CNS PD = P(OS) – P(CNS PFS) to be correct, the ERG had to assume that all RECIST-assessed, first CNS events were also systemic progressions, and therefore captured in the PFS curve. This seems plausible, as the RECIST assessment of progression is used to evaluate systemic progression, rather than localised tumour growth. If the company confirms the ERG's assumption is correct, then subtracting the proportion of patients on the CNS PFS curve from the OS curve (represented by the red circle and curve in Figure 15) will leave the proportion of patients with CNS progression. Equally, if the ERG's assumption is valid, then subtracting the number patients on the PFS curve from the patients on the CNS PFS curve gives the proportion of patients with systemic		Regarding the time to CNS progression analysis: The nature of the competing risks analysis was stated multiple times in the clarification question responses. Firstly, in response to priority question A10. Also, this was stated clearly in in table 1 (in response to question B1), and in addition, discussion of the decision surrounding censoring rules was provided in the answer to B1. Furthermore, this was provided in the original answer to clarification questions, in answer to question A7, where it was clearly stated that "The analysis takes into consideration the possibility that at the time of analysis a patient may have one of the following events (if any – the patient may still be on treatment), and counts only the first one to have occurred".	

progression outside the CNS (i.e. non-CNS disease progression)."			
Page 108: "Also, in the model, it is not clear to the ERG how the CNS RECIST outcomes are "added" to the PFS KM curve"			Not a factual error.

Issue 6 Misrepresentation of evidence

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 27: "It is possible the utility values for overall progressed patients in Roughley et al. 2014 (3) are lower than in ALEX, which would mean that using an unadjusted CNS utility value from Roughley et al. 2014 potentially overestimates the impact of CNS metastases on patients' quality of life."	Retract, or amend as follows: "It is possible the utility values for overall progressed patients in Roughley et al. 2014 are lower *or higher* than in ALEX, which would mean that using an unadjusted CNS utility value from Roughley et al. 2014 potentially overestimates*, or underestimates* the impact of CNS metastases on patients' quality of life."	The direction of bias is equally possible in either direction, and without substantive evidence to suggest bias in either direction, it is without utility to speculate on the influence this would have on the results of this economic evaluation. Furthermore, it is equally plausible that the estimates from Roughley et al are overestimates, which would indicate that the impact of CNS metastasis on patient HRQL is in fact underestimated in the model. It is not for either party to state, without substantiation, whether or to what extent either of these possibilities is true. Further, Roche validated the Roughly figure against a paper by Mulvenna et al 2016 (4), which whilst did not report an average utility, the graphic presented could be interpreted as	Not a factual error.
Page 130: "Given the company's conclusion that the PD state-related utilities identified in the literature are generally lower than the PD state utilities derived from the ALEX trial	Retract paragraph following "it is possible…" as this is speculative and without substantiation		Not a factual error.

(which the company attributed to the availability of TKIs as subsequent therapies in the trial), and because Roughley et al. 2014 did not report the utility associated with progressed patients without brain metastases, it is not possible to assess if the utility values related with general disease progression (without CNS metastases) are comparable in ALEX, and in the paper . It is possible the utility values for overall progressed patients in Roughley et al. 2014 are lower than in ALEX, which would mean that using an unadjusted CNS utility value from Roughley et al. 2014 potentially overestimates the impact of CNS metastases on patients' quality of life. This would, in its turn, lead to an overestimation of the benefit of alectinib, considering its advantageous profile in preventing CNS progression."		generating an even lower utility value for patients with brain metastases	
Page 51: "For PFS and CNS PFS to be internally consistent, both had to include events from the IRC RECIST assessment, or from both the IRC RECIST and IRC CNS RECIST assessment. The ERG's preferred PFS and CNS PFS are	Retract or amend statement to remove comment regarding bias. Example as follows: "For PFS and CNS PFS to be internally consistent, both had to include events from the IRC RECIST assessment, or from both the IRC RECIST and IRC CNS RECIST assessment. The ERG's preferred PFS and CNS PFS are based only on validated RECIST v1.1 because	This statement is not substantiated with evidence and therefore should be retracted or amended.	The ERG has removed the words 'least biased' from the statement of preference.

based only on validated RECIST v1.1 because it is likely to be the least biased and most clinically relevant representation of PD, and the most comparable to how PFS is represented in other NICE technology appraisals."	it is likely to be most clinically relevant representation of PD, and the most comparable to how PFS is represented in other NICE technology appraisals."		
Page 151: "The administration cost applied for IV chemotherapy in the model is the unit cost for administering chemotherapy at the first attendance, for an outpatient attendance. The ERG considered this to be a potential underestimation of chemotherapy treatment, as patients will return for subsequent IV infusions (which are more expensive than initial ones), and might also need hospital admission"	Retract statement and update ERG base case	ERG's interpretation of cost codes is incorrect: subsequent IV infusion (SB15Z) is for delivery of subsequent elements of the same chemotherapy cycle (see description of currency code). Thus, only first IV infusion (SB12Z) should be utilised.	The ERG removed the statement and scenario analysis, as requested by the company.
Page 161: ERG scenario 7 presents only the uncertainty in one direction	The uncertainty surrounding the impact of the HSUV assigned to CNS progression should be presented fairly by also showing the potential for the ICER to be overestimated as well as underestimated	The diagram presented only reports the impact of the HSUV used for CNS progression being an overestimate. For reasons discussed above, there is no justification for implying the bias in in either direction. As such, the impact in both directions should be presented equally.	Not a factual error.

Issue 7 Representation of inappropriate analyses

Description of problem	Description of proposed amendment	Justification for amendment	ERG response

Page 23: "Subgroup analyses suggest [redacted] for those who received subsequent TKIs than those who did not, but conclusions about between-group differences are limited [redacted]"	"Subgroup analyses suggest [redacted].	Unable to draw any conclusions from a non-randomised analysis. Inappropriate given the level of bias.	Not a factual error.
Page 48: "The ERG requested various data about subsequent therapies from the company at the clarification stage because type of therapy received has been shown to have an important effect on overall survival (OS) in this population"	Retract statement		Not a factual error. The statement refers to the ALK+ advanced NSCLC population and does not specifically to the population of ALEX.
Page 84: "The KM plots provided by the company (Figures 3 and 4 of the company's clarification response; [redacted]	"The KM plots provided by the company (Figures 3 and 4 of the company's clarification response; [redacted]		As above.

[redacted]			
Page 93-94: "Subgroup analyses [redacted]	"Subgroup analyses [redacted]		As above.

Issue 8 Error in ERG assumptions for subsequent therapies after alectinib as per ALEX

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 29-30: "In order to estimate the proportion of patients receiving a TKI after alectinib, the ERG assumed the following: a) 64% of patients receive a TKI after alectinib. This estimate assumes that all the 97 alectinib patients with missing data on subsequent treatments in ALEX received a TKI. To these 97 patients add the 13 patients for whom there are data, and are known to have received a	Amend utilising the correct figures as per ALEX	Part a) 68 patients in total had discontinued alectinib at data cut off. Of this, data was available for 31 patients. After accounting for the 2 patients who discontinued due to death, 35 patients had missing data. It's unclear where the how the ERG have resulted in a figure of 110 patients on subsequent TKIs for alectinib, or the 97 patients with missing data. Point b) This figure relates to usage of Yip et al audit data, thus requires amendment (see	a)The ERG agrees with the company that the number of patients with missing data is not correct. This was corrected in the ERG analysis by taking the 35 patients with missing data and re-estimating the proportion of patients receiving a

subsequent TKI b) 31.4% of patients get a TKI after alectinib; c) Taking the minimum known value from ALEX, which is based on the 13 alectinib patients receiving a second-line TKI (Table A). This amounts to 19.1% (13 divided by 152) of patients receiving a post-alectinib TKI. “		Issue 2) Point c) The ERG again is failing to account for patients who die whilst on 1st line treatment: For 6 patients in the crizotinib arm and 2 patients in the alectinib arm 'Death' was the reason for treatment discontinuation.	TKI in this scenario. This assumes that all the 35 alectinib patients with missing data on subsequent treatments in ALEX received a TKI. To these 35 patients add the 13 patients for whom there are data, and are known to have received a subsequent TKI. This amounts to 48 patients receiving TKI after alectinib out of 68 (71% instead of 64% in the ERG’s original analysis). b) Not a factual error. b) Not a factual error. The ERG is taking the 13 patients reported as having received subsequent TKI treatment in ALEX
Page 137: “In order to estimate the proportion of patients receiving a TKI after alectinib, the ERG assumed the following: 1. For scenario 1 described above, it was assumed that 64% of patients receive a TKI after alectinib. This estimate assumes that all the 97 alectinib patients with missing data on subsequent treatments in ALEX received a TKI. To these 97 patients add the 13 patients for whom there are data, and are known to have received a subsequent TKI (Table 14); 2. For scenario 2, it was assumed that 31.4% of patients get a TKI after alectinib; 3. For scenario 3, the ERG took the minimum know value from ALEX, which is based on the 13 alectinib patients			

receiving a second-line TKI (Table 14). This amounts to 19.1% (13 divided by 152) of patients receiving a post-alectinib TKI."			after alectinib (Table 3 in company's clarification response). The ERG found a typo in ERG report, and where it reads "*This amounts to 19.1% (13 divided by 152)*" it should read "*This amounts to 19.1% (13 divided by 68)"*. The ERG has corrected this in the report.

Issue 9 Alectinib and Crizotinib pack purchase timings

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 30: "A full pack of crizotinib provides patients with 30 days of treatments, whereas a pack of alectinib provides 28 days of treatment. As the full-pack cost and administration cost are applied up-front, every 4 cycles (i.e. every 4 weeks or 28 days), two days of crizotinib treatment are wasted in each 4-weekly administration cycle. Therefore, to address this issue, the ERG amended the cost of crizotinib in	Retract statement	Whilst a full pack of crizotinib does provide patients with 30 days treatment, versus 28 days with alectinib, in the UK, lung cancer clinics are held on an exact day during the week, meaning packs are prescribed every 4 weeks, exactly. Thus, two days of crizotinib treatment is wasted in each 4-weekly administration, as has been modelled.	Not a factual error.

the model so one full-pack is purchased every 30 days as opposed to every 28 days."			
Page 149: "A full pack of crizotinib provides patients with 30 days of treatments, whereas a pack of alectinib provides 28 days of treatment. As the full-pack cost and administration cost are applied up-front, every 4 cycles (i.e. every 4 weeks or 28 days), two days of crizotinib treatment are wasted in each 4-weekly administration cycle."			Not a factual error.
Page 161: "The ERG disagrees with the estimation of the cost of crizotinib in the model. A full pack of crizotinib provides patients with 30 days of treatments, whereas a pack of alectinib provides 28 days of treatment. As the full-pack cost and administration cost are applied up-front, every 4 cycles (i.e. every 4 weeks or 28 days), two days of crizotinib treatment are wasted in each 4-weekly administration cycle. Therefore, to address this issue, the ERG amended the cost of crizotinib in the model so one full-pack is purchased every 30 days as opposed to every 28 days"			Not a factual error.

Issue 10 Descriptive errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 19: "Instances of pneumonitis, pulmonary embolism and pyrexia were recorded in both groups"	"Instances of pulmonary embolism and pyrexia were recorded in both groups"	No instances of pneumonitis in the alectinib group.	Not a factual error. CS Table 11 and text on pg 40 state that 2 people in the alectinib group (1%) had pneumonitis as an SAE.
Page 88: "instances of pneumonitis, pulmonary embolism and pyrexia were recorded in both groups"			
Page 48 "Alectinib (Alecensa®, Roche Registration Ltd) is a small molecule tyrosine kinase inhibitor (TKI) which targets both ALK and RET (rearranged during transfection) tyrosine kinase receptors to inhibit tumour cell growth and proliferation"	"Alectinib (Alecensa®, Roche Registration Ltd) is a small molecule tyrosine kinase inhibitor (TKI) which targets both ALK and RET (rearranged during *translocation*) tyrosine kinase receptors to inhibit tumour cell growth and proliferation"	Descriptive error	Not a factual error. The ERG noted that RET was not defined by the company in the CS but can only find RET defined as 'rearranged during transfection' in the literature.
Page 48 "The Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion in October 2017 recommending an extension to the MA to include adults with untreated ALK+ advanced NSCLC based on evidence from ALEX, and the	""The Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion in October 2017 recommending an extension to the MA to include adults with untreated ALK+ advanced NSCLC based on evidence from ALEX, and the updated MA and EPAR was released in *December 2017*"	Marketing authorisation received in December 2017.	The ERG has amended the wording to reflect that the MA was received in December 2017.

updated MA and EPAR was released in January 2018"			
Page 55: "Also within the seven alectinib studies was an RCT of alectinib (600 mg twice daily) versus crizotinib (250 mg twice daily), which the ERG considers outside the NICE final scope1 because it recruited a population who had received prior treatment with crizotinib and platinum-based chemotherapy (ALUR)"	"Also within the seven alectinib studies was an RCT of alectinib (600 mg twice daily) versus *CT (pemetrexed 500mg/m2 q3w or docetaxel 75mg/m2 q3w)*, which the ERG considers outside the NICE final scope because it recruited a population who had received prior treatment with crizotinib and platinum-based chemotherapy (ALUR).	Wrong comparator arm detailed for ALUR	The ERG has corrected this inaccuracy.
Page 63: "The CNS progression data presented in the CS could not be interpreted as a subset of PD as was initially done in the company's economic model, because CNS progression could be assigned by one of two separate IRC processes (RECIST or CNS RECIST); this issue was flagged by the ERG during the clarification process and an adapted model was submitted by the company based on alternative data for CNS PFS and PFS"	"The CNS progression data presented in the CS could not be interpreted as a subset of PD as was initially done in the company's economic model, because CNS progression could be assigned by one of two separate IRC processes (RECIST or CNS RECIST); this issue was flagged *to* the ERG during the clarification process and an adapted model was submitted by the company based on alternative data for CNS PFS and PFS"	ERG did not identify this error: Roche did.	Not a factual error.
Page 76: "The ERG assumes that CNS progressions that met RECIST	Amend calculation to correct value, and mark as AIC	The number of failures in the CPFS curves for RECIST only were [redacted] for alectinib and crizotinib, respectively. The values therefore	The ERG thanks the company for highlighting a typo

criteria represent a patient's systemic PD, and would have been counted in the PFS analysis. It follows that the number of events in the RECIST+CNS RECIST curve ([redacted] alectinib and [redacted] crizotinib) minus the number of events in the RECIST-only curve ([redacted] alectinib and [redacted] crizotinib), should leave the number of events that met CNS RECIST criteria but not RECIST criteria (both curves include primary deaths and secondary CNS events, see below). The numbers from this calculation are [redacted] for alectinib and crizotinib, respectively, which correspond closely to the number of patients in each group recorded as having a CNS progression before systemic PD by IRC RECIST ([redacted] patients in the alectinib and crizotinib groups, respectively; company response to CQ A9a)."		actually correspond exactly. See Issue 15 regarding ACIC marking.	([redacted] alectinib events should have been [redacted]), but the issue remains that this leaves [redacted] and [redacted] events rather than [redacted] and [redacted].
Page 28: "Therefore, in the interest of consistency with the approach taken for the PFS data, the ERG requested that the company used the KM OS curve for the initial period of the model, where the fit of the exponential curve to the KM	Retract statement	This is a misrepresentation: The KM+exponential was provided as a plausible scenario analysis in our initial submission, as well as the updated analysis.	Not a factual error. Roche's reply to ERG's clarification question B6 c states that: "*Roche originally did not fit a parametric tail to the OS KM curve*

data was not very good."			*for both alectinib and crizotinib […].A scenario accounting for this will be added to the updated economic model when provided (extension requested until COB 15h December*".
Page 126: "the ERG requested that the company used the KM OS curve for the initial period of the model, where the fit of the exponential curve to the KM data was not very good. The company incorporated this scenario in their updated model"	"*the company provided the KM+exponential curve as a scenario analysis in both the initial and updated models*"		As above.
Page 133: "Nonetheless, the ERG is concerned with the low compliance rates seen for both treatment arms (62% for alectinib and 52% for crizotinib patients)."	"Nonetheless, the ERG is concerned with the low compliance rates seen for both treatment arms (*67*% for alectinib and *64*% for crizotinib patients)."	Compliance rates wrong: see section B.2.6 of company submission.	Not a factual error, as per Roche's reply to ERG's clarification question B17 d:
Page 139: "Following this, all chemotherapies were assumed to incur the same time on treatment as docetaxel and all other TKIs were assumed to have the same	"Following this, all chemotherapies were assumed to incur the same time on treatment as docetaxel, *crizotinib treatment duration was derived from PROFILE 1007*, and all other TKIs were assumed to have the same treatment length as *ceritinib*.	Other TKIs beyond crizotinib were assumed to have the same treatment duration as ceritinib, not crizotinib.	The ERG thanks the company for highlighting this discrepancy. The text has been amended as

treatment length as crizotinib.”			suggested. Please note that the source of confusion relates to Roche’s reply to the ERG’s clarification question B28: *“Time on treatment was assumed to be in line with the below table, which also provides sources from which the information was taken. All chemotherapies were assumed to have the same time on treatment as docetaxel, all other TKIs were assumed to have the same time on treatment as crizotinib.”*
Page 162-163: Table 55 and 56 All instances of “all changes” are inconsistently defined Lack of clarity regarding what 5a, 5b, 5c, 6a, 6b, 6c stand for within the report.	Clearly state the set of assumptions for each scenario and what is meant by "all changes", the definition of which should be consistent for the scenarios presented	It is not clear what is meant by "all changes", and this definition is different depending on the scenario. In some instances, (Scenario 2, see issue 3), ‘all changes’ appears to refer to only adding capping of CNS curve by OS curve to the scenario, which as previously discussed in issue 3, is not clinically valid and causes negative incidence of CNS progression in the	Not a factual error. ‘All changes’ refers to all changes incorporated in order of reporting in the table. Thus, “ICER with all changes incorporated” in row

		model. However, making the same change when looking at later scenarios does not result in ICERs matching those reported in the scenario analysis table. For instance, implementing scenario 5a+6a by changing named ranges "subs_higher" and "costs_higher" to "yes", "Utility_Option" to "2nd & 3rd line PPS utility" and finally setting both "capCNS" and "newprog" to "yes" results in an ICER of £124,347, which is very different to the £140,467 reported by the ERG. An ICER of £141,973 can be generated by also changing the OS extrapolations to KM + exponential, named range "freq_oncol" to "yes", named range "steroids" to "yes". This is the closest we have been able to get to the definition of "all changes" for scenario 5a + 6a, which is clearly a different definition to that of scenario 2. Finally, it is not clear to the reader, or easy to interpret what 5a, 5b, 5c, 6a, 6b, 6c stand for unless inspecting the model.	2 refers to the ICER incorporating the changes described in row 1 and row 2. The "ICER with all changes incorporated" in row 3 refers to the ICER incorporating all the changes described up to row 3, and so on. Nonetheless, all the results in Table 55 and Table 56 have been updated as a consequence of the changes made to the ERG's analysis in response to this document.
Page 163-164 Table 56: Scenario 1 is incorrect Scenarios 5-7 are not consistently reported with and without PAS	Update with correct figures	Scenario 1: The ICER is incorrectly reported. The results of the scenario analyses were repeated. The result of this replication when not applying the proposed PAS discount on alectinib is identical to the one reported in table 55. Yet, this is not the case when the PAS is applied (ICER generated by Roche: [redacted]).	The ERG needs more details in order to be able to investigate the discrepancy identified by the company. When the ERG replaced the cost of alectinib's pack of £5,032 by [redacted], in cell J13,

		Scenarios 5-7: Results not provided with the proposed alectinib PAS. The results should be consistently presented, so that all of the scenarios presented without the proposed alectinib PAS discount are also presented with it. All of the scenario analyses should be repeated and updated results provided.	tab “Cost Inputs” of the company’s model, the resulting ICER obtained is [redacted] (as reported in Table 56 of the ERG report). Not a factual error.

Issue 11 Lack of clarity

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Regarding secondary CNS events: Page 22: "The ERG could not verify the methods of analysis for CNS PFS fully. PD not involving the CNS was not censored for CNS PFS and so the analysis includes patients experiencing secondary CNS progression"	A clear definition of the meaning of a secondary CNS event should be stated early on in the report	The definition of "secondary CNS events" is not clear. It should be made clear throughout the report that the definition of this is with reference to a CNS event which occurs following a non-CNS event, and not, as would naturally be interpreted, a second CNS event	The ERG agrees that this is important and has added a definition on page 22.
Regarding secondary CNS events: Page 106: "With regards to the modelling of secondary CNS events, even though these are not explicitly modelled, the ERG does not anticipate this creates a problem because a CNS progression always "trumps" a systemic disease progression captured in the PFS curve (see Figure 15) in the model. Therefore, all costs and QALYs are appropriately captured. When these patients experience their first event (a non-CNS progression) they begin to accrue disease progression costs and a lower utility value. However, when the same patients experience a secondary CNS event (because these transitions are not explicitly modelled), they will be captured in the model as a new CNS progression"			Not a factual error.
Regarding ERG preferred ICERs:	Clarify the language explaining that	It is not clear from the language whether	Not a factual error.

Page 33: "The ERG produced three different ICERs, ranging from £129,195 to £140,467, per QALY gained"	these are the ERG preferred ICERs	the three ICERs provided are scenario analyses designed to explore the structural uncertainty surrounding the ERG corrected base-case ICER of £75,079, or what the final ICER selected to represent their most preferred set of assumptions is.	
Regarding treatment beyond progression: Page 23: "Similar to alectinib, patients could receive treatment with crizotinib beyond progression at the investigator's discretion in ALEX, although TTD and PFS curves were very close, in both treatment arms. The ERG is concerned with the implications of the latter for crizotinib in clinical practice. If crizotinib was given for a shorter period of time in ALEX than it would in clinical practice, there might be a negative bias in the observed outcomes from ALEX against crizotinib . Without knowing how alectinib would be prescribed in clinical practice, it is difficult to anticipate the extent, direction, or even existence of a bias in terms of relative effectiveness. However, if alectinib is given according to the marketing authorisation, then it could be argued that ALEX is a fair representation of time on treatment for alectinib but potentially underestimates the time on treatment with crizotinib, compared with clinical practice"	Paragraph amended/clarified	This statement is unclear. In the first sentence it is stated that treatment beyond progression was allowed in both arms, however, later in the paragraph it is stated that alectinib is dosed in line with the marketing authorisation i.e. no treatment beyond progression; this is incorrect.	Not a factual inaccuracy. The later part of the paragraph is referring to how alectinib might be given in clinical practice, not in ALEX.

Issue 12 Incorrect statements regarding what has been provided by Roche

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 23: "HRQoL was difficult to assess systematically because numerical or graphical summary data were not provided, and data have not yet been published from ALEX."	Retract statement	Compliance figures are provided in B.2.6 of the original submission document B. Baseline characteristics of utility analysis were provided in answer to clarification question B20, and additional characteristic information was provided in answer to clarification question B17.	Not a factual error.
Page 49: "The company did not discuss how frequently this occurred or whether it was more common in one group than the other"	Retract statement	This was provided in response to clarification question A8: In this circumstance, 40 crizotinib patients were deemed to have an isolated asymptomatic CNS progression, of which 30 continued to receive crizotinib treatment, as opposed to 5 alectinib patients who were deemed to have an isolated asymptomatic CNS progression, all of whom continued treatment.	The ERG thanks the company for highlighting this and have amended the wording on both pages.
Page 62: "Information was not provided in the CS to assess how frequently patients were treated beyond asymptomatic CNS progression"			
Page 51: "Response outcomes in the CS, all according to RECIST v1. criteria, were objective response rate (ORR; total patients with either complete or partial response), complete response (CR), partial response (PR), rates of stable disease (SD) and PD, and duration of response (DOR). Results in the CS were by INV-assessment and the clinical study	"Response outcomes in the CS, all according to RECIST v1. criteria, were objective response rate (ORR; total patients with either complete or partial response), complete response (CR), partial response (PR), rates of stable disease (SD) and PD, and duration of response (DOR)."	Results of CNS ORR by IRC were also provided in CS (see appendix E).	Not a factual error.

report (CSR)35 included results by IRC.”			
Page 67-68: “The company did not provide sufficient detail about events that could occur in a sequence for individual patients, and how often this happened – e.g. CNS progression by CNS RECIST preceding PD with CNS involvement by RECIST – for the ERG to confirm that events had been counted or censored appropriately in each analysis to avoid double counting”	Retract statement	As reported in the answer to clarification question A9, "A total of 11 patients (5 in alectinib, 6 in crizotinib) had a CNS progression after having a systemic progression by IRC." The censoring rules used for CPFS and rationale for these were also clearly reported in response to question B1.	Not a factual error.
Page 99: “The company did not provide the PSA results for the RECIST analysis (only for the RECIST+CNS RECIST analysis).”	Retract statement	Roche provided a fully functioning economic model to allow the ERG to run the PSA on this if required.	Not a factual error.
Page 103: “Overall, the ERG agrees with the independent fit approach taken by the company as the assessment of the PH assumption undertook by the company shows that PHs do not hold for OS or PFS data. Nonetheless, the company did not assess the PH assumption for the CNS PFS (RECIST-assessed)	Retract last sentence	The results of this test are clear from the intersection of the KM data for CPFS, in either the RECIST+CNS RECIST, or RECIST only event definitions for the CPFS curve. When KMs intersect, the proportional hazards assumption is by definition violated.	Not a factual error.

data."			
Page 107: "Nonetheless, the company did not assess the PH assumption for the CNS PFS (RECIST-assessed) data."	Retract statement	Log cumulative hazard plot provided by Roche: Figure 12 of the answer to B1 demonstrates PH is not met	Not a factual error.
Page 131: "Therefore, the company concluded that literature should be sought to appropriately capture quality of life for these patients and used the Roughley et al. 2014 paper which measured HRQoL using the EQ-5D in 498 patients in France and Germany with NSCLC in one metastatic site, either brain, contralateral lung, adrenal gland, bone or liver. Roughley et al. 2014 estimated utility values for each metastatic site, including a value of 0.52 for brain metastases, which the company applied to all patients entering the CNS-progressed disease state in the economic model"	"Therefore, the company concluded that literature should be sought to appropriately capture quality of life for these patients and used the Roughley et al. 2014 paper which measured HRQoL using the EQ-5D in 498 patients in France and Germany with NSCLC in one metastatic site, either brain, contralateral lung, adrenal gland, bone or liver. Roughley et al. 2014 estimated utility values for each metastatic site, including a value of 0.52 for brain metastases, which the company applied to all patients entering the CNS-progressed disease state in the economic model. *This value was validated against a paper by Mulvenna et al 2016, which whilst did not report an average utility, the graphic presented could be interpreted as generating an even lower utility value for patients with brain metastases*"	ERG excluding a key validation of the data Roche conducted	Not a factual error.
Page 136: "The company did not run a scenario analysis to portray the distribution of patients across subsequent therapies reflecting	"*The ERG did not deem the scenarios run by the company* to portray the distribution of patients across subsequent therapies reflecting clinical practice in the UK *as complete*"	Three scenarios were conducted to reflect UK clinical practice as per the clinical expert feedback received by Roche. This statement is misrepresentative: the ERG only disagrees with the scenarios provided, thus should be	Not a factual error. To the ERG's understanding, the company's QALY analysis of

clinical practice in the UK."		represented this way.	subsequent therapies only included the ALEX data (unlike the cost analysis, which included clinical expert opinion).
Page 150: "The company did not include subsequent therapy administration costs in their cost calculations. The ERG corrected this by applying weekly administration costs (Table 32) to each of the subsequent therapies modelled by the company."	Retract statement	This was provided: See section B.3.5.1.2 in company submission	The ERG has amended the statement to clarify that administration costs were not included in the model but reported in the CS. *"The company did not include subsequent therapy administration costs in the model. The ERG corrected this by applying weekly administration costs (Table 32) to each of the subsequent therapies modelled by the company"*

Issue 13 Description of treatments for CNS metastases, and eligible population

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 31, Page 151:	"Clinical expert opinion sought by the ERG	The following guidance has been issued by	Not a factual error.

"Clinical expert opinion sought by the ERG revealed that there seems to be a consensus on the use of stereotactic radiosurgery (SRS), to treat CNS metastases whenever patients' clinical condition allows it. The issue remains, that only few patients are eligible for SRS as candidates cannot have more than a maximum of two metastatic sites. Therefore, how ineligible patients are managed in UK clinical practice remains unclear."	revealed that there seems to be a consensus on the use of stereotactic radiosurgery (SRS), to treat CNS metastases whenever patients' clinical condition allows it. The issue remains, that only few patients are eligible for SRS as candidates cannot have more than a maximum of *three* metastatic sites. *When more than three brain metastases are diagnosed, WBRT is recommended in patients with RPA class I-II*"	ESMO (5), which is followed closely in UK clinical practice: Brain metastases • Treatment is recommended in RPA class I patients (<65 years old, KI ≥70%, no other extracranial metastases and controlled primary tumour) or class II patients (KI ≥70%, with other extracranial metastases and/or an uncontrolled primary tumour). • In the case of a single metastasis, SRS or resection is the recommended treatment [II, B]. • For two to three metastases, SRS is recommended in patients with RPA class I–II [II, B]. When more than three brain metastases are diagnosed, WBRT is recommended in patients with RPA class I–II [II, B].	
Page 31, Page 151: "While the company suggests that 23% of patients receive SRS and 77% of patients receive WBRT, the ERG's clinical expert agreed on the proportion of patients receiving SRS but considered that the remaining 77% would receive steroids, as opposed to WBRT, given its lack of proven advantage over steroids and its side effects on	Retract statement	There is no evidence or guidance to suggest this is reflective of UK clinical practice. ESMO guidance, which is followed closely in UK clinical practice recommends WBRT, not steroids.	Not a factual error.

patients”			

Issue 14 Incomplete ACIC marking

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 18: “The ORR benefit of alectinib compared with crizotinib was not statistically significant by INV (82.9% vs 75.5%, respectively) and IRC assessments (78.9% vs 72.2%); median DOR was immature but favoured alectinib (not estimable) over crizotinib (11.1 months; HR for alectinib versus crizotinib: 0.36, 95% CI: 0.24 to 0.53).”	No AIC marking required	No AIC marking required	The ERG thanks the company for highlighting the required changes to AIC and CIC, which the ERG has changed in the report.
Page 76, Figure 5			
Page 118, Figure 23			
Page 23: “Subgroup analyses suggest [redacted]”	CIC marking required	Non-randomised analysis that is subject to considerable bias and prone to misinterpretation. Should not be in public domain as not an academically sound analysis	

Page 74-75: "The difference in total number of events (i.e. PD and deaths) between IRC PFS (RECIST; [redacted]) and the adapted IRC PFS (RECIST+CNS RECIST; [redacted]) was [redacted] events, indicating [redacted]." Page 78: "In general, [redacted]" Page 79: "It follows that the number of events in the RECIST+CNS RECIST curve ([redacted] minus the number of events in the RECIST-only curve [redacted], should leave the number of events that met CNS RECIST criteria but not RECIST criteria (both curves include primary deaths and secondary CNS events, see below). The numbers	AIC marking required	Reanalysis of data specifically for NICE. Output is inconsistent with the ALEX data that has formed the basis of the marketing authorisation, and has previously been published. Therefore the UK-specific analysis should not be published for risk of impact on appraisals globally.	

from this calculation are [redacted] to the number of patients in each group recorded as having a CNS progression before systemic PD by IRC RECIST (4 and 24 patients in the alectinib and crizotinib groups, respectively; company response to CQ A9a)."			
Page 110-113: Figure 15, Figure 16, Figure 17, Figure 18			
Page 114: "Therefore, the company used the number of CNS events captured by the RECIST+CNS RECIST analysis ([redacted]) and the number of deaths as first events ([redacted] as per Table 4 in company's reply to clarification question B1) and estimated that for crizotinib, [redacted]% of transitions out of the CNS PFS curve were not deaths ([redacted]) and for alectinib, [redacted]% of transitions out of the CNS PFS curve were not deaths ([redacted]). The ERG found a discrepancy			

between the company's analysis and the results reported in the company's reply to clarification question B1, as the number of CNS events in the crizotinib arm were [redacted] and not [redacted]"			
Page : 115-117 Figure 19, Figure 20, Figure 21, Figure 22			
Page 22: "Six- and 12-month landmark analyses suggest [redacted]"	AIC marking required	Embargo pending publication	
Page 85: "The analyses provide some indication that [redacted], as the company outline, patient numbers are too small to assess any differential impact reliably between arms (response to CQ A6)."			

Issue 15 Clarification of analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 111, Page 173: "In conclusion, the ERG remains unclear on the validity of the incorporation of clinical data into the economic model. It is vital that the company validates/clarifies the following issues: 1. All RECIST-assessed primary CNS events were simultaneously systemic progressions; 2. How were secondary CNS events captured in the CNS PFS KM curves (i.e. systematically or not systematically); 3. How can OS and CNS PFS curves (and whether these are KM or extrapolated curves) cross when primary non-CNS events were censored from the CNS PFS curves."	On each of the points: 1. Clarification is provided - revision optional 2. The wording needs revising to clarify that 2 CNS events cannot be captured, clarification is also provided (also see Issue 11) 3. Clarification is provided - revision optional	1. In the PFS curve, the event definition was the first of non-CNS progression, CNS progression and death. Therefore, all RECIST-assessed primary CNS events were events in the PFS curve 2. This needs rewording as it implies that 2 CNS events can be captured (they cannot); see information provided in Issue 5 (Incorrect interpretation of evidence) for information on how non CNS progressions and handled and on how data on second progressions were captured within the clinical trial. 3. CPFS crosses OS in this case because primary non-CNS progression events were censored in the CPFS curve. When these are not censored in the PFS curve, the CPFS curve cannot possibly cross the OS curve, since CPFS events cannot occur post-mortem	The ERG thanks the company for clarifying point 1 and 3. Regarding point 2, the ERG refers to secondary CNS events as CNS events which took place after a non-CNS event. The need for clarification from the company remains, as in their reply to clarification question A9, the company states that, "*after the first progression event, further progression events have not been systematically captured*". In an apparently contradictory

			statement, the company's reply to question A10 states that, "*any patient who experiences a non-CNS progression prior to CNS-progression is followed until the first of CNS progression or death or loss to follow-up*".

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5. Novello S, Barlesi F, Califano R, Cufer T, Ekman S, Levra MG, et al. Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016;27(suppl 5):v1-v27.

Alectinib for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer [ID925]

ERRATUM

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BMJ Technology Assessment Group

This document contains errata in respect of the ERG report in response to the manufacturer's factual inaccuracy check.

The table below lists the page to be replaced in the original document and the nature of the change:

Page No.	Change
17, 48–49, 59, 64–65, 87, 167	Clarified wording to differentiate CNS PFS and time to CNS progression.
22	Clarified secondary CNS progression as "CNS progression that was secondary to systemic PD"
25, 29, 30, 81, 131, 132 and 146	Wording amended to reflect that the figure of 18% from the crizotinib audit is likely a minimum proportion who receive subsequent therapy.
26	Removed the following text: "The ERG disagrees with the method used by the company to cap the CNS PFS data. Given that the company took the minimum risk each cycle to determine the proportion of patients in the CNS PFS curve, the risk of death (taken from the OS curve) was used from month 20 (approximately) to estimate the CNS PFS curve in the model for alectinib, and from month 50 (approximately) to estimate the CNS PFS curve for crizotinib. Nonetheless, the OS and CNS PFS curves for alectinib do not cross until 42 months. A similar situation is observed for the crizotinib model, where the OS and CNS PFS curves do not cross until 163 months. The ERG does not see a reason why the risk of events in the CNS PFS curve should not be higher than the risk of events in the OS curve. In fact, the CNS PFS curve includes death and progression events, and therefore the of events in the curve should, on average, be higher than the risk of events in the OS curve. Alternatively, the company should have capped the CNS PFS curve by the OS curve when these cross, as the OS curve cannot be below the CNS PFS curve (yielding a negative proportion of patients in the model). The ERG replaced the company's approach by capping the CNS PFS curve by the OS curve."
31	Removed the following text: from bullet point 1 "The ERG estimates the number of newly progressed patients every cycle, instead of relying on a fixed proportion. Therefore, the ERG replaced the company's method (Equation 2) with the following formula: (〖CNS PD〗_(t+1)- 〖CNS PD〗_t)+(〖1-OS〗_(t+1)/〖OS〗_t)*(〖CNS PD〗_t). The ERG disagrees with the method used for the estimation of newly progressed patients in the model as it uses a fixed proportion of CNS events (captured by the CNS RECIST+RECIST measure) throughout the analysis."; Removed the following text from bullet point 2: "The ERG capped the CNS PFS curve by the OS curve. The ERG disagrees with the method used by the company to cap the CNS PFS curve by taking the minimum risk each model cycle for OS, CNS PFS and background survival, to determine the proportion of patients in the CNS PFS curve." Bullet point 3 was renumbered to be bullet point 1.
32	Bullet points were renumbered to account or the changes on page 31; The sentence "Assuming 64% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib" was replaced by "Assuming 71% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib"
33	The sentence "The ERG produced three different ICERs, ranging from £129,195 to £140,467" was replaced by "The ERG produced three different ICERs, ranging from £129,324 to £142,060"; The sentence "When the same proportion of patients is assumed to receive subsequent TKIs, ICER amounts to £132,510, per QALY gained. The three ERG's exploratory ICERs amount to [redacted], [redacted] and [redacted] when the alectinib PAS is applied (Table D)." was replaced by "When the same proportion of patients is assumed to receive subsequent TKIs, ICER amounts to £132,635, per QALY gained. The three ERG's exploratory ICERs amount to [redacted], [redacted] and [redacted] when the alectinib PAS is applied (Table D)."
35,36,37	The results in Table C and in Table D have been updated and scenarios 1 and 2 have been updated according to the changes made in page 31 and page 32.
46	Date of marketing authorisation changed from released in January 2018 to granted in December 2017.
47	"The company did not discuss how frequently this occurred or whether it was more common in one group than the other" changed to "The company indicated that 30/40

	crizotinib patients and 5/5 alectinib patients with isolated asymptomatic CNS progression continued treatment until systemic PD."
49	Removed the words "least biased" from paragraph two.
53	Comparator of ALUR changed from "crizotinib (250 mg twice daily)" to "chemotherapy (pemetrexed or docetaxel)".
60	"Information was not provided in the CS to assess how frequently patients were treated beyond asymptomatic CNS progression, but the ERG compared the curves for time to treatment discontinuation (TTD) with those for PFS, and did not note any large discrepancies for either treatment" changed to "The company indicated that 30/40 crizotinib patients and 5/5 alectinib patients with isolated asymptomatic CNS progression continued treatment until systemic PD, and the ERG did not note any large discrepancies for either treatment when time to treatment discontinuation (TTD) curves were compared with those for PFS."
74	"adapted PFS (RECIST)" changed to "adapted PFS (RECIST+CNS RECIST)"
76	Corrected [redacted] to [redacted].
109/110	The sentence "The company then took the minimum value between the underlying risk in each cycle for the OS, the background survival and the CNS PFS curves, and used it to estimate the proportion of patients in the CNS PFS curve in that cycle." has been replaced with "The company then took the maximum between the risk of dying in each cycle from the OS, the background survival and the CNS PFS curves, and used it to estimate the proportion of patients in the CNS PFS curve in that cycle."
110	The text "The ERG disagrees with the method used by the company to cap the CNS PFS data. Figure 19 shows the underlying risk throughout the economic model timeframe, in the OS curve (estimated with an" has been deleted.
111	The text "exponential distribution […] Section 6" has been deleted. Figure 19 has been deleted.
112	Figure 20 and Figure 21 have been deleted.
113	The ERG removed the text "Therefore, the ERG replaced the company's method (Equation 2) with the formula below. The results are reported in Section 6. (〖CNS PD〗_(t+1)- 〖CNS PD〗_t)+(〖1-OS〗_(t+1)/〖OS〗_t)*(〖CNS PD〗_t)"
133	The sentence "For scenario 1 described above, it was assumed that 64% of patients receive a TKI after alectinib." Has been replaced with "For scenario 1 described above, it was assumed that 71% of patients receive a TKI after alectinib." The sentence "This amounts to 19.1% (13 divided by 152)" has been replaced with "This amounts to 19.1% (13 divided by 68)"
135	"Following this, all chemotherapies were assumed to incur the same time on treatment as docetaxel and all other TKIs were assumed to have the same treatment length as crizotinib." has been changed to "Following this, all chemotherapies were assumed to incur the same time on treatment as docetaxel, crizotinib treatment duration was derived from PROFILE 1007, and all other TKIs were assumed to have the same treatment length as ceritinib."
146	"The company did not include subsequent therapy administration costs in their cost calculations. The ERG corrected this by applying weekly administration costs (Table 32) to each of the subsequent therapies modelled by the company." has been changed to "The company did not include subsequent therapy administration costs in the model. The ERG corrected this by applying weekly administration costs (Table 32) to each of the subsequent therapies modelled by the company"
147	The text on page 147 above the heading "Section 5.4.9.6.2" has been removed from the page. The text "The ERG's alternative analysis for estimating newly progressed patients is explained in Section 5.4.5.2, and the results are reported in Section 6." has been removed.
158	Removed the following text: from bullet point 1 "The ERG estimates the number of newly progressed patients every cycle, instead of relying on a fixed proportion. Therefore, the ERG replaced the company's method (Equation 2) with the following formula: (〖CNS PD〗_(t+1)- 〖CNS PD〗_t)+(〖1-OS〗_(t+1)/〖OS〗_t)*(〖CNS PD〗_t). The ERG disagrees with the method used for the estimation of newly progressed patients in the

	model as it uses a fixed proportion of CNS events (captured by the CNS RECIST+RECIST measure) throughout the analysis."; Removed the following text from bullet point 2: "The ERG capped the CNS PFS curve by the OS curve. The ERG disagrees with the method used by the company to cap the CNS PFS curve by taking the minimum risk each model cycle for OS, CNS PFS and background survival, to determine the proportion of patients in the CNS PFS curve." Bullet point 3 onward were renumbered to take into account the removal of the first two bullet points. The sentence "Assuming 64% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib" was replaced by "Assuming 71% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib"
159	Bullet points were renumbered to account or the changes on page 158;
160, 161	The scenarios portrayed in Table 54 have been updated to reflect the changes made in page 158 and page 159.
162	The sentence "The ERG produced three different ICERs, ranging from £129,195 to £140,467" was replaced by "The ERG produced three different ICERs, ranging from £129,324 to £142,060"; The sentence "When the same proportion of patients is assumed to receive subsequent TKIs, ICER amounts to £132,510, per QALY gained. The three ERG's exploratory ICERs amount to [redacted], [redacted] and [redacted] when the alectinib PAS is applied (Table D)." was replaced by "When the same proportion of patients is assumed to receive subsequent TKIs, ICER amounts to £132,635, per QALY gained. The three ERG's exploratory ICERs amount to [redacted], [redacted] and [redacted] when the alectinib PAS is applied (Table D)."
162 - 165	The results in Table 55 and in Table 56 have been updated according to the changes made in page 158 and page 159..

in line with the NICE final scope. HRQoL in ALEX was measured by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ30) and lung cancer module (EORTC-LC13), and the EuroQol 5 dimensions (EQ-5D-3L). AEs were captured by study physicians who were aware of treatment assignment, according to Common Terminology Criteria for Adverse Events (CTCAE version 4).

The CS included additional outcomes relating to CNS progression that were not listed in the NICE final scope to capture the proposed activity of alectinib in the CNS, which is likely to differentiate it from crizotinib. On the advice of clinical experts, the ERG considered it important to capture this proposed benefit, given the important effects of CNS progression on prognosis and patients' quality of life. The company submitted a CNS PFS endpoint at the clarification stage, including all patients regardless of baseline CNS metastases, when an error was identified with the original time to CNS progression endpoint from ALEX. CNS ORR and DOR were measured in the subset of patients with CNS metastases at baseline (64 and 58 patients in the alectinib and crizotinib groups, respectively).

The company outlined that CNS progression could be picked up via two separate IRC assessments in ALEX: the main RECIST v1.1 to identify systemic PD, and a second modified RECIST assessment defined for the trial to identify intracranial lesions (hereafter referred to as CNS RECIST). The company submitted an adapted PFS outcome at the clarification stage which became their preferred analysis, which counted time to the first event from the main IRC RECIST assessment or the IRC assessment using CNS RECIST. The company's preferred analysis of CNS PFS also counted events from RECIST or CNS RECIST. The ERG considered results from PFS and CNS PFS based on standard RECIST the most clinically relevant, and more comparable to related trials and NICE technology appraisals.

Randomisation in ALEX was carried out centrally and was stratified by Eastern Cooperative Oncology Group performance status (ECOG PS), race and presence of CNS metastases at baseline. Where available, the ERG considers PFS, CNS PFS and ORR assessed by independent review committee (IRC) likely to be less biased than the investigator assessments (INV) because ALEX was an open-label study. HRQoL and safety assessments may also be subject to bias because patients and investigators were aware of treatment assignment.

Median PFS and CNS PFS and associated confidence intervals (CIs) were not reported by the company for analyses based on RECIST+CNS RECIST, but there was a clear benefit of alectinib over crizotinib. The ERG's preferred measure of PFS (IRC RECIST) showed a statistically significant and clinically meaningful benefit of alectinib compared with crizotinib; median PFS 25.7 months for alectinib (95% CI: 19.9 months to not estimable) and 10.4 months for crizotinib (95% CI: 7.7 to 14.6 months). The alectinib benefit was statistically significant across all predefined subgroups (age group, sex, race

category, smoking status, ECOG PS, CNS mets at baseline and prior brain radiation), except those based on very small numbers (active smokers and ECOG PS 2).

ALEX was not powered to detect a statistically significant difference in OS between groups. At the February 2017 data cut-off, median follow-up was 18.6 months in the alectinib group and 17.6 months in the crizotinib group; a similar number of patient in each group had died (35 in the alectinib group and 40 in the crizotinib group; HR 0.76; 95% CI: 0.48 to 1.20; p-value 0.24) and median OS had not been reached in either group. One-year survival rates were similar at 84.3% for alectinib (95% CI: 78.4 to 90.2%) and 82.5% for crizotinib (95% CI: 76.1 to 88.9%). [redacted].

The ORR benefit of alectinib compared with crizotinib was not statistically significant by INV (82.9% vs 75.5%, respectively) and IRC assessments (78.9% vs 72.2%); median DOR was immature but favoured alectinib (not estimable) over crizotinib (11.1 months; HR for alectinib versus crizotinib: 0.36, 95% CI: 0.24 to 0.53).

There was a significant CNS ORR benefit of alectinib compared with crizotinib in patients with measurable CNS lesions at baseline (81.0% vs 50.0, respectively), and in the combined subgroup of patients with measurable or nonmeasurable CNS lesions at baseline (59.4% vs 25.9%, respectively); CNS DOR was longer in the combined subgroup only (HR 0.23; 95% CI 0.10 to 0.53).

Within the HRQoL and patient reported outcomes (PROs), there was no statistically significant difference between groups in the time to confirmed clinically meaningful deterioration on a composite symptom endpoint on the EORTC LC13 or Global Health Status on the EORTC QLQ-C30. Both treatment arms demonstrated clinically meaningful improvement of at least 10 points for multiple lung cancer symptoms (cough, chest pain, pain in other parts, fatigue, and dyspnoea).

Statistically significant differences in PROs favouring alectinib were longer lasting improvement for various symptoms (cough, chest pain, other pain, fatigue), better tolerability for some AEs (diarrhoea, constipation, peripheral neuropathy, nausea/vomiting, appetite loss, and dysphagia), and longer lasting clinically meaningful improvement in HRQoL. In general, numerical or graphical data were not provided to substantiate the differences.

Most patients in both groups reported at least one AE of any cause or grade and the number of patients reporting at least one serious AE, Grade 3–5 AE, fatal AE, or AE leading to treatment discontinuation, were similar. AEs leading to dose reduction and dose interruption were somewhat less frequent in the alectinib group despite longer median treatment duration for alectinib than crizotinib (17.9 vs 10.7, respectively). The rate of treatment-related AEs was higher in the crizotinib group (89%) than the alectinib group (77%), but may be subject to attribution bias because safety assessments were conducted

advanced NSCLC despite the small proportion recruited from UK centres (1%). Baseline characteristics were mostly well balanced between groups, and the treatments were given in line with their marketing authorisations.

Subgroup results were available, or provided at the clarification stage, to assess the impact of key effect moderators outlined by the ERG's clinical experts (ECOG PS, CNS metastases at baseline, and CNS progression during the study, and subsequent therapies).

Economic

The formulae within the economic model are generally sound and the economic model is well constructed. The economic model is based on RCT data, and therefore does not need to rely on indirect comparisons of treatment effectiveness data.

1.4.2 Weaknesses and areas of uncertainty

Clinical

ALEX has not demonstrated that the statistically significant benefits of alectinib over crizotinib for PFS and CNS PFS translate into a difference in OS. Six- and 12-month landmark analyses suggest [redacted], but the number of patients with CNS progression and the immaturity of OS in ALEX mean the between-group difference cannot be assessed reliably.

The company's preferred analyses of PFS and CNS PFS include events from the modified CNS RECIST, which may not reflect how PD would be assessed or managed in UK clinical practice. The company stated that the PFS and CNS PFS analyses based on IRC RECIST+IRC CNS RECIST are, "the most complete and robust analysis of the impact of CNS metastases", but accepted that events captured by CNS RECIST, "may be earlier than would be in clinical practice as CNS RECIST is not routinely used in the NHS" (company clarification response to question A10).

The ERG could not verify the methods of analysis for CNS PFS fully. PD not involving the CNS was not censored for CNS PFS and so the analysis includes patients experiencing CNS progression that was secondary to systemic PD. Variation in the extent of benefit could not be quantified because summary statistics were not available for all analyses. The company did not provide sufficient detail about events that could occur in a sequence, and how often this happened – e.g. CNS progression by CNS RECIST preceding PD with CNS involvement by RECIST – for the ERG to confirm that events had been counted or censored appropriately in each analysis to avoid double counting.

Randomised treatment could be continued beyond isolated asymptomatic CNS progression in ALEX at the investigator's discretion, which the company highlight is not indicated in the marketing

The ERG finds the company's estimates of subsequent therapies in ALEX unlikely to be reflective of clinical practice in the UK as they are based on assumptions rather than on the actual trial data. Furthermore, the ERG disagrees with the company's assumptions made with regards to the proportion of patients receiving subsequent treatments in the UK, included in the company's scenario analysis for costs. The company base case analysis assumed that 29% of alectinib patients receive a subsequent TKI, while 72% of crizotinib patients move on to a subsequent TKI. The company's scenario analysis assumed a subsequent TKI treatment for 60% of alectinib patients, and for 90% of crizotinib patients.

With regards to crizotinib, the England audit data (Yip *et al*, 2017) available suggests that a minimum of 18% of patients who received crizotinib, received a second-line TKI (not accounting for deaths). Nonetheless, the audit results could be an underestimation, because the audit was not limited to first line crizotinib, and as the clinical experts advising the ERG have explained, clinical practice has been rapidly evolving in this setting, with more patients getting access to more treatment options. Nonetheless, this estimate differs greatly from the 72% assumed by the company in their base case analysis. Furthermore, clinical expert opinion provided to the ERG indicates that (although there is no clinical consensus on how to treat progressed patients after alectinib), it would appear plausible that alectinib patients would be fitter than crizotinib patients, and therefore more likely to tolerate subsequent treatment with a TKI. The clinical experts added that, the reason why a relatively low percentage of patients receive a TKI treatment after crizotinib in the UK is related to the development of CNS metastases, which leave the patients too ill to receive a further TKI, and so chemotherapy is the only viable option. As clinical experts anticipate that alectinib will have a protective effect on the CNS compared with crizotinib, it is likely that a higher percentage of alectinib patients receive a subsequent TKI. Again, this is contradictory to the data used by the company, where a considerably higher proportion of patients receives a TKI after crizotinib than after alectinib.

1. Progression with CNS involvement: The ERG has some reservations with regards to CNS data and its incorporation in the economic model. The details of the updated model including the CNS data analysis were described in a short document provided by the company after clarification; therefore, the ERG based its critique on the latter and on inspection of the economic model. The limited information available in the document shed some light on CNS data collection in the trial but is not entirely transparent and so the ERG is still unclear on a few aspects of the company's analysis. The ERG had to make assumptions with regards to the data, which are discussed throughout this report, however, it is important to caveat the ERG's assumptions. If the latter are not correct, then the company's model is flawed as the manipulation of the data in the economic analysis is likely to be incorrect. The ERG remains

unclear on the validity of the incorporation of clinical data into the economic model. It is vital that the company clarifies the following issues:

a) All RECIST-assessed primary CNS events were simultaneously systemic progressions;

b) How were secondary CNS events captured in the CNS PFS KM curves (i.e. systematically or not systematically)?

c) How can OS and CNS PFS curves (and whether these are KM or extrapolated curves) cross when primary non-CNS events were censored from the CNS PFS curves?

The ERG disagrees with the method used for the estimation of newly progressed patients in the model as it uses a fixed proportion of CNS events (captured by the RECIST+CNS RECIST measure) throughout the analysis. A more robust approach would have been to estimate the number of newly progressed patients every cycle, instead of relying on a fixed proportion.

2. Progression-free survival: The ERG generally agrees with the company's approach of selecting the exponential tail to fit the PFS KM data as it provided the most conservative scenario, from a clinical point of view, for alectinib. While for crizotinib, the exponential curve is the second most conservative (with the Weibull curve predicting the lower survival), the ERG considers that choosing different distributions to model PFS across treatment arms is not justified in this case. Furthermore, the combination of using the exponential curve for alectinib and crizotinib, is in itself a conservative approach, as the Weibull curve would have predicted a lower survival for crizotinib. Given that the exponential curve was the worst fitting distribution to the KM PFS

as subsequent therapies in the trial), it is not possible to assess if the utility values related with general disease progression (without CNS metastases) are comparable in ALEX, and in the paper. It is possible the utility values for overall progressed patients in Roughley *et al.* 2014 are lower than in ALEX, which would mean that using an unadjusted CNS utility value from Roughley *et al.* 2014 potentially overestimates the impact of CNS metastases on patients' quality of life. This would, in its turn, lead to an overestimation of the benefit of alectinib, considering its advantageous profile in preventing CNS progression.

The ERG considers that the impact of subsequent therapies on patients' quality of life is a key model driver. As the ERG does not consider the company's estimates of subsequent therapies to be reflective of clinical practice, the ERG ran three scenario analyses to reflect the uncertainty around the changes in clinical practice if alectinib is recommended. These scenarios include the possibility of alectinib patients being more, less, and equally likely than crizotinib patients to receive subsequent treatment with a TKI. All patients not receiving a TKI as subsequent treatment were assumed to receive a non-TKI (i.e. 100% of patients receive subsequent treatment in the ERG's analysis). As clinical experts could not find a consensus on the likely proportion of patients to allocate to these scenarios, the ERG used the ALEX trial data and the England audit data as a form of validation. Given the ERG's concerns that the proportions used by the company (i.e. approximately 70% of crizotinib patients receive a subsequent TKI and 30% of alectinib patients receive a subsequent TKI) are not reflective of clinical practice, the ERG had to make some assumptions with regards to the missing data on the 59% of patients and their subsequent treatments in ALEX. Given the England audit data suggests a minimum of 18% of patients receive a second-line TKI after crizotinib, the ERG assumed that the 31.4% (Table A) known to receive a TKI after crizotinib in ALEX could be a reasonable approximation to the UK clinical practice. In order to estimate the proportion of patients receiving a TKI after alectinib, the ERG assumed the following:

a) 64% of patients receive a TKI after alectinib. This estimate assumes that all the 97 alectinib patients with missing data on subsequent treatments in ALEX received a TKI. To these 97 patients add the 13 patients for whom there are data, and are known to have received a subsequent TKI (Table A);

b) 31.4% of patients get a TKI after alectinib;

c) Taking the minimum known value from ALEX, which is based on the 13 alectinib patients receiving a second-line TKI (Table A). This amounts to 19.1% (13 divided by 152) of patients receiving a post-alectinib TKI.

These analyses are caveated by the fact that CNS impact on patients' quality of life has not been included, and by the fact that the sources for utility values and treatment duration related with subsequent therapies are taken from various literature sources.

Table A. Subsequent therapies captured in ALEX for 41%* of patients who have permanently discontinued study treatment (adapted from clarification response, Table 3)

	Alectinib		Crizotinib	
Treatment	2nd line (n = 68)	3rd line + (n = 68)	2nd line (n = 105)	3rd line + (n = 105)
Any subsequent anti-cancer therapy	31 (45.6%)	9 (13.2%)	40 (38.1%)	4 (3.8%)
Any TKI	13 (19.1%)	5 (7.4%)	33 (31.4%)	3 (2.9%)
Ceritinib	2 (2.9%)	2 (2.9%)	13 (12.4%)	1 (1.0%)
Alectinib	0 (0.0%)	0 (0.0%)	8 (7.6%)	2 (1.9%)
Crizotinib	6 (8.8%)	3 (4.4%)	2 (1.9%)	0 (0.0%)
Other (lorlatinib, brigatinib, gefitinib, entrectinib, erolotinib)	5 (7.4%)	1 (1.5%)	10 (9.5%)	0 (0.0%)
Platinum compound (carboplatin, cisplatin)	16 (23.5%)	3 (4.4%)	6 (5.7%)	0 (0.0%)
Antimetabolite (pemetrexed, gemicitabine)	14 (20.6%)	3 (4.4%)	6 (5.7%)	0 (0.0%)
Taxane (paclitaxel, docetaxel)	3 (4.4%)	0 (0.0%)	0 (0.0%)	1 (1.0%)
Immunostimulant (nivolumab)	0 (0.0%)	2 (2.9%)	0 (0.0%)	0 (0.0%)
Angiogenesis inhibitor (bevacizumab)	2 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other (cyclophosphamide, antineoplastic agent NOS, anti PD-L1, doxorubicin, vincristine)	3 (4.4%)	1 (1.5%)	1 (1%)	0

Abbreviations: NOS, not otherwise specified; PD-L1, programmed death-ligand; TKI, tyrosine kinase inhibitor
*Subsequent therapies are not known for the remaining 59% of patients who have permanently discontinued study treatment.

6. Cost analysis: The ERG considers that the cost estimations in the model are generally sound, but disagrees with the estimation of the cost of crizotinib in the model. A full pack of crizotinib provides patients with 30 days of treatments, whereas a pack of alectinib provides 28 days of treatment. As the full-pack cost and administration cost are applied up-front, every 4 cycles (i.e. every 4 weeks or 28 days), two days of crizotinib treatment are wasted in each 4-weekly administration cycle. Therefore, to address this issue, the ERG amended the cost of crizotinib in the model so one full-pack is purchased every 30 days as opposed to every 28 days.

   The company carried out a scenario analysis assuming a distribution of subsequent therapies in line with current UK practice. The ERG does not consider the estimates used to be reflective of clinical practice in the UK as 90% of crizotinib patients are assumed to receive a subsequent TKI (compared with the minimum of 18% reported in the England audit). Therefore, the ERG ran the three scenarios analyses described in the QALY discussion, to explore the uncertainty around subsequent treatments' costs. To further reflect UK clinical practice, the ERG assumed that the treatments available for subsequent treatment lines consisted on crizotinib and ceritinib (post-alectinib) and ceritinib (post-crizotinib). In order to estimate the distribution of patients allocated to crizotinib or ceritinib post alectinib, the ERG used the data available from ALEX, which shows that 2.9% of alectinib patients received ceritinib and 8.8% of patients received

crizotinib. The ERG reweighted these values, to account for the entire subgroup of patients receiving a TKI post-alectinib. The final proportions used in the ERG's analysis are 25% for ceritinib and 75% for crizotinib.

Clinical expert opinion sought by the ERG revealed that there seems to be a consensus on the use of stereotactic radiosurgery (SRS), to treat CNS metastases whenever patients' clinical condition allows it. The issue remains, that only few patients are eligible for SRS as candidates cannot have more than a maximum of two metastatic sites. Therefore, how ineligible patients are managed in UK clinical practice remains unclear.

Although it seems that there is not a consensus among the clinical community, clinical expert opinion provided to the ERG explained that clinical practice seems to be moving away from WBRT and increasingly using steroids, as supported in the Mulvenna *et al.* 2016 paper. While the company suggests that 23% of patients receive SRS and 77% of patients receive WBRT, the ERG's clinical expert agreed on the proportion of patients receiving SRS but considered that the remaining 77% would receive steroids, as opposed to WBRT, given its lack of proven advantage over steroids and its side effects on patients.

1.3 Summary of exploratory and sensitivity analyses undertaken by the ERG

Economic

The exploratory analyses undertaken by the ERG uses RECIST-based outcomes for PFS and CNS PFS. The analyses consist on the following:

1. The ERG replaced the exponential curves used to estimate OS for alectinib and crizotinib by the KM+exponential tail curves;

2. The ERG's clinical experts advised that the frequency of oncologist visits should be every 4 weeks as opposed to every 5 to 6 weeks. The ERG replaced this in the economic model.

3. The ERG ran three scenario analyses to reflect the uncertainty around the changes in clinical practice if alectinib is recommended. Furthermore, the ERG removed the third line of treatment from the company's analysis as this line of treatment was not incorporated as an option for the cost analysis in the company's model (only second line treatment was included). These scenarios consist on the following:

    a) Assuming 71% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib;

    b) Assuming patients on alectinib are equally likely to receive a subsequent TKI as crizotinib patients (31.4% of patients assumed for both);

    c) Assuming 19.1% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib;

4. The ERG ran the three scenarios analyses described in 3, to estimate the costs of each alternative scenario. To further reflect UK clinical practice, the ERG assumed that the TKI treatments available for subsequent treatment lines consisted on crizotinib (75% of total TKI treatments) and ceritinib (25% of total TKI treatments) (post-alectinib) and ceritinib (post-crizotinib);

5. The ERG conducted exploratory analysis to reflect a scenario where 77% of patients receive steroids rather than WBRT to manage their CNS metastases;

6. Given that CNS-related utility value is one of the key drivers of the economic results, the ERG ran a scenario where the utility associated with CNS progression was varied by a range of values. The base case utility value (0.52) was increased by 1%, 2%, 3%, 4% and 5%.

Results from the ERG analysis are reported in Table B. From a methodological point of view, changing the OS modelling approach from an exponential to a KM+exponential curve has a considerable impact on the company's corrected ICER (£75,079 to £80,146).

The other key model drivers are related to the clinical assumptions incorporated in the economic analysis. The two main drivers are the assumptions related with subsequent therapies in the model, namely the proportion of patients receiving a TKI and a non-TKI after treatment with alectinib or crizotinib. This has implications for the incremental costs, and to a greater extent, for QALY gain related with alectinib. The other key driver of the analysis is the modelling of CNS metastases, in terms of its impact on patients' quality of life (Figure A) and treatment costs.

The ERG reports three exploratory ICERs, reflecting three different scenarios in terms of subsequent therapies received after alectinib (Table C and Table D). The ERG caveats the analyses presented due to the high degree of uncertainty embedded in the ALEX's data regarding patients' subsequent therapies. Related to this, is the estimated survival from ALEX, which as evidence suggests, can be highly dependent on the availability of subsequent treatment with ALK-TKIs.

The assumptions incorporated in the ICERs presented in Table C and Table D include the scenario analyses numbered and described in Table B. The exception is the company's scenario analysis, which assumes that only 23% of patients receive SRS while 77% of patients receive WBRT.

The ERG produced three different ICERs, ranging from £129,324 to £142,060 per QALY gained. The lowest ICER corresponds to the scenario where a lower proportion of alectinib patients (19%) compared with crizotinib patients (31%) receive subsequent TKIs. Conversely, the highest ICER corresponds to the scenario where more alectinib patients (71%) receive subsequent TKIs, compared to crizotinib patients. When the same proportion of patients is assumed to receive subsequent TKIs, ICER amounts to £132,635, per QALY gained. The three ERG's exploratory ICERs amount to [redacted], [redacted] and [redacted] when the alectinib PAS is applied (Table D).

Table B. Results of the ERG's scenario analysis

Analysis from list	Results per patient	Alectinib (1)	Crizotinib (2)	Incremental value (1-2)
0	**Company's corrected base using RECIST outcomes**			
	Total costs (£)	£225,992	£149,354	£76,638
	QALYs	3.82	2.80	1.02
	ICER	**£75,079**		
1	**Replacing the exponential curves used to estimate OS for alectinib and crizotinib by the KM+exponential tail curves**			
	Total costs (£)	£225,841	£149,912	£75,929
	QALYs	3.79	2.84	0.95
	ICER	**£80,146**		
2	**Changing the frequency of oncologist visits to every 4 weeks as opposed to every 5 to 6 weeks**			
	Total costs (£)	£227,309	£150,048	£77,261
	QALYs	3.82	2.80	1.02
	ICER	**£75,689**		
3 a)	**Assuming 71% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib**			
	Total costs (£)	£225,992	£149,354	£76,638
	QALYs	3.83	3.01	0.82
	ICER	**£93,856**		
3 b)	**Assuming 31.4% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib**			

	Total costs (£)	£225,992	£149,354	£76,638
	QALYs	3.78	3.01	0.76
	ICER		**£100,220**	
3 c)	**Assuming 19.1% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib**			
	Total costs (£)	£225,992	£149,354	£76,638
	QALYs	3.76	3.01	0.75
	ICER		**£102,851**	
4 a)	**Assuming 71% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib**			
	Total costs (£)	£241,685	£139,839	£101,846
	QALYs	3.82	2.80	1.02
	ICER		**£99,774**	
4 b)	**Assuming 31.4% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib**			
	Total costs (£)	£228,927	£139,839	£89,088
	QALYs	3.82	2.80	1.02
	ICER		**£87,275**	
4 c)	**Assuming 19.1% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib**			
	Total costs (£)	£224,113	£139,839	£84,274
	QALYs	3.82	2.80	1.02
	ICER		**£82,560**	
5	**Assuming patients receive steroids rather than WBRT to manage their CNS metastases**			
	Total costs (£)	£218,134	£137,108	£81,026
	QALYs	3.82	2.80	1.02
	ICER		**£79,378**	

Abbreviations used in the table: CSR, clinical study report; ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; QALY, quality-adjusted life year; RDI, relative dose intensity; TRAE, treatment-related adverse event.

Figure A. Scenario analysis 6

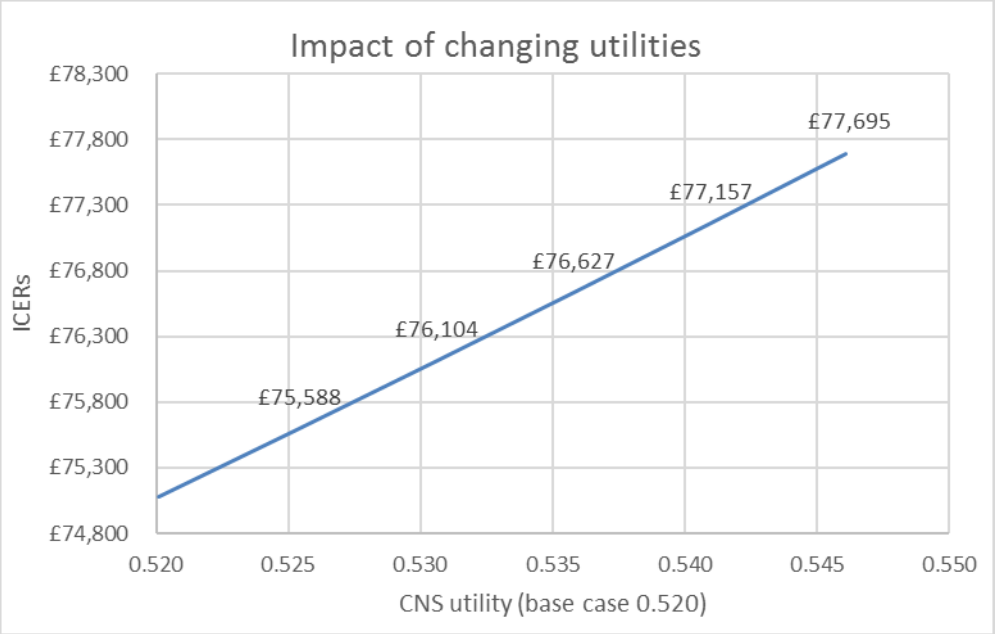


Table C. ERG's alternative base case ICERs

	Results per patient	**Alectinib (1)**	**Crizotinib (2)**	**Incremental value (1-2)**
0	**Company's corrected base using RECIST outcomes**			
	Total costs (£)	£225,992	£149,354	£76,638
	QALYs	3.82	2.80	1.02
	ICER			**£75,079**
1	**Replacing the exponential curves used to estimate OS for alectinib and crizotinib by the KM+exponential tail curves**			
	Total costs (£)	£225,841	£149,912	£75,929
	QALYs	3.79	2.84	0.95
	ICER (compared with base case)			£80,146
	ICER with all changes incorporated			**£80,146**
2	**Changing the frequency of oncologist visits to every 4 weeks as opposed to every 5 to 6 weeks**			
	Total costs (£)	£227,309	£150,048	£77,261
	QALYs	3.82	2.80	1.02
	ICER (compared with base case)			£75,689
	ICER with all changes incorporated			**£80,803**
Company's SA	**Company's scenario analysis assuming that 23% of patients receive SRS and 77% of patients receive WBRT**			
	Total costs (£)	£219,830	£139,751	£80,079
	QALYs	3.82	2.80	1.02
	ICER (compared with base case)			£78,450
	ICER with all changes incorporated			**£84,407**
3a+4a	**Assuming 71% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib**			

	Total costs (£)	£241,685	£139,839	£101,846
	QALYs	3.83	3.01	0.82
	ICER (compared with base case)			£124,727
	ICER with all changes incorporated			**£142,060**
3b+4b	**Assuming 31.4% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib**			
	Total costs (£)	£228,927	£139,839	£89,088
	QALYs	3.78	3.01	0.76
	ICER (compared with base case)			£116,501
	ICER with all changes incorporated			**£132,635**
3c+4c	**Assuming 19.1% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib**			
	Total costs (£)	£224,113	£139,839	£84,274
	QALYs	3.76	3.01	0.75
	ICER (compared with base case)			£113,099
	ICER with all changes incorporated			**£129,324**
	Abbreviation used in table: ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; QALYs, quality-adjusted life years; RDI, relative dose intensity.			

Table D. ERG's alternative base case ICERs with alectinib PAS

	Results per patient	**Alectinib (1)**	**Crizotinib (2)**	**Incremental value (1-2)**
0	**Company's corrected base using RECIST outcomes**			
	Total costs (£)	[redacted]	£145,064	[redacted]
	QALYs	3.82	2.80	1.02
	ICER			[redacted]
1	**Replacing the exponential curves used to estimate OS for alectinib and crizotinib by the KM+exponential tail curves**			
	Total costs (£)	[redacted]	£145,618	[redacted]
	QALYs	3.79	2.84	0.95
	ICER (compared with base case)			[redacted]
	ICER with all changes incorporated			[redacted]
2	**Changing the frequency of oncologist visits to every 4 weeks as opposed to every 5 to 6 weeks**			
	Total costs (£)	[redacted]	£145,758	[redacted]
	QALYs	3.82	2.80	1.02
	ICER (compared with base case)			[redacted]
	ICER with all changes incorporated			[redacted]
Company's SA	**Company's scenario analysis assuming that 23% of patients receive SRS and 77% of patients receive WBRT**			
	Total costs (£)	[redacted]	£135,461	[redacted]
	QALYs	3.82	2.80	1.02
	ICER (compared with base case)			[redacted]

	ICER with all changes incorporated			[redacted]
3a+4a	**Assuming 71% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib**			
	Total costs (£)	[redacted]	£139,839	[redacted]
	QALYs	3.83	3.01	0.82
	ICER (compared with base case)			[redacted]
	ICER with all changes incorporated			[redacted]
3b+4b	**Assuming 31.4% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib**			
	Total costs (£)	[redacted]	£139,839	[redacted]
	QALYs	3.78	3.01	0.76
	ICER (compared with base case)			[redacted]
	ICER with all changes incorporated			[redacted]
3c+4c	**Assuming 19.1% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib**			
	Total costs (£)	[redacted]	£139,839	[redacted]
	QALYs	3.76	3.01	0.75
	ICER (compared with base case)			[redacted]
	ICER with all changes incorporated			[redacted]
	Abbreviation used in table: ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; QALYs, quality-adjusted life years; RDI, relative dose intensity.			

the high proportion of patients with Eastern Cooperative Oncology Group performance score (ECOG PS) of 0 or 1.

Only three patients (1%) were recruited from UK centres, 97 (32%) from other Western European countries (Italy, Spain, Portugal, France and Switzerland), 42 from North America (14%), and 124 (41%) from Asia (South Korea, Hong Kong, Thailand, Singapore, Taiwan and China); other recruitment regions included Australasia, Eastern Europe and South America. The ERG's clinical experts advised that the baseline characteristics and prior non-systemic therapies are nonetheless reflective of patients in England, but highlighted that the provision of subsequent therapies after discontinuation of the randomised treatment is unlikely to be similar. The ERG requested various data about subsequent therapies from the company at the clarification stage because type of therapy received has been shown to have an important effect on overall survival (OS) in this population[27, 28] (discussed in more detail in Section 4.3).

The ERG considers the data presented within the submission to be representative of patients with ALK+ advanced NSCLC in England and to be relevant to the decision problem that is the focus of this single technology appraisal (STA).

1.4 Intervention

Alectinib (Alecensa®, Roche Registration Ltd) is a small molecule tyrosine kinase inhibitor (TKI) which targets both ALK and RET (rearranged during transfection) tyrosine kinase receptors to inhibit tumour cell growth and proliferation.[14] Animal models showed alectinib to induce tumour regression and prolong survival, with activity in the CNS.[15]

The European Medicines Agency (EMA) issued a marketing authorisation (MA) for alectinib in February 2017 for patients with ALK+ advanced NSCLC previously treated with crizotinib,[29] based on evidence from two single-arm studies.[30, 31] A NICE STA was scheduled for the pretreated indication (TA438), but the company failed to submit evidence so alectinib is currently not available on the NHS for ALK+ advanced NSCLC. The Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion in October 2017 recommending an extension to the MA to include adults with untreated ALK+ advanced NSCLC based on evidence from ALEX, and the updated MA and EPAR was granted in December 2017. The United States Food and Drug Administration (FDA) approved alectinib for patients with crizotinib-pretreated ALK+ metastatic NSCLC in December 2015, which was extended to all ALK+ metastatic NSCLC in November 2017.[32]

The intervention in the ALEX study was alectinib for adults with untreated ALK+ advanced NSCLC, in line with the extended MA and the NICE final scope.[1] Patients assigned to alectinib were given 600

mg (as four 150 mg capsules) orally twice daily in line with the EPAR [29] A lower dose (300 mg twice daily) was used in J-ALEX which is used as supportive evidence only.

In their response to clarification, the company outlined a discrepancy between the design of ALEX and the MA for alectinib with regards to treatment with alectinib beyond progressive disease (PD), stating that:

"whilst a patient with asymptomatic isolated CNS progressive disease could, at the discretion of the investigator, remain on treatment in the ALEX trial, there are no such criteria in the anticipated license of alectinib. As such, in UK clinical practice, all patients will discontinue treatment at progressive disease, irrespective of symptoms."

The company indicated that 30/40 crizotinib patients and 5/5 alectinib patients with isolated asymptomatic CNS progression continued treatment until systemic PD. The EPAR for alectinib states that treatment with alectinib should be continued until PD or unacceptable toxicity[29] The ERG considers that this asymptomatic CNS progression may not be detected in clinical practice, but notes from clinical experts and related STAs (TA500 and TA422) that treatment with ALK-TKIs in UK clinical practice may be guided by symptoms rather than radiographic evidence of PD, particularly if it is at a single site and subsequent treatment options are limited. Comparison of ALEX time to treatment discontinuation (TTD) and PFS curves suggest treatment beyond PD was uncommon in both groups. There was no consensus between the ERG's clinical experts regarding how often this occurs in UK clinical practice, under what circumstances (e.g. patient factors and availability of an alternative treatment), and the potential impact on OS.

1.5 Comparators

The NICE final scope[1] lists the first-generation ALK-TKI, crizotinib (Xalkori®, Pfizer Ltd), as the only relevant comparator for alectinib in the population of interest, which was the comparator used in the ALEX study. The ERG's clinical experts confirmed that, at the time the scope was finalised, crizotinib was the only relevant comparator as it has become standard 1L therapy for patients in England with ALK+ advanced NSCLC. As outlined in Section 2, ceritinib, a second-generation ALK-TKI, has since received NICE approval for the same indication (November 2017), and its final appraisal determination (FAD) states that its benefits over crizotinib mean it may replace crizotinib as the preferred 1L option. While ceritinib is now a relevant comparator for this STA, it was not at the time the NICE scope was finalised, or indeed by the time the company submitted evidence for alectinib. The ERG thus considers that evidence submitted by the company covers the comparators that were relevant at the time of submission.

Patients assigned to received crizotinib in ALEX were given 250 mg orally, twice daily (500 mg daily dose) in line with its European MA for use in ALK+ NSCLC.[33] Reasons for interruption and

discontinuation were in line with the SmPC. As with alectinib, patients could receive treatment beyond asymptomatic CNS progression in ALEX at the investigator's discretion.

1.6 Outcomes

All outcomes listed in the NICE final scope[1] were included in the company submission (CS), namely:

- OS;
- PFS;
- Response;
- Adverse effects (AEs) of treatment;
- Health-related quality of life (HRQoL).

Outcomes not specified in the final scope for which evidence was presented in the submission are:

- Duration of response (DOR);
- Time to CNS progression (reanalysed at the clarification stage as 'CNS PFS') – including the growth or spread of existing CNS metastases or the development of CNS metastases during the study;
- CNS response, and DOR, for patients with CNS metastases at baseline.

The primary outcome in ALEX was investigator-assessed (INV) PFS, defined as the time from randomisation to progression by Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST v1.1)[34] or death from any cause. INV PFS in the ITT population was initially presented as the company's preferred PFS analysis in the CS and results for PFS assigned by an independent review committee (IRC), a secondary outcome in ALEX, were presented to substantiate the results.

Time to CNS progression was a secondary outcome in the ALEX trial that was not listed in the NICE final scope.[1] After consultation with clinical experts, the ERG considered that it was important to reflect CNS activity in the review of cost effectiveness. CNS progressions are a common site of progression in ALK+ NSCLC with distinct clinical and cost implications, and the company propose the activity of alectinib in the CNS is an important benefit that is not reflected fully by PFS.

The ERG noted inconsistencies between the analysis of time to CNS progression and PFS in the submitted evidence, and asked the company to clarify how events were counted in each analysis. The company confirmed that time to CNS progression had been represented erroneously as a function of PFS in the CS because CNS progression could be captured by either one of two separate IRC procedures

in ALEX: one for systemic progression for the main IRC PFS outcome (based on RECIST v 1.1), and a second specifically to identify intracranial CNS lesions using a modified version of RECIST (hereafter referred to as "CNS RECIST"). The company provided a reanalysis of time to CNS progression at the clarification stage, hereafter referred to as CNS progression-free survival (CNS PFS).

For PFS and CNS PFS to be internally consistent, both had to include events from the IRC RECIST assessment, or from both the IRC RECIST and IRC CNS RECIST assessment. The ERG's preferred PFS and CNS PFS are based only on validated RECIST v1.1 because it is likely to be the most clinically relevant representation of PD, and the most comparable to how PFS is represented in other NICE technology appraisals. The company chose PFS and CNS PFS based on RECIST+CNS RECIST as their preferred analyses because they were the, "the most complete and robust analysis of the impact of CNS metastases", but accepted that events captured by CNS RECIST, "may be earlier than would be in clinical practice as CNS RECIST is not routinely used in the NHS" (company clarification response to question A10).

OS was defined as expected as time from randomisation to death from any cause in the ITT population. ALEX was not powered to detect a significant difference in OS and the median had not been reached in either group at the time of the primary analysis; the immaturity of OS is noted as a key limitation of the ALEX data and is discussed in Section 4.3.

The NICE final scope[1] did not list any subgroups of interest but the CS included INV PFS results by age (<65 vs ≥65 years old), sex, race (Asian vs non-Asian), smoking status, ECOG PS (0 or 1 vs 2), presence of CNS metastases at baseline and patients with pre-treatment radiation therapy for CNS lesions. At the clarification stage, the ERG asked for the same subgroups for IRC PFS (detailed in the clinical study report [CSR]), and *post-hoc* subgroup analyses for OS by type of subsequent therapy and presence of CNS metastases at baseline. The subgroup analyses were not run on the company's preferred PFS based on RECIST+CNS RECIST events.

Response outcomes in the CS, all according to RECIST v1.1[34] criteria, were objective response rate (ORR; total patients with either complete or partial response), complete response (CR), partial response (PR), rates of stable disease (SD) and PD, and duration of response (DOR). Results in the CS were by INV-assessment and the clinical study report (CSR)[35] included results by IRC. The CS also reported CNS response and duration of CNS response for the subset of patients with CNS lesions at baseline, based on a separate modified CNS RECIST process undertaken by the IRC.

Adverse effects (AEs) were recorded for all patients who received at least one dose of the study drug, which was all patients in the intention to treat (ITT) population (n = 303). AEs were recorded by investigators at each patient visit, either reported by the patient or noted by study personnel, until 4 weeks after the last dose of study drug (CSR,[35] pg 2033); severity was graded according to the National

1.6.1 Critique of data extraction

The company presented a Preferred Reporting Items for Systematic Reviews (PRISMA) flow diagram to illustrate the study selection process (Figure 37, Appendix 10.1). The PRISMA diagram shows the number of citations identified from the three electronic databases and the hand searches, and gives reasons for exclusion at the abstract review and full-text appraisal stages (Figure 37, Appendix 10.1). Full details of the abstracts identified in handsearching (Table 9, CS Appendix D1.1), exclusion criteria, lists of excluded studies (Tables 7 and 8, Appendix D1.1), unpublished studies identified from trial registries (Table 11, 12 and 13, CS Appendix D1.1), and ongoing studies with trial protocols only (Table 14, CS Appendix D1.1) were all provided in Appendix D1.1.

The PRISMA flow diagram shows that 34 studies were included in the company's SLR process, but the ERG counted 28 studies across several tables presented in CS Appendix D1.1 (Tables 10, 15, 16 and 17). The ERG collated a summary of the 28 included studies from these tables for information (Table 60, Appendix 10.1) to illustrate the large degree of variation between study treatments and prior therapies resulting from the broad inclusion criteria. The ERG could not identify the six remaining studies not listed in any of the tables listing included studies.

Within the 28 included studies for which information as available, the ERG notes that 21 did not assess alectinib (Table 60, Appendix 10.1). Of the seven studies of alectinib, the ERG considers that J-ALEX,[26] submitted as supportive evidence only and not included in the review of cost-effectiveness, does not provide relevant evidence because it included patients who were pretreated with chemotherapy, and used half the dose of alectinib compared with that used in ALEX (300 mg twice daily instead of 600 mg twice daily). Also within the seven alectinib studies was an RCT of alectinib (600 mg twice daily) versus chemotherapy (pemetrexed or docetaxel), which the ERG considers outside the NICE final scope[1] because it recruited a population who had received prior treatment with crizotinib and platinum-based chemotherapy (ALUR).[40] The four remaining alectinib studies identified in the company's SLR either assessed the lower 300 mg twice daily dose or recruited mixed pretreated populations (Hida 2016,[41] Iwama 2017,[42] Metro 2016,[43] and Tamura 2017[44]; see Table 60).

The ERG thus considers ALEX to provide the only relevant comparative evidence for alectinib versus the comparator of interest in the population defined in the NICE final scope.[1] The ERG agrees with the company that J-ALEX provides supportive evidence only. The ERG also agrees that three other phase III open-label RCTs of patients with untreated ALK+ NSCLC (Population A; PROFILE 1014,[37] ASCEND-4[38] and PROFILE 1029[39]) and three phase III open-label RCTs in pretreated ALK+ NSCLC populations (Populations B and D) provide relevant contextual evidence to support the review of cost-effectiveness and inform subsequent therapy post-progression survival in the economic model. The

than the alectinib group (11%) had been lost to follow-up or declined to participate, and most others were being followed for OS after discontinuation of the study drug (10% of the alectinib group and 24% of the crizotinib group).

The primary outcome of ALEX was INV PFS, defined as the time from randomisation to disease progression according to Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST v1.1), or death from any cause. The company clarified that investigator-assessed (INV) PFS was chosen as the primary outcome because 8-weekly scans could be assessed in real-time to inform the event-driven analysis of PFS. The primary analysis of INV PFS was based on a data cut-off of 9 February 2017.

Centralised assessment of PFS by an independent review committee (IRC), also according to RECIST v1.1, occurred at the same data cut-off to support PFS results by INV assessment. The ERG and its clinical experts considered PFS by IRC likely to be the less biased of the two PFS outcomes because of the open-label study design.

Time to CNS progression was a predefined secondary outcome in the ALEX trial that was not listed in the NICE final scope[1] and was measured in the ITT population to capture the growth or spread of baseline CNS metastases or the development of CNS metastases during the study. After consultation with clinical experts, the ERG considered that it was important to reflect CNS progressions in the review of cost effectiveness. As outlined in Sections 2 and 3.4, CNS progressions are a common site of progression in NSCLC with distinct clinical and cost implications, and the company propose the activity of alectinib in the CNS is an important benefit that is not captured adequately by the PFS endpoint.

During the clarification process, the company outlined that CNS progression could be picked up by either one of two separate IRC procedures: the main process for identifying systemic progression (based on RECIST v 1.1), and a second specifically to identify intracranial CNS progression using a modified version of RECIST (hereafter referred to as 'CNS RECIST'). After an error was identified with the analysis, the company provided a reanalysis of CNS progression at the clarification stage referred to as CNS PFS, and submitted a new PFS analysis as their preferred analysis; both incorporated events from RECIST and CNS RECIST, which had implications on the clinical relevance and comparability of the results to related STAs (Section 3.4 and 4.3.2).

Response was also captured according to RECIST v1.1 criteria, and measures included objective response rate (ORR; total patients with either complete or partial response), complete response (CR), partial response (PR), and rates of stable disease (SD) and PD. Results in the CS were by INV assessment and the clinical study report (CSR)[35] included results by IRC. CNS response was also recorded for the subset of patients with CNS lesions at baseline, based on the modified CNS RECIST described above. Duration of response (DOR) was also reported, for all responders and separately for

those with CNS lesions at baseline, defined as the time from documented CR or PR to progressive disease or death from any cause. Full IRC and INV response data were available in the CSR.[35]

Patient-reported outcomes (PROs) were collected every four weeks until the end of treatment assessment, and included the EuroQol 5-Dimensions 3-Levels tool (EQ-5D-3L) for overall health status, the European Organisation for Research and Treatment of Cancer Quality of Life Core 30 questionnaire (EORTC QLQ-C30), and the EORTC lung cancer module (EORTC LC13).

Adverse effects (AEs) were recorded for all patients who received at least one dose of the study drug, which was all patients in the ITT population (n = 303). AEs were recorded by investigators who were aware of treatment assignment at each patient visit, until 4 weeks after the last dose of study drug (CSR,[35] pg 2033); severity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4 (NCI CTCAE v4).

As per Figure 2, treatment was planned until PD, unacceptable toxicity, withdrawal of consent or death. However, at the clarification stage, the company emphasised that patients with asymptomatic CNS progression could remain on treatment at the discretion of the investigator. While this is not indicated in the marketing authorisation for alectinib, the ERG considers that asymptomatic CNS progression may not be detected in clinical practice. The company anticipate that, in UK clinical practice, all patients will discontinue treatment at PD, irrespective of symptoms (see Section 3.2), but the ERG notes from clinical experts and related STAs (TA500 and TA422) that treatment with ALK-TKIs in UK clinical practice may be guided by symptoms rather than radiographic evidence of PD, particularly if it is at a single site and subsequent treatment options are limited. The company indicated that 30/40 crizotinib patients and 5/5 alectinib patients with isolated asymptomatic CNS progression continued treatment until systemic PD, and the ERG did not note any large discrepancies for either treatment when time to treatment discontinuation (TTD) curves were compared with those for PFS.

Crossover to the alternative treatment at PD, unacceptable toxicity or withdrawal of consent was not part of the study protocol but patients could receive the alternative treatment as subsequent therapy if it was available and clinically indicated at their local centre. After discontinuation of the study drug, the protocol stated that patients would be followed up for long-term survival and collection of subsequent therapy information. Subsequent therapy data were requested by the ERG at the clarification stage but the company confirmed they had only been captured for 41% of the 173 patients (68 alectinib and 105 crizotinib) who had progressed and permanently discontinued study treatment (Table 7). A higher proportion of patients who received 1L crizotinib received a TKI at 2L (31.4%) than those who received alectinib (19.1), a higher proportion of alectinib-treated patients received 2L platinum chemotherapy (23.5%) than those who received crizotinib (5.7%), and a similar number received the alternative study drug off protocol (7.6% alectinib to crizotinib and 8.8% crizotinib to alectinib, respectively). The ERG

Table 8. Summary of ALEX efficacy outcomes included in the CS from clinical cut-off 9th February 2017

Outcome	Description	Measurement	Analysis	Preference	Pop	Subgroups
Outcomes covered by NICE final scope[1]						
Progression free survival (PFS)	INV: Time from randomisation to investigator-assigned date of first-documented PD or death (any cause)	RECIST v1.1, 8-weekly scans assessed real-time by the investigator	KM, stratified log-rank, stratified cox regression (HR, 95% CI)	Original	ITT	Age, sex, race, smoking status, ECOG PS, CNS mets at BL, prior brain radiation
	IRC: Time from randomisation to IRC-assigned date of first-documented PD or death (any cause)	RECIST v1.1, 8-weekly scans assessed by IRC	KM, stratified log-rank, stratified cox regression (HR, 95% CI)	ERG	ITT	
	IRC: incorporating events based on CNS RECIST criteria	RECIST v1.1 + CNS RECIST combined	KM, stratified log-rank, stratified cox regression (HR, 95% CI)	Company	ITT	NA
Overall survival (OS)	Time from randomisation to the date of death (any cause)	NA	KM, stratified log-rank, stratified cox regression (HR, 95% CI)	NA	ITT	Subsequent tx, CNS at BL (*post-hoc*)
Objective response rate (ORR)	Percentage of patients with complete or partial response (CR or PR) by INV (IRC also available in CSR)	RECIST v1.1, based on 8-weekly scans	Clopper-Pearson with 95% CI for rates, Mantel-Haenszel for difference	NA	ITT	
Health-related quality of life (HRQoL)	EQ-5D-3L	4-weekly until PD, 8-weekly for 6 months, then 12-weekly	Mixed model (treatment, sex, age, rage, CNS mets at BL, PD as variables)	ERG and company	ITT	CNS mets at BL
	EORTC QLQ-C30 and LC 13	4-weekly until PD: symptoms, treatment/ disease burden	Time to deterioration, % with clinically meaningful improvement (≥10 points), mean change from BL (SD)	NA	ITT	NA
Additional outcomes not in NICE final scope						
Duration of response (DOR)	Time from first documented CR or PR to first documented PD or death	Based on ORR data, RECIST v1.1 8-weekly	KM, cox proportional regression (HR, 95% CI)	NA	CR or PR	CNS mets at BL
CNS progression	Time to CNS progression (original) and reanalysis as CNS PFS: time from randomisation to IRC CNS progression or death	RECIST v1.1 + CNS RECIST combined	Original time to CNS progression: Log-rank cumulative incidence, Gray's competing risks; CNS PFS stratified log-rank and cos regression.	Company	ITT	+/- pre-treatment radiation therapy for CNS lesions
		RECIST-only		ERG		
CNS ORR, PR and DOR	IRC-assigned intracranial response in those with CNS mets at BL	CNS RECIST	Clopper-Pearson with 95% CI for rates, Mantel-Haenszel for difference	NA	CNS mets at BL	NA

Abbreviations: BL, baseline; CI, confidence interval; CNS, central nervous system; CNS mets, CNS metastases; CSR, clinical study report; EORTC LC13, lung cancer module; EORTC QLQ30, EORTC core 30 questionnaire; EQ-5D-3L, ERG, evidence review group; HR, hazard ratio; INV, investigator-assessed; IRC, independent review committee; ITT, intent-to-treat; NA, not applicable; RECIST, Response Evaluation Criteria in Solid Tumours; SD, standard deviation, tx, treatment.

The intent-to-treat (ITT) population, including all randomised patients, was used for the INV PFS, IRC PFS, CNS PFS, ORR and OS analyses. The safety population was used for AE analyses, defined as all patients who had received at least one dose of study medication (which was the full ITT population). Duration of response (DOR) included all patients meeting RECIST criteria for partial response (PR) or complete response (CR), i.e. the ORR population. The ERG understands that CNS-specific ORR included only patients with CNS metastases at baseline, and CNS-specific DOR included patients with baseline CNS lesions that met criteria for CNS ORR by CNS RECIST.

PFS, OS and DOR were analysed using the Kaplan-Meier method to estimate medians with 95% confidence intervals (CIs) for each arm and survival curves. Stratified Cox proportional regression models including treatment were used to estimate relative treatment effects expressed as a hazard ratio (HR) with 95% CI. At the clarification stage, the company confirmed that the proportional hazards assumption does not hold for OS or PFS, supporting the fitting of independent curves for the review of cost-effectiveness.

The original analysis of CNS progression, not listed in the NICE final scope,[1] used a log-rank test including death and non-CNS progression as competing risks, to compare time to CNS progression only in patients who had not experienced prior non-CNS progression or died. The CS described the outcome as being based on RECIST criteria, but the company confirmed at the clarification stage that the analysis included the first CNS event from two separate IRC procedures: the main IRC assessment for PD based on RECIST v1.1, and a separate IRC assessment using CNS RECIST to assess intracranial disease (see Section 4.2.1). The company confirmed that the two assessments meant CNS progressions could not be interpreted as a subset of PD assigned by RECIST v1.1, which invalidated the way CNS progressions had been assumed as a proportion of all progressions for the assessment of cost effectiveness.

At the clarification stage, the company provided more information about trial procedures for assessing PD and CNS progression, and submitted a revised analysis referred to as CNS PFS, plus new analyses of PFS for internal consistency (Table 9). The company's preferred analysis of PFS, hereafter referred to as 'adapted PFS', incorporated CNS events from the separate IRC CNS RECIST assessment to reflect their preferred analysis of CNS PFS and ensure internal consistency in the economic model. The company stated that the analyses based on IRC RECIST+IRC CNS RECIST are, "the most complete and robust analysis of the impact of CNS metastases", but accepted that events captured by CNS RECIST, "may be earlier than would be in clinical practice as CNS RECIST is not routinely used in the NHS" (company clarification response to question A10). The ERG considers PFS and CNS PFS based on RECIST-only events more applicable to UK clinical practice. The company did not provide sufficient detail about events that could occur in a sequence for individual patients, and how often this happened – e.g. CNS progression by CNS

The ERG is concerned that CNS RECIST is not widely used and may be a more sensitive than RECIST, and that incorporating events based on that assessment could lead to different conclusions than would be drawn based on IRC PFS (RECIST). As such., the ERG attempted to clarify how often patients had an event that met criteria for CNS progression by CNS RECIST before it met RECIST criteria for PD, and notes this happened more frequently in the crizotinib group than the alectinib group (24 vs 4, respectively; company response to CQ A9). Furthermore, the mean time between the events was 71 days and 43 days, respectively (company response to CQ A9). The company confirmed that events captured by CNS RECIST, "may be earlier than would be in clinical practice as CNS RECIST is not routinely used in the NHS" (response to CQ A10).

The ERG understands that any given patient could be represented differently in IRC PFS (RECIST) and adapted PFS analysis (RECIST+CNS RECIST) because patients could have more than one 'type' of progression event captured over the course of ALEX. The ERG considered that, if CNS progression was likely to meet CNS RECIST criteria before RECIST criteria, there would be inconsistency between IRC PFS (RECIST) and adapted PFS (RECIST+CNS RECIST) where both happened during ALEX. There is no inconsistency in scenarios where the first event captured was death or a PD by RECIST, which would be counted as the primary event in the company's and the ERG's preferred option.

Given the reservations of the ERG's clinical experts about the clinical plausibility of OS observed in ALEX in the UK setting, the ERG compared the ALEX IRC PFS data (RECIST) with other RCTs, clinical expert opinion, and results from real-world cohorts. Median IRC PFS on crizotinib in ALEX is comparable to PFS observed for crizotinib in PROFILE 1014 (10.9 months), the J-ALEX study (10.2 months), and the audit of crizotinib use in England (9.8 months).[48] The ERG's clinical experts expected median PFS on crizotinib to be between 6 and 12 months, which is in line with the company's explanation that the curve divergence after 6 months most likely reflects where patients begin to relapse on crizotinib (CS pg 29). However, the experts expected that nearly all patients would have progressed on crizotinib by 24 months, [redacted].

The ERG's clinical experts did not have experience with alectinib because it is not yet available for use in any indication in the UK, but median IRC PFS was similar in ALEX and J-ALEX (25.8 and 25.9 months, respectively). As described in Section 3, the ERG does not consider J-ALEX relevant to the scope of this STA. The ERG did not identify any relevant real-world KM data for alectinib to substantiate the clinical plausibility of the company's PFS extrapolations for the company's review of cost-effectiveness.

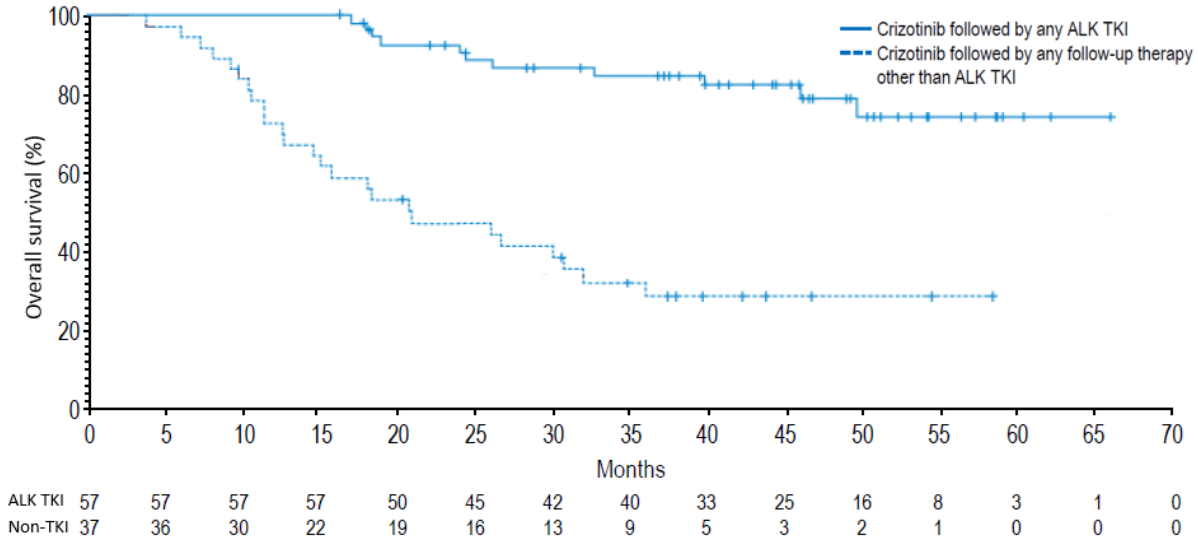
The ERG assumes that CNS progressions that met RECIST criteria represent a patient's systemic PD, and would have been counted in the PFS analysis. It follows that the number of events in the RECIST+CNS RECIST curve ([redacted]) minus the number of events in the RECIST-only curve ([redacted]), should leave the number of events that met CNS RECIST criteria but not RECIST criteria (both curves include primary deaths and secondary CNS events, see below). The numbers from this calculation are [redacted] to the number of patients in each group recorded as having a CNS progression before systemic PD by IRC RECIST (4 and 24 patients in the alectinib and crizotinib groups, respectively; company response to CQ A9a).

Neither CNS PFS analysis (RECIST+CNS RECIST or RECIST-only) censored patients who had non-CNS PD (i.e. PD not involving the CNS) prior to a CNS event, meaning some CNS events in the analysis were secondary to systemic PD. The company justified this approach because censoring non-CNS PD caused the curves to cross the OS curve, but the ERG does not understand why this would be the case (see Section 5.4.5.2). The company did not provide a breakdown of the number of primary and secondary CNS events included in the analyses based on RECIST+CNS RECIST or RECIST-only, and the ERG could not use the data provided to calculate them with any certainty. The inclusion of secondary events may not be justified because there was inconsistency in the company's response to clarification regarding whether they were captured systematically. One answer stated that, "follow-up for additional progressions was not routinely conducted once the first progression was seen on RECIST" (response to CQ B1) and another that, "any patient who experiences a non-CNS-progression prior to CNS-progression is followed until the first of CNS progression or death or loss to follow-up" (response to CQ A10).

The ERG considers that CNS PFS (RECIST) and CNS PFS (RECIST+CNS RECIST) both demonstrate the protective effect of alectinib in the CNS. The ERG considers the CNS PFS (RECIST) to provide the most consistent analysis of CNS progression with PFS (RECIST), which are likely to be the most clinically relevant and comparable to other STAs. The ERG highlights that non-CNS PD was not censored in either analysis meaning secondary CNS events are represented, which makes the results difficult to interpret in relation to PFS.

4.3.2 Response

More patients in the alectinib group met criteria for ORR according to RECIST v1.1 than the crizotinib group according to the INV [redacted], but [redacted] odds ratios (OR) indicate the difference between groups isn't statistically significant (Table 10). [redacted] Figure 9. Crizotinib OS by subsequent ALK-TKI or non-ALK-TKI use in PROFILE 1014 (adapted from Mok 2017[28]; comparison with chemotherapy not shown)



While crossover to the alternative treatment was not permitted in ALEX, nine patients in the alectinib group received crizotinib as a subsequent TKI, and 10 patients in the crizotinib received subsequent alectinib. The KM plots provided by the company (Figures 3 and 4 of the company's clarification response; [redacted].

The ERG explored the subsequent therapy data from ALEX provided by the company for possible imbalances that may have over- or underestimated the relative effect of alectinib compared with crizotinib in ALEX (Appendix 10.5, Table 67). Of the patients who have permanently discontinued treatment, 31/68 patients in the alectinib group (13 of which had a 2L TKI) and 40/105 patients in the crizotinib group (33 of which had a 2L TKI) had any 2L therapy recorded. The extent of missing information (54.4% of the alectinib group and 61.9% of the crizotinib group) means the full subsequent therapy profile could be substantially different to the subset; it is unknown what proportion of the missing data represents those who haven't received 2L therapy and what proportion have but haven't had it recorded. If it is assumed that none of the patients in the missing subset received 2L therapy after 1L crizotinib, the percentage (33/105; 31.4%) remains higher than the 18/99 patients reported as

receiving a second-generation TKI after crizotinib in the audit of crizotinib use in England (though this is seen as a minimum because the figure does not include deaths on 1L therapy).[48] The audit could also be an underestimate because it is not limited to 1L crizotinib use.

one or more common comparators (e.g. best supportive care), and decided any potential for increased precision was likely to be outweighed by clinical heterogeneity introduced by incorporating indirect evidence.

As such, the ERG agrees with the company that the head-to-head ALEX study provides the most reliable evidence to inform the decision problem of interest to this STA. Where there was uncertainty in the robustness or clinical plausibility of evidence from ALEX, the ERG consulted its clinical experts and referred to related studies identified in the company's systematic literature review (SLR; see Section 4.1).

1.7 Summary and conclusions of clinical effectiveness sections

- A positive opinion was recommended by the CHMP on 12 October 2017, and marketing authorisation granted on 18 December 2017, to extend the existing marketing authorisation for alectinib after 1L crizotinib to include 1L treatment. The updated EPAR concludes that, "the superiority of alectinib over crizotinib in treatment-naïve patients with advanced ALK-positive NSCLC has been further substantiated" by the primary results of ALEX.

- Evidence from the multicentre phase III randomised trial, ALEX, closely matches the NICE final scope for this STA[1]:

    - Population: 303 adults with untreated, histologically confirmed ALK+ advanced NSCLC;

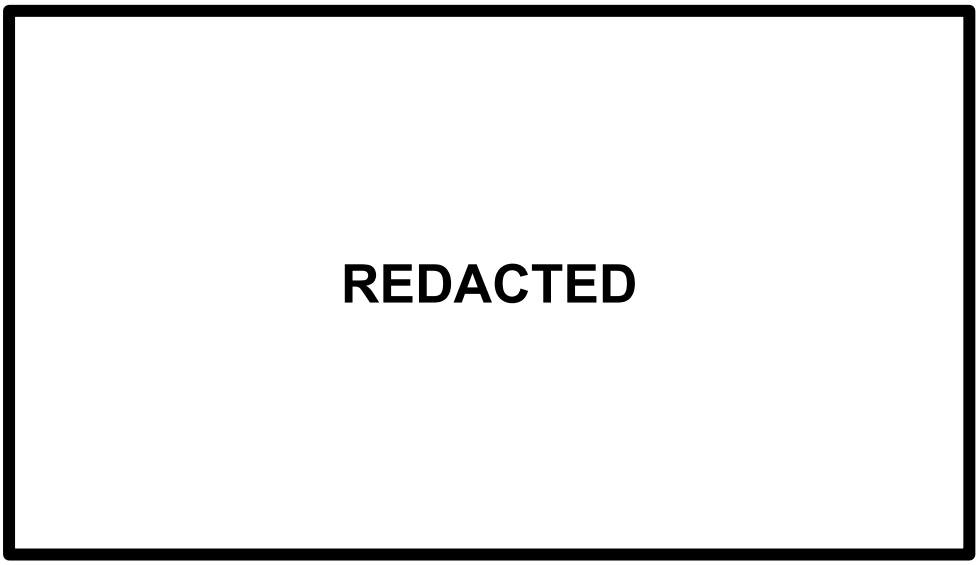
    - Intervention: alectinib 600 mg twice daily (n = 152), in line with the MA;

    - Comparator: crizotinib 250 mg twice daily (n = 151), in line with the MA;

    - Outcomes: OS, PFS, response, (ORR and DOR) HRQoL and AEs. In addition, time to CNS progression (reanalysed as CNS PFS at the clarification stage) and CNS response are presented, which, on the advice of clinical experts, the ERG considered appropriate to capture the CNS activity of alectinib. CNS metastases are common for patients with ALK+ NSCLC and impact prognosis and quality of life.

- The ERG considered direct results from ALEX to cover the scope sufficiently. While precision may have been increased for some outcomes by pooling results from ALEX with indirect evidence identified in the company's SLR (i.e. via one or more common comparators in related RCTs of alectinib and crizotinib), any benefit was likely to be outweighed by added clinical heterogeneity.

Figure 18. Alectinib and crizotinib CNS PFS KM curves (RECIST-only)



Even though the company selected the Gamma distribution to fit and extrapolate CNS PFS KM data in the alectinib and crizotinib arms of the model (measures of fit reported in Table 15), the curves were also adjusted by the relative risk of the OS curves. The ERG notes that the company did not report this adjustment in any written document provided to the ERG. Therefore, the ERG's description of the company's approach is based on model investigation, and the rationale behind the company's decision in unknown.

Table 15. Goodness of fit statistics for CNS PFS KM data

	Alectinib		**Crizotinib**	
Distribution	AIC	BIC	AIC	BIC
Exponential	273.12	276.14	322.43	325.45
Weibull	274.41	280.46	319.79	325.83
Log-normal	273.51	279.56	312.96	318.99
Gamma	275.51	284.58	313.97	323.02
Log-logistic	274.16	280.21	316.30	322.33
Gompertz	275.12	281.16	323.54	329.57
Abbreviations used in the table: AIC, Akaike information criteria; BIC, Bayesian information criteria				

In order to estimate the final CNS PFS curve in the model, the company began by fitting a Gamma distribution to the KM CNS PFS data. Following on from that, the company estimated the risk of CNS progression in each cycle (by diving the proportion of patients in the CNS PFS curve in t+1 by the proportion of patients in the CNS PFS curve in t) and compared it to the risk of death of ALK+ NSCLC patients (the proportion of patients in the OS curve in t+1 divided by the proportion of patients in the OS curve in t), and the risk of death in the general UK population, in each model cycle, by treatment arm. The company then took the maximum between the risk of dying in each cycle from the

OS, the background survival and the CNS PFS curves, and used it to estimate the proportion of patients in the CNS PFS curve in that cycle. The ERG reports the equation used by the company in Equation 1 for transparency purposes.

Equation 1. Company's estimation of CNS PFS patients in the model

$$Nr\ pts\ in\ the\ CNS\ curve = \%\ CNS\ PFS_t * \left(minimum\ \left(\frac{\%\ CNS\ PFS_{t+1}}{\%\ CNS\ PFS_t}, \frac{\%\ OS_{t+1}}{\%\ OS_t}, \frac{\%\ BS_{t+1}}{\%\ BS_t} \right) \right)$$

The company's updated analysis also estimated newly progressed patients (only for CNS progression). The company states that the proportion of transitions out of the CNS PFS curve which were (and were not) deaths in ALEX was used to track the proportion of patients in each cycle which enter the progressed CNS heath state. These proportions were assumed to be fixed throughout the analysis as the company considered that a stratified analysis would lead to an excessive subdivision of the data and result in a biased analysis. Therefore, the company used the number of CNS events captured by the RECIST+CNS RECIST analysis ([redacted]) and the number of deaths as first events ([redacted] as per Table 4 in company's reply to clarification question B1) and estimated that for crizotinib, [redacted]% of transitions out of the CNS PFS curve were not deaths ([redacted]) and for alectinib, [redacted]% of transitions out of the CNS PFS curve were not deaths ([redacted]). The ERG found a discrepancy between the company's analysis and the results reported in the company's reply to clarification question B1, as the number of CNS events in the crizotinib arm were [redacted] and not [redacted]. The ERG corrected this in the company's model and presents the results in Section 6. The company used the estimated number of newly progressed CNS patients (Equation 2) to calculate the marginal costs of CNS progression in the economic analysis.

Equation 2. Company's estimation of newly progressed patients in the model

$$Newly\ progressed\ patients = \%\ CNS\ PFS_t * \left(1 - \frac{\%\ CNS\ PFS_{t+1}}{\%\ CNS\ PFS_t}\right) * fixed\ \%\ of\ events,$$

where the fixed proportion of events was 62% and 88% for alectinib and crizotinib, respectively.

5.4.5.2.2 ERG critique

The ERG notes that the Gamma distribution seems to be one of the worst fitting curves, according to the AIC and BIC criteria reported by the company. The lognormal or the log-logistic curves seem to provide better measures of fit. In the company's base case analysis, replacing the Gamma curve by the lognormal or log-logistic has a negligible impact on the model results. The ERG agrees with the company's assessment, even when the ERG changed the capping method in the analysis.

Figure 19. Relative risk for OS, CNS PFS and background survival for alectinib

Figure deleted as a result of the factual accuracy check

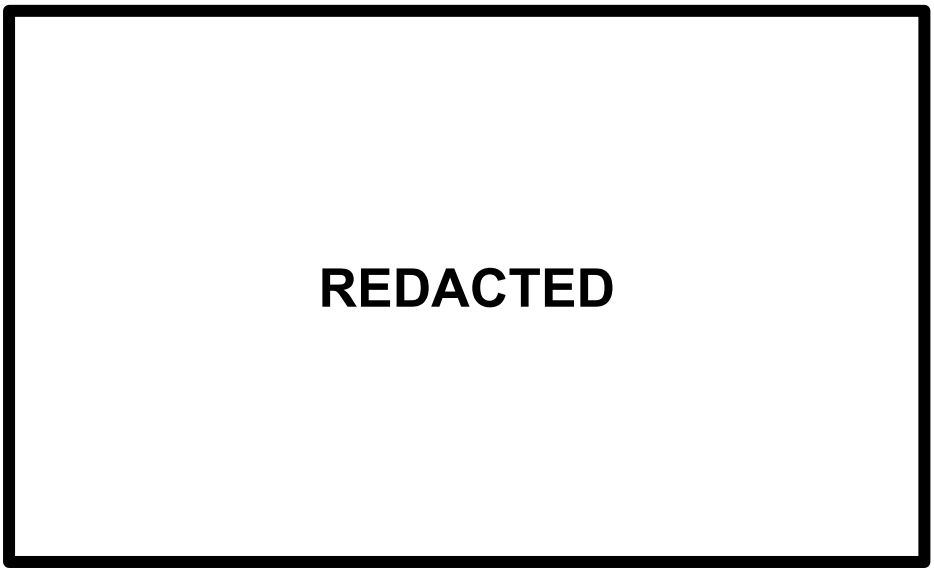
Figure 20. Survival curves for alectinib

Figure deleted as a result of the factual accuracy check

Figure 21. Relative risk for OS, CNS PFS and background survival for crizotinib

Figure deleted as a result of the factual accuracy check

Figure 22. Survival curves for crizotinib



The ERG disagrees with the method used for the estimation of newly progressed patients in the model as it uses a fixed proportion of CNS events (captured by the RECIST+CNS RECIST measure) throughout the analysis. A more robust approach would have been to estimate the number of newly progressed patients every cycle, instead of relying on a fixed proportion.

5.4.5.3 Progression-free survival

The company originally chose the INV PFS outcomes for its base case analysis. However, as a result of the clarification stage, the company changed the PFS data in its base case model to reflect the IRC-assessed PFS. The KM PFS curve for the IRC PFS is shown Figure 23.

The company used the merged ALEX data on second and third line treatment (Table 14) to estimate the proportion of patients receiving treatment after alectinib or crizotinib. The combined values, reweighted to account for the fact that not all patients had their data collected on subsequent therapies, is reported in Table 27.

Table 27. Estimation of subsequent therapies in the company's model

	Alectinib (N=152, n=68)		Crizotinib (N=151, n=105)	
Treatment	n	%	n	%
Any subsequent anti-cancer therapy	40	59%	44	42%
Any TKI	19	48%	36	82%
Ceritinib	4	10%	14	32%
Alectinib	0	0%	10	23%
Crizotinib	9	23%	2	5%
Other (lorlatinib, brigatinib, gefitinib, entrectinib, erolotinib)	6	13%	10	23%
Platinum compound (carboplatin, cisplatin)	19	48%	6	13%
Antimetabolite (pemetrexed, gemicitabine)	17	43%	6	13%
Taxane (paclitaxel, docetaxel)	3	8%	1	2%
Immunostimulant (nivolumab)	2	5%	0	0%
Angiogenesis inhibitor (bevacizumab)	2	5%	0	0%
Other (cyclophosphamide, antineoplastic agent NOS, anti PD-L1, doxorubicin, vincristine)	4	10%	1	2%
Total	66	165%	50	114%
Patients on TKIs	-	**29%***		**72%'**
Patients on non-TKIs	-	**71%^**		**28%+**

Abbreviations: NOS, not otherwise specified; PD-L1, programmed death-ligand; TKI, tyrosine kinase inhibitor
* 48% divided by 165%
^ 1 minus 29%
' 82% divided by 114%
+ 1 minus 72%

Not surprisingly, the incremental QALYs gained with alectinib reduce in this scenario analysis, as a higher proportion of crizotinib patients receive a subsequent TKI, compared with the proportion of patients receiving a TKIs in the alectinib arm. As a result, the impact of the company's scenario analysis was large, with the ICER increasing from £72,544 to £95,820 using list prices. Due to the incompleteness of data on subsequent treatments received across treatment arms in ALEX, the scenario analysis provided by the company needs to be interpreted with extreme caution.

The ERG considers the estimates used in the economic model are likely to be a poor reflection of clinical practice. With regards to crizotinib, the England audit data[48] available suggests that a minimum of 18% of patients who received crizotinib, received a second-line TKI (Section 4). Nonetheless, the audit estimates could be underestimated because the audit was not limited to first line crizotinib, and as the clinical experts advising the ERG have explained, clinical practice has been rapidly evolving in this setting, with more patients getting access to more subsequent treatment options. This estimate differs greatly from the 72% assumed by the company in their analysis. Furthermore, clinical expert opinion

provided to the ERG indicated that (although there is not clinical consensus on how to treat progressed patients after alectinib), it would appear plausible that alectinib patients would be fitter than crizotinib patients, and therefore more likely to tolerate subsequent treatment with a TKI than crizotinib patients. The clinical experts added that the reason why in the UK a relatively low percentage of patients receives TKI treatment after crizotinib is related to the development of CNS metastases, which leave the patients too ill to receive a further TKI, therefore only having chemotherapy as an option. As clinical experts anticipate that alectinib will have a protective effect on the CNS, compared with crizotinib, it is likely that a higher percentage of alectinib patients receive a subsequent TKI. Again, this is contradictory to the data used by the company in the model, where a considerably higher proportion of patients receives a TKI after crizotinib than after alectinib (72% vs 28%).

The ERG also agrees with the company that this scenario analysis is flawed by not including the impact of CNS on patients' quality of life, therefore underestimating the benefit of alectinib. Another important point, is the possibility that people continuing treatment beyond disease progression may have a better quality of life than those with progressed disease who switch treatment.

Overall, the ERG considers that the impact of subsequent therapies on patients' quality of life is potentially a key model driver. The company did not run a scenario analysis to portray the distribution of patients across subsequent therapies reflecting clinical practice in the UK. Therefore, the ERG ran three scenario analyses to reflect the uncertainty around the changes in clinical practice if alectinib is recommended. These scenarios consist of the following:

1. Assuming patients on alectinib are more likely to receive a subsequent TKI than crizotinib patients;

2. Assuming patients on alectinib are equally likely to receive a subsequent TKI as crizotinib patients;

3. Assuming patients on alectinib are less likely to receive a subsequent TKI than crizotinib patients.

All patients not receiving a TKI as subsequent treatment were assumed to receive a non-TKI (i.e. 100% of patients receive subsequent treatment in the ERG's analysis). As clinical experts could not find a consensus on the likely proportion of patients to allocate to these scenarios, the ERG used the ALEX trial data and the England audit data as a form of validation. Given the ERG's concerns that the proportions used by the company (approximately 70% of crizotinib patients receive a subsequent TKI and 30% of alectinib patients receive a subsequent TKI) are not reflective of clinical practice, the ERG had to make some assumptions with regards to the missing data on the 59% of patients and their subsequent treatments in ALEX. Given the England audit data suggests a minimum of 18% of patients

receive a second-line TKI after crizotinib, the ERG assumed that the 31.4% (Table 14) receiving a TKI after crizotinib in ALEX could be a reasonable approximation to the UK clinical practice. In order to estimate the proportion of patients receiving a TKI after alectinib, the ERG assumed the following:

1. For scenario 1 described above, it was assumed that 71% of patients receive a TKI after alectinib. This estimate assumes that all the 97 alectinib patients with missing data on subsequent treatments in ALEX received a TKI. To these 97 patients add the 13 patients for whom there are data, and are known to have received a subsequent TKI (Table 14);

2. For scenario 2, it was assumed that 31.4% of patients get a TKI after alectinib;

3. For scenario 3, the ERG took the minimum know value from ALEX, which is based on the 13 alectinib patients receiving a second-line TKI (Table 14). This amounts to 19.1% (13 divided by 68) of patients receiving a post-alectinib TKI.

This analysis is caveated by the fact that CNS impact on patients' quality of life has not been included in the analysis, and that the sources for utility values and treatment duration related with subsequent therapies are derived from various literature sources.

Furthermore, these analyses need to be accompanied by the respective costs of receiving subsequent therapies, which are discussed in Section 5.4.9. In their scenario analysis, the company included a third line treatment option in the model, with respective QALYs. However, in the cost analysis, patients in the model only receive up to two treatment lines. For consistency purposes, the ERG removed the third-line treatment option from the QALY analysis, when combining the cost and QALY analysis together (Section 6).

1.7.1 Resources and costs

The costs included in the economic model are listed below and discussed in detail in this section:

- Acquisition and administration costs associated with the intervention and comparator (Section 5.4.9.1);
- Acquisition and administration costs associated with subsequent treatments (Section 5.4.9.2);
- Disease management costs (Section 5.4.9.3);
- Costs of managing adverse events (Section 5.4.9.4);
- Other costs (Section 5.4.9.5).

5.4.9.2 Subsequent therapy costs

The company's updated base case model includes a "basket" of subsequent treatments to reflect the ALEX treatment regimen, as opposed to the anticipated market share of ceritinib, crizotinib and docetaxel obtained from the company's clinical experts (used in the company's original model). However, it is important to note that subsequent therapy data were only available for 41% of the 173 patients (68 alectinib and 105 crizotinib) in ALEX who progressed and permanently discontinued study treatment. Moreover, acquisition costs were not available for three developmental products (loratinib, brigatinib and entrectinib) received by 13 patients (6 alectinib and 7 crizotinib) in ALEX as subsequent therapies, therefore the company disregarded these for costing purposes.

Based on the available treatment options in ALEX, summarised in Table 30, the company calculated a weighted average cost per cycle on the assumption that 100% of patients in the model receive second line treatment. The company also assumed all subsequent treatments are mutually exclusive and second line treatments, although some were received as combination treatments and as third or further line therapies in ALEX.

At clarification, the company also provided an additional scenario analysis to address the ERG's clinical expert's view that docetaxel is not the only chemotherapy agent used to treat ALK+ NSCLC in the UK, as modelled by the company in their initial submission. In this scenario, also summarised in Table 30, the company assumed pemetrexed and docetaxel are given as single therapies, and pemetrexed in combination with carboplatin (or cisplatin) are given as combination therapies. The composition of the chemotherapy market share was also adjusted to reflect the company's expected values, but the market shares for second line ceritinib, alectinib, crizotinib and overall chemotherapies remained equal to the company's initial submission.

As described in Section 5.4.8.1.4, the company derived the mean time on subsequent treatment from alternative clinical trials and published literature in the second line setting, as ALEX did not accurately capture the length of time patients spent on subsequent therapies. Following this, all chemotherapies were assumed to incur the same time on treatment as docetaxel, crizotinib treatment duration was derived from PROFILE 1007, and all other TKIs were assumed to have the same treatment length as ceritinib.

Table 30. Subsequent therapy shares and time on treatment (reproduced from the economic model provided at clarification)

Drug	Alectinib n (%)	Crizotinib n (%)	Mean duration (weeks)	Duration source
Revised base case				
Ceritinib	4 (7%)	14 (24%)	41.89	ASCEND - 5 [38]
Alectinib	0 (0%)	10 (17%)	60.20	ALUR [74]

Crizotinib	9 (15%)	2 (3%)	48.14	PROFILE 1007 [75]
Gefitinib	0 (0%)	2 (3%)	41.89	ASCEND - 5 [38]
Erlotinib	0 (0%)	1(2%)	41.89	ASCEND - 5 [38]
Cisplatin	7 (12%)	5 (8%)	8.83	ALUR [74]
Carboplatin	12 (20%)	1 (2%)	8.83	ALUR [74]
Pemetrexed	15 (25%)	5 (8%)	8.83	ALUR [74]
Gemcitibine	2 (3%)	1 (2%)	8.83	ALUR [74]
Paclitaxel	3 (5%)	0 (0%)	8.83	ALUR [74]
Docetaxel	0 (0%)	1 (2%)	8.83	ALUR [74]
Nivolumab	2 (3%)	0 (0%)	9.97	NICE TA484*
Bevacizumab	2 (3%)	0 (0%)	25.13	Heist et al. 2008*[78]
Cyclophosphamide	1 (2%)	0 (0%)	8.83	ALUR [74]
Doxorubicin	1 (2%)	0 (0%)	8.83	ALUR [74]
Vincristine	1 (2%)	0 (0%)	8.83	ALUR [74]
Scenario analysis				
Ceritinib	0%	90%	41.89	ASCEND - 5 [38]
Alectinib	0%	0%	60.20	ALUR [74]
Crizotinib	60%	0%	48.14	PROFILE 1007 [75]
Chemotherapy	40%	10%	8.83	ALUR [74]
Composition of chemotherapy				
Docetaxel	85%	85%	8.83	ALUR [74]
Pemetrexed	5%	5%	8.83	ALUR [74]
Pemetrexed + carboplatin	5%	5%	8.83	ALUR [74]
Pemetrexed + cisplatin	5%	5%	8.83	ALUR [74]
*Bevacizumab and nivolumab have a maximum number of cycles defined within the product SPC or NICE recommendations, however are applied for simplicity until progression. Mean duration = median duration * number of weeks per month				

The acquisition cost of subsequent therapies in Table 31 reports the list price, however, ceritinib, alectinib, crizotinib, gefitinib, erlotinib and nivolumab are subject to confidential PASs. Based on the average weight (66.6kg) and height (164.7cm) of patients included in ALEX, a body surface area of 1.73m^2 was assumed for patients in the model to calculate doses dependent on surface area, or body weight.

Table 31. Drug acquisition costs used in the cost-effectiveness model for subsequent therapies (reproduced from updated economic model)

Drug	Composition	Pack volume	Price per pack	Cost per unit	Frequency	Source	Weekly cost*
Alectinib (oral tablet)	150 mg/ tablet	224	£5032	£22.5	1200mg daily	Alectinib dose: 600mg administered orally twice-daily from day 1 (total: 1200mg). List price: Alecensa 150mg x 224 Capsules: £5032.00 [79]	£1,262
Crizotinib (oral tablet)	250 mg/ tablet	60	£4689	£78.2	500 mg daily	Crizotinib dose: 250 mg administered orally twice-daily from day 1 (total: 500mg). List price: £4689	£1,098

5.4.9.6.1 Subsequent therapy costs

Based on the available trial data, not all subsequent therapies received by patients in ALEX have marketing authorisation for use in the UK, for the treatment of NSCLC. In addition, 13 patients in ALEX received developmental products (loratinib, brigatinib and entrectinib) whose acquisition costs were not available. Furthermore, the company assumed that 100% of patients in the model receive second line treatment. The ERG considers it reasonable to assume all patients receive subsequent therapies once they progress, as this seems reflective of current clinical practice with crizotinib, but notes that the data on subsequent therapies in ALEX is not robust due to its incompleteness.

The company carried out a scenario analysis assuming a distribution of subsequent therapies in line with current UK practice, as per clinical expert advice provided to the company (Table 30). The ERG does not consider the estimates used to be reflective of clinical practice in the UK as 90% of crizotinib patients are assumed to receive a subsequent TKI (compared with the 18% reported in the England audit, which is viewed as a minimum given that the figure does not consider deaths on first-line therapy). Therefore, the ERG ran three scenarios analyses (previously described in Section 5.4.8.2.2), to explore the uncertainty around subsequent treatments.

To further reflect UK clinical practice, the ERG assumed that the treatments available for subsequent treatment lines consisted on crizotinib and ceritinib (post alectinib) and ceritinib (post crizotinib).In order to estimate the distribution of patients allocated to crizotinib or ceritinib post alectinib, the ERG used the data available from ALEX, which shows that 2.9% of alectinib patients received ceritinib and 8.8% of patients received crizotinib. The ERG reweighted these values, to account for the entire subgroup of patients receiving a TKI post-alectinib. The final proportions used in the ERG's analysis are 25% for ceritinib and 75% for crizotinib. Results are reported in Section 6. The ERG caveats this analysis by the fact that ceritinib is currently not recommended for treatment after alectinib. Nonetheless, there was uncertainty within the ERG's clinical experts and the experts consulted for TA500 (ceritinib),10 about whether crizotinib, a first-generation ALK-TKI, would be used as a second line treatment after a second-generation ALK-TKI, such as alectinib. Given the acknowledged differences between first- and second-generation ALK-TKIs, some clinical experts considered it counterintuitive that crizotinib would be given after failure on a superior class of therapy. Therefore, the ERG assumed that ceritinib could be a treatment option after alectinib. The results of this analysis are reported in Section 6, however, the ERG notes that removing ceritinib as a possible TKI therapy after alectinib lead to a decrease in the ERG's exploratory ICERs of £1000 per QALYs gained.

The company did not include subsequent therapy administration costs in the model. The ERG corrected this by applying weekly administration costs (Table 32) to each of the subsequent therapies modelled by the company. However, the impact on the final ICER was found to be negligible.

5.4.9.6.2 Management of CNS metastases

As explained in Section 5.4.5.2, the ERG disagrees with the company's method for estimating newly progressed CNS patients. However, the ERG agrees that newly progressed CNS patients should be estimated in order to apply the marginal cost for CNS progression in the economic analysis

Clinical expert opinion sought by the ERG revealed that there seems to be a consensus on the use of SRS to treat CNS metastases whenever patients' clinical condition allows it. The issue remains, that only few patients are eligible for SRS as candidates cannot have more than a maximum of two metastatic sites. Therefore, how ineligible patients are managed in UK clinical practice remains unclear.

Although it seems that there is not a consensus among the clinical community, clinical expert opinion provided to the ERG explained that clinical practice seems to be moving away from WBRT and increasingly using steroids, as supported in the Mulvenna *et al.* 2016 paper.[91] While the company suggests that 23% of patients receive SRS and 77% of patients receive WBRT, the ERG's clinical expert agreed on the proportion of patients receiving SRS but considered that the remaining 77% would receive steroids, as opposed to WBRT, given its lack of proven advantage over steroids and its side effects on patients.

Therefore, the ERG considers the company's scenario analysis to be more reflective of clinical practice than the company's base case. The ERG also conducted exploratory analysis to reflect a scenario where the 77% of patients receiving WBRT would be managed with steroids. Given the company assumption that 100% of patients receive steroids (dexamethasone) for the management of their CNS metastases,

Table 53. Results of company's base case analysis corrected by the ERG using RECIST (PAS for alectinib)

Therapy	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Crizotinib	£145,064	2.80	–	–	–
Alectinib	[redacted]	3.82	[redacted]	1.02	[redacted]

1.8 ERG scenario analysis

The scenario analyses undertaken by the ERG are explained throughout Section 5 of the report. The exploratory analyses undertaken by the ERG uses RECIST outcomes for PFS and CNS PFS. The analyses consist on the following:

1. The ERG replaced the exponential curves used to estimate OS for alectinib and crizotinib by the KM+exponential tail curves;

2. The ERG's clinical experts advised that the frequency of oncologist visits should be every 4 weeks as opposed to every 5 to 6 weeks. The ERG replaced this in the economic model.

3. The ERG ran three scenario analyses to reflect the uncertainty around the changes in clinical practice if alectinib is recommended. Furthermore, the ERG removed the third line of treatment from the company's analysis as this line of treatment was not incorporated as an option for the cost analysis in the company's model (only second line treatment was included). These scenarios consist on the following:

    a. Assuming 71% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib;

    b. Assuming patients on alectinib are equally likely to receive a subsequent TKI as crizotinib patients (31.4% of patients assumed for both);

    c. Assuming 19.1% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib;

4. The ERG ran the three scenarios analyses described in 3, to estimate the costs of each alternative scenario. To further reflect UK clinical practice, the ERG assumed that the TKI treatments available for subsequent treatment lines consisted on crizotinib (75% of total TKI treatments) and ceritinib (25% of total TKI treatments) (post alectinib) and ceritinib (post crizotinib);

5. The ERG conducted exploratory analysis to reflect a scenario where 77% of patients receive steroids rather than WBRT to manage their CNS metastases;

6. Given that CNS-related utility value is one of the key drivers of the economic results, the ERG ran a scenario where the utility associated with CNS progression was varied by a range of values. The base case utility value (0.52) was increased by 1%, 2%, 3%, 4% and 5%.

Results from the ERG analysis are reported in Table 54. From a methodological point of view, changing the OS modelling approach from an exponential to a KM+exponential curve has a considerable impact on the company's corrected ICER (£75,079 to £80,146).

The other key model drivers are related to the clinical assumptions incorporated in the economic analysis. The two main drivers are the assumptions related with subsequent therapies in the model, namely the proportion of patients receiving a TKI and a non-TKI after treatment with alectinib or crizotinib. This has implications for the incremental costs, and to a greater extent, for QALY gain related with alectinib. The other key driver of the analysis is the modelling of CNS metastases, in terms of its impact on patients' quality of life and treatment costs (Figure 36).

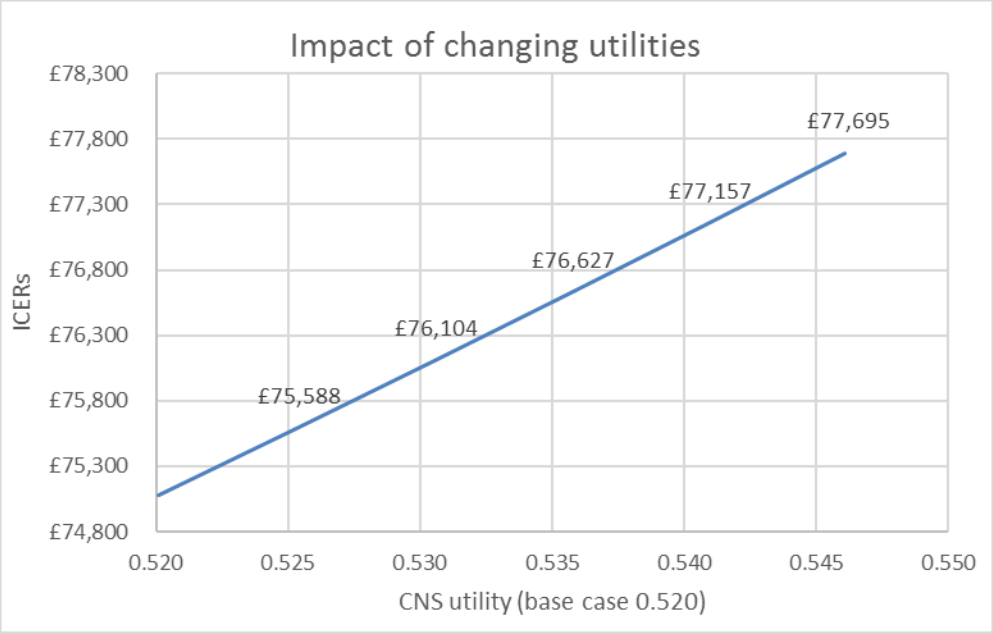
The impact of varying the combined costs and QALYs related with subsequent treatments on the final ICER is reported in the next subsection.

Table 54. Results of the ERG's scenario analysis

Analysis from list	Results per patient	Alectinib (1)	Crizotinib (2)	Incremental value (1-2)
0	**Company's corrected base using RECIST outcomes**			
	Total costs (£)	£225,992	£149,354	£76,638
	QALYs	3.82	2.80	1.02
	ICER		**£75,079**	
1	**Replacing the exponential curves used to estimate OS for alectinib and crizotinib by the KM+exponential tail curves**			
	Total costs (£)	£225,841	£149,912	£75,929
	QALYs	3.79	2.84	0.95
	ICER		**£80,146**	
2	**Changing the frequency of oncologist visits to every 4 weeks as opposed to every 5 to 6 weeks**			
	Total costs (£)	£227,309	£150,048	£77,261
	QALYs	3.82	2.80	1.02
	ICER		**£75,689**	
3 a)	**Assuming 71% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib**			
	Total costs (£)	£225,992	£149,354	£76,638
	QALYs	3.83	3.01	0.82
	ICER		**£93,856**	
3 b)	**Assuming 31.4% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib**			
	Total costs (£)	£225,992	£149,354	£76,638
	QALYs	3.78	3.01	0.76
	ICER		**£100,220**	
3 c)	**Assuming 19.1% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib**			
	Total costs (£)	£225,992	£149,354	£76,638
	QALYs	3.76	3.01	0.75
	ICER		**£102,851**	
4 a)	**Assuming 71% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib**			
	Total costs (£)	£241,685	£139,839	£101,846
	QALYs	3.82	2.80	1.02
	ICER		**£99,774**	
4 b)	**Assuming 31.4% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib**			
	Total costs (£)	£228,927	£139,839	£89,088
	QALYs	3.82	2.80	1.02
	ICER		**£87,275**	
4 c)	**Assuming 19.1% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib**			
	Total costs (£)	£224,113	£139,839	£84,274

	QALYs	3.82	2.80	1.02
	ICER	**£82,560**		
5	**Assuming patients receive steroids rather than WBRT to manage their CNS metastases**			
	Total costs (£)	£218,134	£137,108	£81,026
	QALYs	3.82	2.80	1.02
	ICER	**£79,378**		
Abbreviations used in the table: CSR, clinical study report; ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; QALY, quality-adjusted life year; RDI, relative dose intensity; TRAE, treatment-related adverse event.				

Figure 36. Scenario analysis 6



1.9 ERG base case ICER

In this section, the ERG reports three ICERs, reflecting three different scenarios in terms of subsequent therapies received after alectinib. The ERG caveats the analyses presented with the high degree of uncertainty embedded in the ALEX's data regarding patients' subsequent therapies. Related to this, is the estimated survival from ALEX, which as evidence suggests, can be highly impacted by the availability of subsequent treatment with ALKs. Although it is not possible to draw final conclusions from the naïve comparison undertaken by the ERG comparing the ALEX and the PROFILE 1014 data, it could be argued that if ALEX data were to be adjusted to real-life data, the survival predictions for crizotinib would be more conservative (with the potential impact on alectinib being unknown). The ERG considers that ALEX does not provide robust evidence to substantiate a long-term OS benefit of alectinib compared with crizotinib. Furthermore, comparative OS data from ALEX may not be a reasonable reflection of what would be seen in UK clinical practice because treatment beyond PD may differ for alectinib and crizotinib in practice, and subsequent therapies available to patients in ALEX do not reflect the UK pathway for ALK+ advanced NSCLC.

The assumptions incorporated in the ICERs presented in Table 55 include the scenario analyses numbered and described in Section 6.2. The exception is the company's scenario analysis discussed in Section 5.4.9.6.1, which assumes that only 23% of patients receive SRS, while 77% of patients receive WBRT.

The ERG produced three different ICERs, ranging from £129,324 to £142,060 per QALY gained. The lowest ICER corresponds to the scenario where a lower proportion of alectinib patients (19%) compared with crizotinib patients (31%) receive subsequent TKIs. Conversely, the highest ICER corresponds to the scenario where more alectinib patients (71%) receive subsequent TKIs, compared to crizotinib patients. When the same proportion of patients is assumed to receive subsequent TKIs, ICER amounts to £132,635, per QALY gained. The three ERG's exploratory ICERs amount to [redacted], [redacted] and [redacted] when the alectinib PAS is applied (Table 56).

Table 55. ERG's alternative base case ICERs

	Results per patient	Alectinib (1)	Crizotinib (2)	Incremental value (1-2)
0	**Company's corrected base using RECIST outcomes**			
	Total costs (£)	£225,992	£149,354	£76,638
	QALYs	3.82	2.80	1.02
	ICER			**£75,079**
1	**Replacing the exponential curves used to estimate OS for alectinib and crizotinib by the KM+exponential tail curves**			
	Total costs (£)	£225,841	£149,912	£75,929
	QALYs	3.79	2.84	0.95
	ICER (compared with base case)			£80,146
	ICER with all changes incorporated			**£80,146**
2	**Changing the frequency of oncologist visits to every 4 weeks as opposed to every 5 to 6 weeks**			
	Total costs (£)	£227,309	£150,048	£77,261
	QALYs	3.82	2.80	1.02
	ICER (compared with base case)			£75,689
	ICER with all changes incorporated			**£80,803**
Company's SA	**Company's scenario analysis assuming that 23% of patients receive SRS and 77% of patients receive WBRT**			
	Total costs (£)	£219,830	£139,751	£80,079
	QALYs	3.82	2.80	1.02
	ICER (compared with base case)			£78,450
	ICER with all changes incorporated			**£84,407**
3a+4a	**Assuming 71% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib**			
	Total costs (£)	£241,685	£139,839	£101,846
	QALYs	3.83	3.01	0.82

	ICER (compared with base case)			£124,727
	ICER with all changes incorporated			**£142,060**
3b+4b	**Assuming 31.4% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib**			
	Total costs (£)	£228,927	£139,839	£89,088
	QALYs	3.78	3.01	0.76
	ICER (compared with base case)			£116,501
	ICER with all changes incorporated			**£132,635**
3c+4c	**Assuming 19.1% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib**			
	Total costs (£)	£224,113	£139,839	£84,274
	QALYs	3.76	3.01	0.75
	ICER (compared with base case)			£113,099
	ICER with all changes incorporated			**£129,324**
	Abbreviation used in table: ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; QALYs, quality-adjusted life years; RDI, relative dose intensity.			

Table 56. ERG's alternative base case ICERs with alectinib PAS

	Results per patient	**Alectinib (1)**	**Crizotinib (2)**	**Incremental value (1-2)**
0	**Company's corrected base using RECIST outcomes**			
	Total costs (£)	[redacted]	£145,064	[redacted]
	QALYs	3.82	2.80	1.02
	ICER			[redacted]
1	**Replacing the exponential curves used to estimate OS for alectinib and crizotinib by the KM+exponential tail curves**			
	Total costs (£)	[redacted]	£145,618	[redacted]
	QALYs	3.79	2.84	0.95
	ICER (compared with base case)			[redacted]
	ICER with all changes incorporated			[redacted]
2	**Changing the frequency of oncologist visits to every 4 weeks as opposed to every 5 to 6 weeks**			
	Total costs (£)	[redacted]	£145,758	[redacted]
	QALYs	3.82	2.80	1.02
	ICER (compared with base case)			[redacted]
	ICER with all changes incorporated			[redacted]
Company's SA	**Company's scenario analysis assuming that 23% of patients receive SRS and 77% of patients receive WBRT**			
	Total costs (£)	[redacted]	£135,461	[redacted]
	QALYs	3.82	2.80	1.02
	ICER (compared with base case)			[redacted]
	ICER with all changes incorporated			[redacted]
3a+4a	**Assuming 71% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib**			

	Total costs (£)	[redacted]	£139,839	[redacted]
	QALYs	3.83	3.01	0.82
	ICER (compared with base case)			[redacted]
	ICER with all changes incorporated			[redacted]
3b+4b	**Assuming 31.4% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib**			
	Total costs (£)	[redacted]	£139,839	[redacted]
	QALYs	3.78	3.01	0.76
	ICER (compared with base case)			[redacted]
	ICER with all changes incorporated			[redacted]
3c+4c	**Assuming 19.1% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib**			
	Total costs (£)	[redacted]	£139,839	[redacted]
	QALYs	3.76	3.01	0.75
	ICER (compared with base case)			[redacted]
	ICER with all changes incorporated			[redacted]
	Abbreviation used in table: ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; QALYs, quality-adjusted life years; RDI, relative dose intensity.			

2 OVERALL CONCLUSIONS

Clinical

Alectinib (Alecensa®; Roche) has a European marketing authorisation that covers adults with untreated anaplastic lymphoma kinase positive (ALK+) advanced non-small-cell lung cancer (NSCLC). Results from the randomised controlled trial (RCT), ALEX, indicate substantial benefits of alectinib on progression free survival (PFS) and time to progression in the central nervous system (CNS PFS) compared with current standard therapy, crizotinib. One-year survival and response rates were similar between the two treatments, and overall survival (OS) and duration of response (DOR) were immature at the most recent data cut. [redacted].

There was a consistent benefit of alectinib for PFS across all predefined subgroups, except those based on very few patients. Evidence from exploratory analyses of the ALEX data suggest the PFS benefit of alectinib may be most pronounced compared with crizotinib for those with CNS metastases at baseline, and alectinib led to more frequent and longer CNS response than crizotinib for those patients. Results from safety assessments and patient-reported outcomes in ALEX give some indication that alectinib may have some tolerability benefits over crizotinib, but time to symptom deterioration and global health status is not significantly different between the two treatments.

Evidence underpinning the company submission (CS) was based solely on ALEX, which closely matches the decision problem outlined in the final scope issued by the National Institute for Health and Care Excellence (NICE).[1] The ERG agrees that an indirect comparison was not required to provide estimates of comparative effectiveness. ALEX was open-label but was otherwise judged to be largely free from internal biases. The ERG thus considers outcomes assigned by independent review committee (IRC) more reliable than those assessed by study investigators.

The company conducted alternative analyses of time to CNS progression (CNS PFS) after an error was identified after a question asked by the ERG during the clarification process to provide more robust comparative clinical effectiveness results. The company mostly reported methods with sufficient transparency to enable the ERG to critique and validate the findings, and conduct its own analyses. The ERG considers the analyses of PFS and CNS PFS based on standard RECIST criteria more clinically applicable than those incorporating events assessed with the CNS RECIST also used in ALEX.

The ERG had some concerns that the long-term effects of alectinib compared with crizotinib have not been captured adequately in ALEX to assess the clinical plausibility of extrapolations required for the evaluation of cost-effectiveness. Outcomes observed in ALEX may not be reflected in UK clinical practice due to differences in patient baseline characteristics, access to subsequent therapies and treatment beyond disease progression. Exploratory analyses requested by the ERG at the clarification

Alectinib for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer [ID925]

Addendum

March 2018

This report was commissioned by the NIHR HTA Programme as project number 14/92/01

BMJ Technology Assessment Group

SUMMARY

The ERG requested additional demographic data and utility data from the Adelphi NSCLC Disease Specific Programme to assess:

- if the populations between Roughley *et al.* 2014[1] and the ALEX trial are comparable; and
- if there is a difference in quality of life in patients who have progressed with central nervous system (CNS) involvement and those who have progressed without CNS involvement.

The ERG produced this document in response to the additional data obtained from the Adelphi NSCLC Disease Specific Programme.

Based on the additional data, patients in ALEX with progressed disease (PD) have a higher utility (0.725) than patients with one metastatic site (i.e. overall PD) in Roughley *et al.* 2014 (mean, 0.65; standard deviation [SD], 0.34). The ERG believes this difference is partly explained by patients' age, smoking status and Eastern Cooperative Oncology Group (ECOG) score, where patients in ALEX appear to be fitter and younger than patients in the Roughley *et al.* 2014 study (Table 1). However, the ERG's confidence in this finding is somewhat reduced given the number of missing EQ-5D data for patients with one metastatic site (177 out of 498 missing).

Table 1: Patient demographics and baseline characteristics in ALEX (ITT population) compared with patient demographics in Roughley *et al.* 2014 (provided by the Adelphi NSCLC Disease Specific Programme)

Demographic	Roughley *et al.* (patients with one metastatic site) n=498	ALEX (ITT population) Alectinib n=152	ALEX (ITT population) Crizotinib n=151
Mean age (SD)	62.2 (10.5)	56.3 (12.0)	53.8 (13.5)
Male, n (%)	326 (66.4)	68 (45)	64 (42)
ECOG performance score n (%)			
Missing	1	-	-
0	152 (30.6)	142 (93)	141 (93)
1	249 (50.1)		
2	85 (17.1)	10 (7)	10 (7)
3	10 (2.8)	-	-
4	1 (0.2)	-	-
Current Smoker n (%)			
Missing	3	-	-
Yes/ active smoker	225 (45.1)	12 (8)	5 (3)
Ex-smoked/ former smoker	189 (38.2)	48 (32)	48 (32)
No/ non-smoker	83 (16.8)	92 (61)	98 (65)

Abbreviations in table: ECOG, Eastern Cooperative Oncology Group; ITT, intention-to-treat; SD, standard deviation
Table produced by the ERG

Nonetheless, Roughley *et al.* 2014[1] demonstrates that patients who have progressed with CNS involvement may have a lower quality of life than those who have progressed without CNS involvement (0.65 vs 0.52).

Overall, the ERG considers that using a CNS utility value directly from Roughley *et al.* 2014[1] overestimates the impact of progression involving the CNS on quality of life when clinical effectiveness is based on the ALEX trial. This would, in turn, lead to an overestimation of the benefit of alectinib, considering its advantageous profile in preventing CNS progression. To address this issue, the ERG explored a scenario which applies a percentage decrement (0.52/0.65) to the PD utility in ALEX (0.725). Following this, the CNS utility value in the model (0.52) is replaced with 0.58.

It is important to note that the model cannot apply TKI-related utility values and CNS utility values in the same scenario, without complex manipulation. For this reason, the ERG presents a scenario which applies the alternative CNS utility (0.58) and retains the company's subsequent treatment distributions.

Results also include the following assumptions found in the ERG's base case analysis:

- Company's corrected base using RECIST outcomes;
- Replacing the exponential curves used to estimate overall survival (OS) for alectinib and crizotinib by the KM+exponential tail curves;
- Changing the frequency of oncologist visits to every 4 weeks as opposed to every 5 to 6 weeks;
- Company's scenario analysis assuming that 23% of patients receive stereotactic radiotherapy (SRS) and 77% of patients receive whole-brain radiotherapy (WBRT).

Results using list prices and the alectinib agreed patient access scheme (PAS) discount are provided in Table 2 and Table 3, respectively.

Table 2. Results using the utility decrement calculated from Roughley *et al.* 2014 (list price)

	Alectinib	**Crizotinib**	**Inc.**
Total costs	£220,981	£141,015	£79,965
Total QALYs	3.81	2.94	0.87
ICER			£92,084
Abbreviations in table: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year			

Table 3. Results using the utility decrement calculated from Roughley *et al.* 2014 (Alectinib PAS)

	Alectinib	**Crizotinib**	**Inc.**
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	3.81	2.94	0.87

ICER	[redacted]
Abbreviations in table: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year	

References

1. 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 Health* 2014; **17**: A650.

Alectinib for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer [ID925]

ERRATUM

This report was commissioned by the NIHR HTA Programme as project number 16/112/11

BMJ Technology Assessment Group

This document contains errata in respect of the ERG report due to discrepancies in the ERG report and economic model.

The table below lists the page to be replaced in the original document and the nature of the change:

Page No.	Change
162-163	Values in Table 55 for scenario 3a+4a corrected
163-164	Values in Table 56 for scenario 3a+4a corrected

The assumptions incorporated in the ICERs presented in Table 55 include the scenario analyses numbered and described in Section 6.2. The exception is the company's scenario analysis discussed in Section 5.4.9.6.1, which assumes that only 23% of patients receive SRS, while 77% of patients receive WBRT.

The ERG produced three different ICERs, ranging from £129,324 to £142,060 per QALY gained. The lowest ICER corresponds to the scenario where a lower proportion of alectinib patients (19%) compared with crizotinib patients (31%) receive subsequent TKIs. Conversely, the highest ICER corresponds to the scenario where more alectinib patients (71%) receive subsequent TKIs, compared to crizotinib patients. When the same proportion of patients is assumed to receive subsequent TKIs, ICER amounts to £132,635, per QALY gained. The three ERG's exploratory ICERs amount to [redacted], [redacted] and [redacted] when the alectinib PAS is applied (Table 56).

Table 55. ERG's alternative base case ICERs

	Results per patient	Alectinib (1)	Crizotinib (2)	Incremental value (1-2)
0	**Company's corrected base using RECIST outcomes**			
	Total costs (£)	£225,992	£149,354	£76,638
	QALYs	3.82	2.80	1.02
	ICER			**£75,079**
1	**Replacing the exponential curves used to estimate OS for alectinib and crizotinib by the KM+exponential tail curves**			
	Total costs (£)	£225,841	£149,912	£75,929
	QALYs	3.79	2.84	0.95
	ICER (compared with base case)			£80,146
	ICER with all changes incorporated			**£80,146**
2	**Changing the frequency of oncologist visits to every 4 weeks as opposed to every 5 to 6 weeks**			
	Total costs (£)	£227,309	£150,048	£77,261
	QALYs	3.82	2.80	1.02
	ICER (compared with base case)			£75,689
	ICER with all changes incorporated			**£80,803**
Company's SA	**Company's scenario analysis assuming that 23% of patients receive SRS and 77% of patients receive WBRT**			
	Total costs (£)	£219,830	£139,751	£80,079
	QALYs	3.82	2.80	1.02
	ICER (compared with base case)			£78,450
	ICER with all changes incorporated			**£84,407**
3a+4a	**Assuming 71% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib**			
	Total costs (£)	£244,263	£139,839	£104,424

	QALYs	3.84	3.01	0.83
	ICER (compared with base case)			£126,265
	ICER with all changes incorporated			**£142,060**
3b+4b	**Assuming 31.4% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib**			
	Total costs (£)	£228,927	£139,839	£89,088
	QALYs	3.78	3.01	0.76
	ICER (compared with base case)			£116,501
	ICER with all changes incorporated			**£132,635**
3c+4c	**Assuming 19.1% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib**			
	Total costs (£)	£224,113	£139,839	£84,274
	QALYs	3.76	3.01	0.75
	ICER (compared with base case)			£113,099
	ICER with all changes incorporated			**£129,324**
	Abbreviation used in table: ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; QALYs, quality-adjusted life years; RDI, relative dose intensity.			

Table 56. ERG's alternative base case ICERs with alectinib PAS

	Results per patient	**Alectinib (1)**	**Crizotinib (2)**	**Incremental value (1-2)**
0	**Company's corrected base using RECIST outcomes**			
	Total costs (£)	[redacted]	£145,064	[redacted]
	QALYs	3.82	2.80	1.02
	ICER			[redacted]
1	**Replacing the exponential curves used to estimate OS for alectinib and crizotinib by the KM+exponential tail curves**			
	Total costs (£)	[redacted]	£145,618	[redacted]
	QALYs	3.79	2.84	0.95
	ICER (compared with base case)			[redacted]
	ICER with all changes incorporated			[redacted]
2	**Changing the frequency of oncologist visits to every 4 weeks as opposed to every 5 to 6 weeks**			
	Total costs (£)	[redacted]	£145,758	[redacted]
	QALYs	3.82	2.80	1.02
	ICER (compared with base case)			[redacted]
	ICER with all changes incorporated			[redacted]
Company's SA	**Company's scenario analysis assuming that 23% of patients receive SRS and 77% of patients receive WBRT**			
	Total costs (£)	[redacted]	£135,461	[redacted]
	QALYs	3.82	2.80	1.02
	ICER (compared with base case)			[redacted]
	ICER with all changes incorporated			[redacted]

3a+4a	**Assuming 71% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib**			
	Total costs (£)	[redacted]	£139,839	[redacted]
	QALYs	3.84	3.01	0.83
	ICER (compared with base case)			[redacted]
	ICER with all changes incorporated			[redacted]
3b+4b	**Assuming 31.4% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib**			
	Total costs (£)	[redacted]	£139,839	[redacted]
	QALYs	3.78	3.01	0.76
	ICER (compared with base case)			[redacted]
	ICER with all changes incorporated			[redacted]
3c+4c	**Assuming 19.1% of alectinib patients receive a subsequent TKI, compared with 31.4% of patients in crizotinib**			
	Total costs (£)	[redacted]	£139,839	[redacted]
	QALYs	3.76	3.01	0.75
	ICER (compared with base case)			[redacted]
	ICER with all changes incorporated			[redacted]
	Abbreviation used in table: ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; QALYs, quality-adjusted life years; RDI, relative dose intensity.			