ERG STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Brigatinib for ALK-positive advanced non-small cell lung cancer that has not been previously treated with an ALK inhibitor [ID1468]

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UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: Brigatinib for ALK-positive advanced non-small cell lung cancer that has not been previously treated with an ALK inhibitor [ID1468]

Produced by: Liverpool Reviews & Implementation Group (LR*i*G)

Authors: Janette Greenhalgh, Senior Research Fellow (Clinical Effectiveness), LR*i*G, University of Liverpool

Tosin Lambe, Research Associate (Health Economics), LR*i*G, University of Liverpool

James Mahon, Director, Coldingham Analytical Services, Berwickshire

Sarah Nevitt, Research Associate (Medical Statistician), LR*i*G, University of Liverpool

Katherine Edwards, Research Fellow (Clinical Effectiveness), LR*i*G, University of Liverpool

Rebecca Bresnahan, Research Fellow (Clinical Effectiveness), LR*i*G, University of Liverpool

Angela Boland, Director, LR*i*G, University of Liverpool

Sophie Beale, Research Associate, LR*i*G, University of Liverpool

Yenal Dundar, Research Fellow (Information Specialist), LR*i*G, University of Liverpool

Ashley Marsden, Senior Medicines Information Pharmacist, North West Medicines Information Centre, Liverpool

John Green, Medical Oncologist, The Clatterbridge Cancer Centre NHS Foundation Trust, Liverpool

Correspondence to: Janette Greenhalgh, Senior Research Fellow, Liverpool Reviews and Implementation Group, University of Liverpool, Whelan Building, The Quadrangle, Brownlow Hill, Liverpool L69 3GB

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Contributions of authors:

Janette Greenhalgh	Project lead, critical appraisal of the clinical evidence and supervised the final report
Tosin Lambe	Critical appraisal of the economic evidence
James Mahon	Critical appraisal of the economic model
Sarah Nevitt	Critical appraisal of the statistical evidence
Katherine Edwards	Critical appraisal of the clinical evidence
Rebecca Bresnahan	Critical appraisal of the clinical evidence
Angela Boland	Critical appraisal of the clinical and economic evidence, editorial input
Sophie Beale	Critical appraisal of the clinical and economic evidence, editorial input
Yenal Dundar	Critical appraisal of the clinical evidence
Ashley Marsden	Critical appraisal of the company submission
John Green	Clinical advice and critical appraisal of the clinical evidence

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LIST OF ABBREVIATIONS

AE	adverse event
ALEX	ALK in NSCLC Trial of BO28984
ALK	anaplastic lymphoma kinase
ALK+	anaplastic lymphoma kinase positive
ALTA-1L	ALK in Lung Cancer Trial of AP26113
BIRC	blinded independent review committee
CI	confidence interval
CNS	central nervous system
CPK	creatine phosphokinase
CSR	Clinical Study Report
CTCAE	common terminology criteria for adverse events
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30
EQ-5D-3L	EuroQol 5-dimensions 3-level questionnaire
FDA	US Food and Drug Administration
FE	fixed effect
HR	hazard ratio
HRQoL	health-related quality of life
IA1	first interim analysis
IA2	second interim analysis
ICER	incremental cost effectiveness ratio
ITC	indirect treatment comparison
ITT	intention-to-treat
KM	Kaplan-Meier
MAIC	matching-adjusted indirect comparison
NE	not estimable
NCI	National Cancer Institute
NLCA	National Lung Cancer Audit
NSCLC	non-small cell lung cancer
OR	odds ratio
ORR	overall response rate
OS	overall survival
PAS	patient access scheme
PD	progressive disease
PFS	progression-free survival
PRO	patient reported outcomes
PSS	personal social services

QALYs	quality adjusted life years
QoL	quality of Life
RCT	randomised controlled trial
RE	random effect
RECIST	Response Evaluation Criteria in Solid Tumours
RPSFTM	rank preserving structural failure time model
SAE	serious adverse event
SmPC	Summary of Product Characteristics
TEAE	treatment emergent adverse event
TKI	tyrosine kinase inhibitor
TRAE	treatment-related adverse event
TSAP	trial statistical analysis plan

1 EXECUTIVE SUMMARY

The remit of the Evidence Review Group (ERG) is to comment on the clinical and cost effectiveness evidence submitted to the National Institute for Health and Care Excellence (NICE) as part of the Single Technology Appraisal (STA) process. Clinical and economic evidence has been submitted to NICE by Takeda UK in support of the use of brigatinib to treat anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) that has not been previously treated with an ALK inhibitor. Brigatinib was granted marketing authorisation in April 2020 by the European Medicines Agency (EMA) as a monotherapy for the treatment of adult patients with ALK-positive advanced NSCLC previously not treated with an ALK inhibitor.

1.1 Critique of the decision problem in the company's submission (Section 2.5)

The decision problem addressed in the company submission (CS) reflects the final scope issued by NICE, except that the company did not provide evidence for the comparison of brigatinib versus ceritinib. However, market share data indicated that only between 0% to 2% of patients treated in the NHS received ceritinib. Clinical advice to the company and the ERG confirmed that ceritinib is rarely used in NHS clinical practice and, therefore, it is not a relevant comparator. The ERG agrees with the company that alectinib, rather than crizotinib, is the most relevant comparator for this appraisal.

1.2 Summary of the key issues in the clinical effectiveness evidence

1.2.1 Included trials (Section 3.2.1)

The company provided direct clinical effectiveness evidence for the comparison of brigatinib versus crizotinib from the ALTA-1L trial. The ALTA-1L trial is an ongoing phase III, open-label, multi-centre (92 sites), international (19 countries) randomised controlled trial (RCT) comparing treatment with brigatinib (n=137) versus crizotinib (n=138). The ERG considers the ALTA-1L trial is a good quality trial.

1.2.2 Trial patient characteristics (Section 3.2.2)

Clinical advice to the ERG was that the baseline characteristics of ALTA-1L trial patients were generally comparable with the characteristics of similar patients treated in the NHS.

1.2.3 Statistical approach used to analyse trial data (Section 3.2.4)

The ERG considers that the pre-planned statistical approach used to analyse the ALTA-1L trial was appropriate.

1.2.4 Efficacy results (Section 3.3)

The company presented results from the second interim analysis (IA2) of the ALTA-1L trial (data cut-off date: 28 June 2019) based on median follow-up of 24.9 months in the brigatinib arm.

Blinded independent review committee (BIRC)-assessed progression-free survival (PFS) was statistically significantly longer in the brigatinib arm compared to the crizotinib arm. Overall survival (OS) results did not show that (at the 5% significance level) treatment with brigatinib was statistically significantly superior to treatment with crizotinib. However, OS data from the ALTA-1L trial were immature; median OS had not been reached in either treatment arm. Overall, 70 deaths (46.7% of the events required for the final analysis of OS) had occurred, 33 deaths (24.1%) among patients randomised to the brigatinib arm and 37 deaths (26.8%) among patients randomised to the crizotinib arm. Further, OS results were confounded due to the high proportion of patients in the crizotinib arm who received brigatinib on disease progression (98.6% of patients who progressed on crizotinib). The company applied Rank Preserving Structural Failure Time Model (RPSFTM) methods to adjust for treatment crossover. Whilst the ERG considers that it was appropriate to use RPSFTM methods and that these methods seem to have been implemented correctly, the available OS data did not allow a robust analysis of the impact of crossover.

The ALTA-1L trial intracranial outcome (PFS and overall response rate [ORR]) results favoured brigatinib over crizotinib; however, small patient numbers and low confirmed responses make the magnitude of treatment effect for the intracranial ORR outcome uncertain.

1.2.5 Health-related quality of life and safety data (Sections 3.4 and 3.5)

The ALTA-1L trial health-related quality of life (HRQoL) questionnaire results favoured brigatinib; however, the ERG cautions that patient responses to HRQoL questionnaires may have been influenced by prior knowledge of treatment.

The safety data in the ALTA-1L trial were generally consistent with the known safety profile of brigatinib. No new safety concerns or risks were identified.

Clinical advice to the company and ERG was that brigatinib has a different, but comparable, safety profile to alectinib.

1.2.6 Indirect evidence (Section 3.6)

To estimate the relative efficacy of brigatinib versus alectinib, the company carried out BIRC-assessed PFS, investigator-assessed PFS and OS indirect treatment comparisons (ITCs) (anchored and unanchored matching-adjusted indirect comparisons [MAICs]) using data from

the ALTA-1L and ALEX trials. The company also carried out unweighted Bucher ITCs (without population adjustment) for reference.

The ERG considers that the anchored MAICs and unweighted Bucher ITC methods used by the company were appropriate and seem to be correctly implemented. The assumption underpinning an unanchored MAICs is that all prognostic factors/ treatment effect modifiers are accounted for. Failure to meet this assumption leads to unreliable unanchored MAIC results. The company was unable to demonstrate that this assumption was valid and the ERG, therefore, considers, that results from the company's unanchored MAICs should not be used to inform decision making.

The PFS ITCs did not demonstrate (at the 5% significance level) that treatment with brigatinib was statistically significantly superior to treatment with alectinib.

Due to the immaturity of the ALTA-1L trial OS data, and due to concerns regarding the robustness of the company RPSFTM analyses, the ERG does not consider that any of the company's OS ITCs are reliable; the ERG considers that the best available OS estimate for the comparison of the efficacy of brigatinib versus alectinib is the OS HR generated by the anchored MAIC with RPSFTM adjustment for "all switchers", without re-censoring.

1.3 Summary of the key issues in the cost effectiveness evidence

1.3.1 Comparators (Section 6.1)

The ERG agrees with the company that alectinib is the standard of care in the NHS and, therefore, a comparison of the cost effectiveness of brigatinib versus crizotinib is not relevant when determining whether brigatinib is a cost effective option for patients treated in the NHS.

1.3.2 Overall survival (Section 6.1.1)

The main driver of the uncertainty around cost effectiveness results is the validity of the OS estimates used in the company model. The ALTA-1L trial crizotinib results are confounded by crossover and the RPFSTM adjusted OS estimates are considered unreliable. The OS estimates used to reflect the experience of patients treated with alectinib have been generated by applying the HR generated by the company's unanchored MAIC to OS data from the brigatinib arm of the ALTA-1L trial. However, the ERG does not consider that the company's unanchored MAIC results are suitable for decision making. Given the immaturity of the company OS data and the unreliability of the results from the company's ITCs, it is not possible to generate robust OS estimates. Without robust OS estimates, it is not possible to generate robust cost effectiveness results. The ERG has not, therefore, generated a preferred incremental cost effectiveness ratio (ICER) per quality adjusted life year (QALY) gained.

1.3.3 Indirect evidence (Section 6.1.1)

The company recognised the weakness of their OS ITC results and carried out a cost comparison/cost minimisation analysis to determine the cost effectiveness of brigatinib versus alectinib. The ERG, however, considers that these results should not be used to inform decision making as the company has not established that the effectiveness of brigatinib is equal or non-inferior to the effectiveness of alectinib. Failure to demonstrate equivalence or non-inferiority before undertaking a cost minimisation analysis introduces the risk that an inferior treatment to standard of care could be preferred on price alone, without properly assessing the trade-off associated with any differences in efficacy.

1.3.4 Other issues (Sections 6.1.2, 6.1.3, 6.1.4 and 6.1.5)

The ERG identified four further areas of concern, namely use of incorrect utility values, use of PFS data to model ToT, health state partitioning and absence of modelling of treatment waning. For the comparison of brigatinib versus alectinib, implementing all these amendments favoured brigatinib.

Whilst, the ERG has not undertaken any scenario analyses using alternative OS HRs, using the 11 different OS ITC HR result options available in the company model, the base case ICERs for the comparison of brigatinib versus alectinib range from £147,222 (incremental cost and QALY= [redacted] and [redacted] QALYs respectively; ITC approach=unadjusted Bucher, "official switchers", with re-censoring) to £1,520,162 (incremental cost and QALY= [redacted] and [redacted] QALYs respectively; ITC approach=anchored MAIC, "all switchers", with re-censoring).

1.3.5 ERG conclusions (Sections 6.3)

The ERG considers that any assessment of the cost effectiveness of brigatinib versus alectinib can only be speculative at this time. As the data from the ALTA-1L trial become more mature, the uncertainty around the OS benefit of brigatinib versus crizotinib may reduce as the impact of crossover becomes more accurately estimated as more OS events occur.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

Lung cancer is the third most common type of cancer in the UK,[1] with approximately 39,000 cases diagnosed in England and Wales in 2017.[2] Lung cancer is the leading cause of cancer-related mortality in the UK (age standardised mortality rate=61.4 per 100,000 persons[2]). Lung cancer is classified into two main types: non-small cell lung cancer (NSCLC), which represents 88% of cases of lung cancer in England and Wales,[2] and small cell lung cancer. Symptoms of lung cancer may include a persistent cough, breathlessness, unexplained weight loss and ongoing chest infections. Patients with brain metastases may also experience confusion, drowsiness, severe headaches and weakness in the limbs.[3]

There are two main categories of NSCLC: non-squamous type carcinomas (which include adenocarcinomas and large cell carcinomas) and squamous type cell carcinomas.[4,5] A number of genetic events have been identified as oncogenic drivers, including anaplastic lymphoma kinase (ALK) rearrangements, epidermal growth factor receptor (EGFR) mutations, B-Raf (BRAF) mutations and ROS proto-oncogene 1 (ROS1) rearrangements.[5] The growth of cancer cells is caused in part by the ALK gene translocations in an estimated 3% to 5% of people with NSCLC.[6-9]

At diagnosis, the median age of patients with ALK-positive NSCLC is between 49 to 53 years.[10-12] In contrast, at diagnosis, the median age of the whole NSCLC population is 71 years.[13] Patients with ALK-positive NSCLC tend to have little or no smoking history and tumours of adenocarcinoma histology (rarely squamous cell). It is estimated that 20% to 30% of patients with ALK-positive NSCLC have brain metastases at diagnosis,[14-18] and median survival rates for these patients range between 3 months and 14.8 months.[19] The prognosis for patients with brain metastases may be influenced by factors including age, performance status, site and number of brain metastases.[19]

Targeted ALK-positive advanced NSCLC treatments have been developed. Tyrosine kinase inhibitors (TKIs), such as alectinib, ceritinib, crizotinib, and brigatinib, are biologically similar in that they work to block the action of the ALK fusion protein to inhibit the abnormal growth and development of cancer cells. However, there are known differences between these ALK-inhibitors. For example, crizotinib is less effective than other ALK-inhibitors on central nervous system (CNS) disease due to its limited ability to penetrate the blood-brain barrier.[20] More recent second-generation ALK-inhibitors (alectinib and brigatinib) are known to have improved diffusion across the blood-brain barrier and have been shown to be more effective than crizotinib in treating CNS metastases.[21]

2.2 Company's overview of current service provision

The company representation of the current treatment pathway for patients with ALK-positive advanced NSCLC has been reproduced in Figure 1. Clinical advice to the Evidence Review Group (ERG) is that Figure 1 is an accurate reflection of NHS clinical practice in the UK. The company's proposed positioning of brigatinib (Figure 2) is as a first-line treatment option for patients with ALK-positive advanced NSCLC who have not previously been treated with an ALK inhibitor.

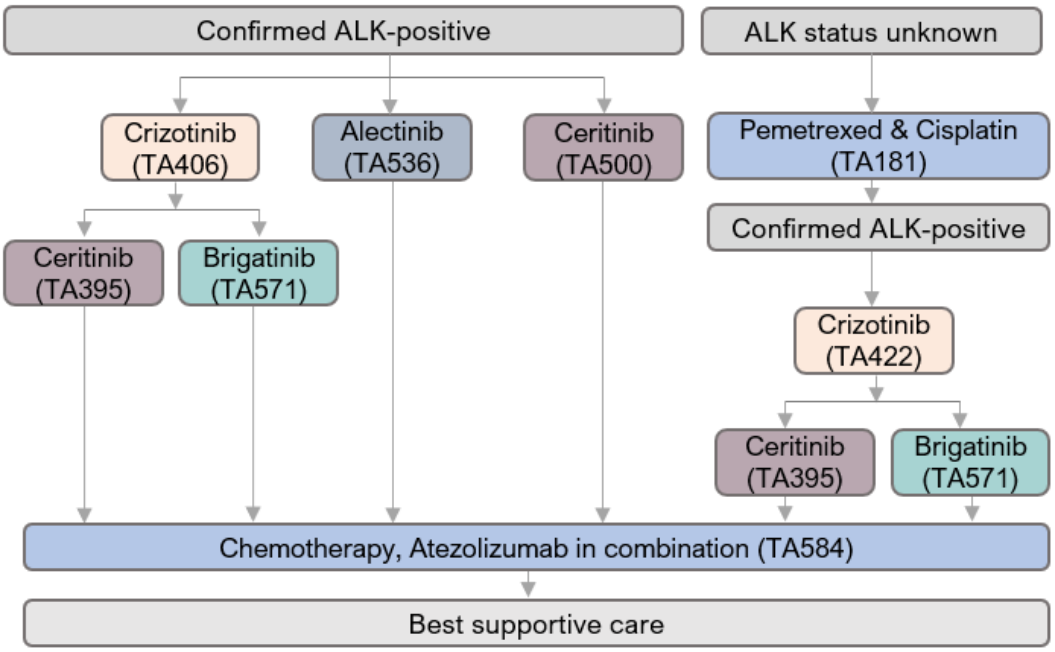

Figure 1 Current treatment pathway for patients with ALK-positive advanced NSCLC

ALK=anaplastic lymphoma kinase; NSCLC=non-small cell lung cancer
Source: CS, Figure 1

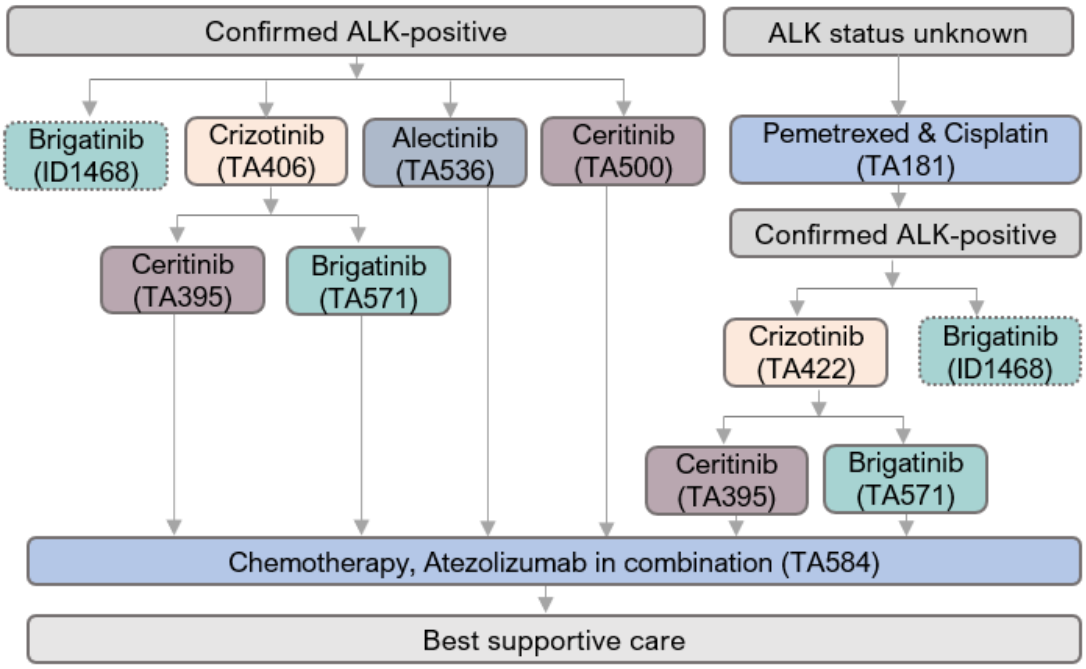

Figure 2 Proposed treatment pathway for patients with ALK-positive advanced NSCLC

ALK=anaplastic lymphoma kinase; NSCLC=non-small cell lung cancer
Source: CS, Figure 2

Testing for ALK status in the NHS

NICE guidelines recommend ALK status testing for all patients diagnosed with non-squamous NSCLC, as the mutation is most common in this subgroup.[22,23] Data from the National Lung Cancer Audit for 2017 show that up to 90% of patients with lung cancer were tested and the median time from biopsy to result was 17 days (interquartile range: 13 to 23 days).[24] Clinical advice to the ERG is that, in the NHS, samples from patients with non-squamous NSCLC are routinely tested for the ALK mutation, although some patients may wait up to 3 to 4 weeks for their result. Further, it may take two to three attempts to obtain a sample and this can delay an ALK-positive diagnosis. For these reasons, some patients may begin chemotherapy treatment prior to their ALK-status being confirmed.

Treatment of patients with tumours of unknown ALK status

The company has indicated (Figure 1) that first-line treatment for patients with NSCLC and tumours of unknown ALK-status is chemotherapy.[25] Clinical advice to the ERG was that approximately 20% to 25% of patients seen in NHS practice would begin chemotherapy either as an immediate form of treatment or while awaiting the results of genetic testing.

Crizotinib is currently the only ALK-inhibitor recommended by NICE as a treatment for patients with advanced NSCLC who have received chemotherapy.[26] The ERG notes that brigatinib has been recommended by NICE[27] as an option following treatment failure with crizotinib.

Treatment of patients with confirmed ALK-status

Current ALK-inhibitor treatments recommended by NICE for treating patients with ALK-positive NSCLC are shown in Table 1. The mechanisms of action of alectinib, ceritinib and crizotinib are similar. However, there are differences between them in terms of their structural composition, binding properties, and level of ALK inhibition.[28,29]

Table 1 ALK treatment options for patients with ALK-positive NSCLC

ALK inhibitor	Recommendations by NICE
1st generation inhibitors	
Crizotinib	In 2006, crizotinib was recommended by NICE as a treatment option for patients with untreated ALK-positive NSCLC (TA406)[30] and for ALK-positive NSCLC previously treated with chemotherapy (TA422)[26]
2nd generation inhibitors	
Alectinib	In June 2018, alectinib was recommended by NICE as a treatment option for patients with untreated ALK-positive advanced NSCLC (TA536)[31]
Ceritinib	In January 2018, ceritinib was recommended by NICE as a treatment option for patients with untreated ALK-positive NSCLC (TA500)[32]

ALK= anaplastic lymphoma kinase; NSCLC= non-small cell lung cancer
Source: extracted from the CS, p18 and NICE[26,30-32]

Crizotinib is a first-generation ALK inhibitor, and was the first ALK-inhibitor to be recommended by NICE as a treatment option for patients with ALK-positive NSCLC, both for untreated patients and for those previously treated with chemotherapy.[26,30] Alectinib and ceritinib are second-generation ALK inhibitors that are first-line treatment options for patients with ALK-positive NSCLC.[31,32]

The company considers that brigatinib and alectinib are biologically similar treatments as both are second-generation tyrosine kinase inhibitors (TKIs) (see clarification letter response to question A15).

2.3 Brigatinib

As summarised by the company (CS, Table 2

- Brigatinib is a highly selective, potent, TKI that binds to, and inhibits, the action of several kinases, including ALK and ALK fusion proteins. The inhibition of ALK kinase disrupts the signalling pathway and inhibits tumour cell growth

- On 1 April 2020, the European Medicines Agency (EMA) granted an extension to the marketing authorisation for brigatinib (alunbrig®) to licence its use as a monotherapy for the treatment of adult patients with ALK-positive advanced NSCLC previously not treated with an ALK inhibitor

- Brigatinib is administered orally. The recommended starting dose is 90mg once daily for an initial 7 days, then 180mg once daily as long as clinical benefit is observed.[33]

2.4 Number of patients eligible for treatment with brigatinib

The company used data from the NLCA Audit Annual Report 2018 (for the audit period 2017)[2] and the Surveillance, Epidemiology and End Results (SEER) Program Cancer Statistics review 1975-2016[34] to estimate that 13,911 patients in England, Wales, Guernsey and Jersey had confirmed Stage IIIB/IV NSCLC. Of these, 12,520 patients were estimated to have had an ALK test[32] and 3.5% of the tested patients were found to have had tumours with the ALK mutation.[9] The company, therefore, estimated that 438 patients with advanced ALK-positive NSCLC were likely to be eligible for first-line treatment with an ALK-inhibitor (Table 2).

Table 2 Estimated number of patients in England and Wales eligible for treatment with brigatinib

Parameter	Number of patients	Source
Number of reported cases with confirmed NSCLC	34,591	Number of reported cases of lung cancer across England, Wales, Guernsey and Jersey from NLCA annual report 2018[2]
Proportion of patients with Stage IIIB/IV disease (55.03%)	19,036	NLCA annual report 2018[2]
Proportion of patients with confirmed stage IIIb/IV NSCLC with non-squamous histology (73.08%)	13,911	SEER Cancer Statistics Review[34]
Proportion of patients with non-squamous histology NSCLC to have ALK-status test (90%)	12,520	Ceritinib NICE submission (TA500)[32]
Proportion of patients with non-squamous histology NSCLC that are ALK-positive and who are eligible for first-line treatment with ALK inhibitor (3.50%)	438	Gubens et al 2017[9]

ALK=anaplastic lymphoma kinase; ALK-positive=anaplastic lymphoma kinase positive; NLCA=National Lung Cancer Audit; NSCLC=non-small cell lung cancer; SEER=Surveillance, Epidemiology and End Results Program
Source: Data extracted from company budget impact assessment report included in the company model

2.5 Critique of company's definition of decision problem

A summary of the ERG's comparison of the decision problem outlined in the final scope[35] issued by NICE and that addressed in the CS is presented in Table 3. Each parameter is discussed in more detail in the text following the table (Section 2.5.1 to Section 2.5.8).

Table 3 Comparison between the final scope issued by NICE and the decision problem addressed by the company

Parameter	Final scope issued by NICE (original wording)	Decision problem addressed in the company submission with rationale	ERG comment
Population	Adults with ALK-positive advanced NSCLC that has not been previously treated with an ALK inhibitor	As per scope	As per scope
Intervention	Brigatinib	As per scope	As per scope
Comparator(s)	• Alectinib • Ceritinib • Crizotinib	• Alectinib • Crizotinib	The company (CS, Table 1) does not consider that ceritinib is a relevant comparator because it is rarely used in the NHS, as demonstrated by its negligible market share value of only 0% to 2% (April 2019 to January 2020). Whilst direct evidence is available from the ALTA-1L trial for the comparison of the effectiveness of brigatinib versus crizotinib, the company and the ERG consider that alectinib is the most relevant comparator
Outcomes	The outcome measures to be considered include: • OS • PFS • RR • AEs • HRQoL	As per scope	The company has provided OS, PFS, ORR, AE and HRQoL data for the comparison of the effectiveness of treatment with brigatinib versus crizotinib from the ALTA-1L trial (see Section 3.3 for details. There is no direct evidence for the comparison of the effectiveness of brigatinib versus alectinib. The company has carried out indirect treatment comparisons using data from the ALTA-1L and ALEX trials to generate comparative OS and PFS results
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality adjusted life year If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the	-	The company has provided cost effectiveness results in the form of ICERs per QALY gained for the comparisons of brigatinib versus crizotinib and brigatinib versus alectinib. The company has also assumed that the effectiveness of brigatinib and alectinib are the same and has carried out a cost minimisation analysis

	same indication, a cost-comparison may be carried out The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared Costs will be considered from an NHS and PSS perspective The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account		Outcomes were assessed over a 30-year time period. The ERG considers that 30 years is sufficiently long to reflect differences in costs or outcomes between the technologies being compared Costs were calculated from the perspective of the NHS The PAS price for brigatinib and list prices for the comparator drugs were used in the company analyses
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator	-	The company has not identified any equity issues. The company does not consider that treatment with brigatinib meets the NICE End of Life criteria[36]

AE=adverse event; ALK=anaplastic lymphoma kinase; HRQoL=health-related quality of life; ICER=incremental cost effectiveness ratio; NSCLC=non-small cell lung cancer; ORR=overall response rate; OS=overall survival; PAS=Patient Access Scheme; PFS=progression-free survival; PSS=personal social services; RR=response rate; QALY=quality adjusted life year
Source: Final scope[35] issued by NICE and CS, Table 1

2.5.1 Source of key clinical effectiveness evidence

The primary source of the evidence presented by the company is the ALTA-1L[37] trial. This is an open label, multi-centre, phase III, randomised controlled trial (RCT), that compares the clinical effectiveness of brigatinib (n=137) versus crizotinib (n=138).

2.5.2 Population

In line with the final scope[35] issued by NICE, the company has presented clinical effectiveness evidence for patients with ALK-positive advanced NSCLC who have not been previously treated with an ALK inhibitor.

2.5.3 Intervention

In April 2020, the EMA granted a marketing authorisation for brigatinib as a monotherapy for adult patients with ALK-positive advanced NSCLC not previously treated with an ALK-inhibitor.[33] Brigatinib is also recommended by NICE as an option for the treatment of adult patients with ALK-positive NSCLC who have received previous treatment with crizotinib.[38] Patients randomised to the crizotinib arm of the ALTA-1L trial were permitted to receive brigatinib on disease progression. Thus, the crizotinib arm of the ALTA-1L trial reflects NHS practice for patients who receive first-line treatment with crizotinib rather than alectinib.

Brigatinib is an oral TKI. The recommended starting dose of brigatinib is 90mg once daily for 7 days, followed by 180mg once daily for as long as clinical benefit can be observed.[33] This is the dosing regimen used in the ALTA-1L trial.

2.5.4 Comparators

The comparator treatments listed In the final scope[35] issued by NICE are alectinib, ceritinib and crizotinib.

Alectinib

In the absence of a head-to-head trial comparing the clinical effectiveness of brigatinib versus alectinib, the company performed indirect treatment comparisons (ITCs) using data from the ALTA-1L and ALEX[39] trials. The company considers that alectinib is the standard of care in the NHS and the most relevant comparator to brigatinib. The company (CS, p12) bases this decision on (i) alectinib having a market share value of 76% (January 2020), and ii) during the NICE appraisal of brigatinib as a second-line treatment for patients with ALK-positive NSCLC (TA571[38]), it was acknowledged that most people now start treatment with alectinib. Clinical advice to the ERG is that alectinib is the standard of care in the NHS.

The company considers that brigatinib and alectinib are biologically similar treatments as both are second-generation tyrosine kinase inhibitors (TKIs) (see clarification letter response to question A15).

Ceritinib

The company has not presented clinical effectiveness evidence for the comparison of brigatinib versus ceritinib. Reasons given by the company (CS, Table 1) for this were i) since alectinib was recommended by NICE[31] in mid-2018, use of ceritinib has been 'extremely limited' (the market share value of ceritinib was between 0% and 2% for the period between April 2019 and January 2020), and ii) clinical advice to the company was that the use of ceritinib in UK practice was 'negligible' due to safety and efficacy concerns. Clinical advice to the ERG was that the use of ceritinib in the NHS is limited.

Crizotinib

Direct evidence demonstrating the comparative effectiveness of brigatinib versus crizotinib is available from the ALTA-1L[37] trial.

2.5.5 Outcomes

The outcomes listed in the final scope[35] issued by NICE are overall survival (OS), progression free-survival (PFS), response rates (RR), AEs and HRQoL. Clinical advice to the ERG is that these are the most relevant outcomes for patients with ALK-positive advanced NSCLC. The company has provided evidence relating to treatment with brigatinib versus crizotinib from the ALTA-1L trial for all of these outcomes (see Section 3.3 for details).

To generate clinical effectiveness data (OS and PFS) for the comparison of brigatinib versus alectinib, the company used data from the ALTA-1L and ALEX trials to perform ITCs (see Section 3.3 for details).

2.5.6 Economic analysis

As specified in the final scope[35] issued by NICE, the cost effectiveness of treatment was expressed in terms of the incremental cost per quality adjusted life year (QALY) gained, outcomes were assessed over a 30-year time period and costs were considered from an NHS perspective. The company has also carried out a cost minimisation analysis. The validity of results from this type of analysis relies on the assumption that the effectiveness of alectinib is at least non-inferior to that of brigatinib.

The company's cost effectiveness results were generated using the Patient Access Scheme (PAS) price for brigatinib and list prices for all other treatments. Alectinib and crizotinib are available to the NHS at confidential discounted prices that are not known to the company.

The company does not consider that brigatinib meets the NICE End of Life criteria.[36]

2.5.7 Subgroups

No subgroup analyses were specified in the final scope[35] issued by NICE.

2.5.8 Other considerations

The company did not identify any equity or equality issues (CS, Section B.1.4).

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review

The full details of the process used by the company to conduct a systematic search, and the methods used to identify relevant evidence for the clinical efficacy and safety of brigatinib versus other TKI interventions in patients with ALK-positive NSCLC who have not been previously treated with an ALK inhibitor are presented in the CS (Appendix D). The searches carried out by the ERG led to the identification of one published paper[40] that had not been identified by the company. The paper [40]presents updated OS results from the ALEX trial and was published online on 11th May 2020 (outside of the company's searching timeframe). Overall, the ERG considers the methods used by the company to conduct a systematic review of the clinical effectiveness evidence were good (Table 4).

Table 4 ERG appraisal of systematic review methods

Review process	ERG	Note
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes	See CS, Appendix D.1.1.3, Table 3
Were appropriate sources searched?	Yes	See CS, Appendix D.1.1.2
Was the timespan of the searches appropriate?	Yes	Databases were searched from inception to the 03 January 2020. Conference proceedings published up to 3 years before the search date were hand searched
Were appropriate search terms used?	Yes	No additional ERG comments
Were the eligibility criteria appropriate to the decision problem?	Yes	No additional ERG comments
Was study selection applied by two or more reviewers independently?	Yes	No additional ERG comments
Was data extracted by two or more reviewers independently?	Yes	In response to question C1 of the clarification letter, the company confirmed that two independent reviewers performed data extraction and a third reviewer arbitrated any discrepancies
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Yes	The company used the Cochrane risk of bias tool (RoB 1.0)[41]
Was the quality assessment conducted by two or more reviewers independently?	Yes	In response to question C1 of the clarification letter, the company confirmed that two independent reviewers conducted quality assessment and a third reviewer arbitrated any discrepancies
Were attempts to synthesise evidence appropriate?	Yes	See Section 3.3.4 and Section 3.6.2 for an in-depth discussion of the company's methods and the ERG's critique of the syntheses of direct and indirect evidence

Source: LR*i*G in-house checklist

3.2 ERG summary and critique of clinical effectiveness evidence

3.2.1 Included trials

Direct evidence

The company identified one trial, the ALTA-1L trial, that provided direct evidence for the comparison of the effectiveness of brigatinib versus crizotinib for patients with ALK-positive advanced NSCLC that has not been previously treated with an ALK inhibitor.

Indirect evidence

The ALEX[39] trial was a head-to-head trial that compared the clinical effectiveness of alectinib versus crizotinib. The company used data from the ALEX trial to estimate the efficacy of brigatinib versus alectinib, via ITCs.

The company identified two further studies[42,43] that provided clinical effectiveness evidence for the comparison of alectinib versus crizotinib. However, the company did not use these studies[42,43] to provide clinical evidence or to inform the economic model because the company considered that the patient populations in each trial (Asian populations only) were not representative of UK patients with ALK-positive NSCLC Table 5). The ERG agrees with the company that it was appropriate to exclude the J-ALEX trial[43] from the ITCs as the dose of alectinib received by patients in that trial was lower than the European licensed dose.[33] However, the ERG considers that ALESIA trial[42] data can be used to inform indirect comparisons of the effectiveness of brigatinib versus alectinib (see Appendix 9.3).

The company identified one study[44] that provided clinical effectiveness evidence for the comparison of treatment with ceritinib versus chemotherapy. However, because the company did not consider that ceritinib was a relevant comparator, this study[44] was not included in any company ITC. The company reasons for excluding the three studies,[42-44] and ERG comments, are provided in Table 5.

Table 5 Trials excluded from the company's SLR with the company's reasons for exclusion and ERG comment

Trial	Comparison	Company's reason for exclusion	ERG comment
J-ALEX[43]	Alectinib versus crizotinib	The patient population (Asian population) is not representative of the UK clinical population. Alectinib dose (300mg twice per day) is not representative of UK clinical practice (600mg twice per day in accordance with the SmPC)[45] Evidence from the trial was not considered by the EMA during the licensing process for alectinb or by Roche in company submission to NICE for alectinib (TA536) [46]	It was appropriate to exclude the J-ALEX trial because the trial dose of alectinib differs from that used in NHS clinical practice
ALESIA[42]	Alectinib versus crizotinib	The patient population (Asian population) is not representative of the UK clinical population. Evidence from the ALESIA trial was not considered by the EMA during the licensing process for alectinib or by Roche in company submission to NICE for alectinib (TA536)[46]	It was inappropriate to exclude the ALESIA trial solely on the basis that the trial included an Asian only study population. The ERG considers that the ALESIA trial provides relevant evidence that can be used to inform an ITC of brigatinib versus alectinib (see Appendix 9.3)
ASCEND-4[44]	Ceritinib versus chemotherapy (pemetrexed + [cisplatin or carboplatin])	The company does not consider that ceritinib is a relevant comparator because it is rarely used in NHS clinical practice (CS, Table 1)	Ceritinib is rarely used in NHS clinical practice (market share is between 0% and 2%)[47]

EMA=European Medicines Agency; SmPC=Summary of Product Characteristics
Source: Adapted from CS, Appendix D.1.1.8, p84

3.2.2 Summary of the relevant clinical effectiveness evidence

Results from the ALTA-1L trial and the ALEX trial are used to inform the company OS and PFS ITCs of brigatinib versus alectinib. The company has presented the methods from the ALTA-1L trial and provided an extensive comparison between the methods used to undertake the ALTA-1L trial and the ALEX trial (CS, Section 2.3). The ERG agrees that there are important differences between the ALTA-1L trial and the ALEX trial but considers that these trials are similar enough to be included in ITCs. The ERG's critique of the methods used by the company to conduct their ITCs is presented in Section 3.6 of this ERG report.

The ALTA-1L trial

The primary source of the evidence presented by the company is the ALTA-1L[37] trial. This is an open label, multi-centre, phase III, international RCT, that compares the clinical effectiveness of brigatinib (n=137) versus crizotinib (n=138). The ALTA-1L trial is being carried out in 19 countries across 92 sites (six of these sites [n=36 trial patients] are in the UK). Of the 275 patients participating in the ALTA-1L trial, 27% had received prior chemotherapy treatment.

The ALEX trial

The ALEX trial was an open-label, multi-centre, international, phase III RCT. Only three patients (1.0%)[48] were recruited from the UK.

The key characteristics of the ALTA-1L and the ALEX trials are summarised in Table 6.

Table 6 Key characteristics of the ALTA-1L and ALEX trials

Trial parameters	ALTA-1L trial Brigatinib versus crizotinib	ALEX trial Alectinib versus crizotinib
Design	• Phase III, open-label, multi-centre, international, RCT, N=275 • 92 study sites located in: Austria, Denmark, France, Germany, Italy, Luxembourg, Netherlands, Norway, Spain, Sweden, Switzerland, United Kingdom (n=36 patients), Australia, Hong Kong, Taiwan, Singapore, South Korea, United States and Canada	• Phase III, open-label, multi-centre, international RCT, N=303 • 98 study sites location in: South Korea, United States, Italy, Hong Kong, Thailand, Canada, Russian Federation, Australia, Singapore, Taiwan, Portugal, Turkey, New Zealand, Israel, Ukraine, Costa Rica, Mexico, Serbia, United Kingdom (n=3 patients), Poland, China, Switzerland, France, Spain, Bosnia and Herzegovina, Brazil, Chile, Egypt, Guatemala
Patient population	• Adults (≥18 years of age) with histologically or cytologically confirmed Stage IIIB (locally advanced or recurrent and was not a candidate for multimodality therapy) or Stage IV NSCLC that is ALK-positive • ECOG performance status ≤2 • ≥1 measurable lesion as defined by RECIST v1.1 • No previous treatment with any TKI(s), including ALK-targeted TKIs	• Adults (≥18 years of age) with histologically or cytologically confirmed Stage IIIB (locally advanced or recurrent and was not a candidate for multimodality therapy) or Stage IV NSCLC that is ALK-positive • ECOG performance status ≤2 • ≥1 measurable lesion as defined by RECIST v1.1 • No prior systemic treatment for advanced, recurrent or metastatic NSCLC
Primary outcome	• PFS, as assessed by blinded independent review committee, was defined as the time from randomisation to the first documented PD using RECIST v1.1, or death due to any cause, whichever occurs first	• PFS, as assessed by the investigator, was defined as the time from randomisation to the first documented PD using RECIST v1.1, or death due to any cause, whichever occurs first
Median length of follow-up for PFS	• Brigatinib arm: 24.9 months • Crizotinib arm: 15.2 months	• Alectinib arm: 37.8 months • Crizotinib 23.0 months

ALK=anaplastic lymphoma kinase; BIRC=blinded independent review committee; ECOG=Eastern Cooperative Oncology Group; NSCLC=non-small cell lung cancer; PD=progressive disease; PFS=progression-free survival; RCT=randomised controlled trial; RECIST=response evaluation criteria in solid tumours; TKI=tyrosine kinase inhibitor
Source: Adapted from CS, Table 5 and Table 8

Differences in trial characteristics between the ALTA-1L and ALEX trials

In the CS (Section B.2.3.2), the company has highlighted several differences between the ALTA-1L and ALEX trial characteristics (Table 7)

Table 7 Differences in trial characteristics between the ALTA-1L and ALEX trials

Trial characteristic	ALTA-1L trial: brigatinib vs crizotinib	ALEX trial: alectinib vs crizotinib	ERG comment
Inclusion of patients who had prior chemotherapy for advanced disease	Permitted by the trial protocol	Not permitted by the trial protocol	The ERG agrees that this is a key difference (see below)
Treatment crossover after disease progression	Permitted by the trial protocol	Not permitted by the trial protocol	The ERG agrees that this is a key difference (see below)
Stratification factors	• Presence of baseline brain metastases (yes or no) • Completion of at least one full cycle of chemotherapy for locally advanced or metastatic disease (yes or no)	• Presence of baseline CNS metastases (yes or no) • ECOG performance status (0 or 1 versus 2) • Race (Asian or non-Asian)	The ERG does not consider that this is a key difference
Primary outcome	BIRC-assessed PFS	Investigator-assessed PFS	The ERG agrees that this is a key difference (see below)
Definition of disease progression	• Progressive disease • Death • Local radiotherapy for CNS lesions	• Progressive disease • Death	The ERG agrees that this is a key difference (see below)
Median follow-up time (months)	• IA1: 11.0 (brigatinib arm)[37] • IA2: 24.9 (brigatinib arm)[49]	• Primary: 18.6 (alectinib arm)[39] • Follow-up: 27.8 (alectinib arm)[50] • Final: 37.8 (alectinib arm)[51]	The ERG does not consider this is a key difference
ALK-testing	Local test to enrol patients	Central laboratory test to enrol patients	The ERG does not consider that this is a key difference

ALK=anaplastic lymphoma kinase; BIRC=blinded independent review committee; CNS=central nervous system; ECOG=Eastern Cooperative Oncology Group; ITC=indirect treatment comparison; PFS=progression-free survival
Source: Adapted from CS, Table 6, Section 2.3.2 (p33-36)

Inclusion of patients who had prior chemotherapy

The ERG agrees with the company (CS, p38) that a subgroup of patients with ALK-positive NSCLC is treated with chemotherapy, prior to confirmatory test results, and that crizotinib is the only ALK inhibitor that is recommended by NICE for patients with ALK-positive advanced NSCLC who have received prior chemotherapy. Clinical advice to the ERG is that patients

who have received prior treatment with chemotherapy account for 20% to 25% of the population treated in the NHS with advanced ALK-positive NSCLC. The ERG notes that this is consistent with the proportion of patients in the ALTA-1L trial (26.5%) who had received prior chemotherapy.

Treatment crossover after disease progression

The company reports (CS, p33) that patients who were randomised to the crizotinib arm of the ALTA-1L trial were permitted to receive treatment with brigatinib on disease progression. In contrast, patients randomised to the crizotinib arm of the ALEX trial were not permitted to receive treatment with alectinib (although, 6.6% of crizotinib patients did receive treatment with alectinib). The ERG agrees with the company (CS, p34) that the ALTA-1L trial treatment protocol reflects current NHS practice for patients who received crizotinib as a first-line treatment (or after chemotherapy) and that crossover confounds any comparison of the brigatinib versus crizotinib ALTA-1L OS data.

Assessment of the primary outcome

The ERG agrees with the company (CS, p35) that using a blinded independent review committee (BIRC) to assess PFS (rather than unblinded investigators), reduces the risk of bias. However, the ERG notes that the ALEX trial included BIRC–assessed PFS as a secondary outcome; however, the results from this analysis were consistent with the primary outcome (investigator-assessed PFS). Additionally, the ERG considers that unblinded investigator-assessed outcomes are more reflective of NHS clinical practice than BIRC-assessed outcomes.

Definition of disease progression

Clinical advice to the company (CS, p35) and to the ERG is that the ALTA-1L trial definition of disease progression is more representative of NHS clinical practice than the definition of disease progression used in the ALEX trial. The ALTA-1L trial definition of disease progression is a RECIST progression, radiotherapy for brain metastases or death, whichever occurs first. In contrast, the ALEX trial defined a PFS event as a RECIST progression or death, whichever occurs first.

Baseline characteristics of patients recruited into the ALTA-1L and ALEX trials

The ALTA-1L trial

Full details of the baseline characteristics of patients participating in the ALTA-1L trial are provided in the CS (Table 9) and a summary is provided in Table 8 of this ERG report. The ERG agrees with the company (CS, p36) that the baseline characteristics of patients participating in the ALTA-1L trial were well-balanced between the treatment arms. Clinical

advice to the ERG is that the patients in the ALTA-1L trial are generally representative of patients with ALK-positive NSCLC treated in the NHS, including the proportions of patients who had received treatment with chemotherapy for locally advanced or metastatic disease. However, clinical advice to the ERG is that, compared with NHS practice, there are some differences in terms of race, namely the ALTA-1L trial included a higher proportion of Asian patients (39.3%), and a lower proportion of Black patients (0.7%).

Table 8 ALTA-1L trial baseline patient characteristics (ITT population)

Baseline characteristic	Brigatinib (n=137)	Crizotinib (n=138)	Total (N=275)
Age, years			
Mean (SD)	57.9 (13.46)	58.6 (11.42)	58.2 (12.46)
Median	58.0	60.0	59.0
Sex, n (%)			
Female	69 (50.4)	81 (58.7)	150 (54.5)
Race, n (%)			
Asian	59 (43.1)	49 (35.5)	108 (39.3)
Black or African American	0	2 (1.4)	2 (0.7)
White	76 (55.5)	86 (62.3)	162 (58.9)
Unknown	2 (1.5)	1 (0.7)	3 (1.1)
Brain metastasis at baseline, n (%)			
	40 (29.2)	41 (29.7)	81 (29.5)
Prior chemotherapy for locally advanced/metastatic disease, n (%)			
	36 (26.3)	37 (26.8)	73 (26.5)
Prior radiotherapy to the brain, n (%)			
	18 (13.1)	19 (13.8)	37 (26.9)
ECOG performance status, n (%)			
0	54 (39.4)	53 (38.4)	107 (38.9)
1	76 (55.5)	78 (56.5)	154 (56.0)
2	7 (5.1)	7 (5.1)	14 (5.1)
Cigarette smoking history, n (%)			
Never	84 (61.3)	75 (54.3)	159 (57.8)
Former	50 (36.5)	56 (40.6)	106 (38.5)
Current	3 (2.2)	7 (5.1)	10 (3.6)
Disease stage, n (%)			
IIIB	8 (5.8)	12 (8.7)	20 (7.3)
IV	129 (94.2)	126 (91.3)	255 (92.7)
Median time since initial diagnosis, months			
All patients	1.68	1.48	1.61

ECOG=Eastern Cooperative Oncology Group; SD=standard deviation
Source: Adapted from CS, Table 9

The ALEX trial

The baseline characteristics of patients participating in the ALEX trial are summarised in Table 35 (Appendix 9.1.1). The ERG considers that, in the ALEX trial, patient baseline characteristics were well-balanced between the treatment arms. Clinical advice to the ERG is that, compared with the population of patients seen in NHS practice, Asian patients were over-represented (45.5% of patients were Asian) in the ALEX trial.[39]

The company highlights (CS, pp37-38) that compared with the ALEX trial (40%), the ALTA-1L trial (30%) included a lower proportion of patients with brain metastases at baseline. The ERG considers that the proportions of patients in the ALTA-1L and ALEX trials with brain metastases are quite similar, however, the ERG also acknowledges the importance of brain metastases as a prognostic factor/treatment effect modifier (discussed further in Section 3.6.2). The company also highlights that 26.5% of patients in the ALTA-1L trial had received prior chemotherapy for locally advanced or metastatic disease (clinical advice to the ERG was that 20-25% of people in the NHS receive chemotherapy), whereas the patients in the ALEX trial were untreated in this setting.

3.2.3 Quality assessment of the ALTA-1L and the ALEX trials

The company conducted a quality assessment of the ALTA-1L and ALEX trials using the Cochrane Risk of Bias tool[41] (see CS, Appendix D.1.3, Table 13 and Table 14).

Quality assessment of the ALTA-1L trial

The company considers that the ALTA-1L trial has a low risk of bias across all six risk of bias domains, with the exception of performance bias (Table 13, CS, Appendix D.1.3, Table 13). The company judged that the ALTA-1L trial was at high risk of performance bias because it was an open-label trial and, therefore, participants and study personnel were not blinded to treatment. The company, however, notes that the trial was at low risk of detection bias because the primary outcome (PFS) was assessed by a BIRC.

The ERG considers that the ALTA-1L trial is at low risk of performance bias (Table 9) because the majority of the outcomes were objective outcomes (e.g., PFS, OS and overall response rate [ORR]) and were, therefore, unlikely to be influenced by the lack of blinding. The ERG agrees that the trial is at high risk of performance bias for HRQoL as this can be influenced by patients' knowledge of their treatment allocation. Overall, the ERG agrees with the company that the ALTA-1L trial is a good quality trial (CS, p85).

Table 9 ALTA-1L trial risk of bias assessment summary

Bias domain	Company assessment	ERG assessment
Selection bias (random sequence generation)	Low	Low
Selection bias (allocation concealment)	Low	Low
Performance bias	High	Low
Detection bias	Low	Low
Attrition bias	Low	Low
Reporting bias	Low	Low
Other bias	Low	Low

Source: Adapted from CS, Appendix D.1.3, Table 13

Quality assessment of the ALEX trial

The company considered that the ALEX trial was at low risk of bias across four risk of bias domains: selection bias, attrition bias, reporting bias and other bias (Table 14, Appendix D.1.3 to the CS). However, the company considered that the ALEX trial was at high risk of performance bias (due to the open-label study design), and high risk of detection bias because the primary outcome (PFS) was assessed by an investigator who was not blinded to the treatment allocation of patients (Table 14, Appendix D.1.3 to the CS).

The ERG disagrees with the company's judgment that the trial was at high risk of performance and detection bias (Table 10). The majority of ALEX trial outcomes were objective and thus were less susceptible to the placebo effect than subjective outcomes. Furthermore, although the primary outcome was investigator-assessed PFS, the ALEX trial included independent review committee-assessed PFS as a secondary outcome. The independent review committee decisions were used to confirm the investigator's judgments.

The company stated that, with regard to attrition bias (Table 14, Appendix D.1.3 to the CS), although an intention-to-treat analysis (ITT) approach was used to analyse the ALEX trial primary outcomes, treatment withdrawals were not reported. However, the ERG notes that treatment withdrawals were fully reported in Figure 1 of the Peters 2017[39] publication and, therefore, the ERG does not consider that this is a valid criticism of the ALEX trial. The company has not provided an overall quality rating for the ALEX trial. The ERG, however, considers that the ALEX trial was a good quality trial.

Table 10 ALEX trial risk of bias assessment summary

Bias domain	Company assessment	ERG assessment
Selection bias (random sequence generation)	Low	Low
Selection bias (allocation concealment)	Low	Low
Performance bias	High	Low
Detection bias	High	Low
Attrition bias	Unclear	Low
Reporting bias	Low	Low
Other bias	Low	Low

Source: Adapted from CS, Appendix D.1.3, Table 12

3.2.4 Statistical approach adopted for the ALTA-1L trial

Information relevant to the statistical approach taken by the company has been extracted from the CS and from other documents provided in response to clarification question A1, namely the interim analysis 2 (IA2, data cut-off date 28 June 2019) clinical study report (CSR) [52] the most recent versions of the trial protocol (version 3.0, dated 17 May 2018)[53] and the statistical analysis plan (TSAP, version 4.0, dated 19 August 2019).[54] A summary of the ERG checks of the pre-planned statistical approach used by the company to analyse data from the ALTA-1L trial is provided in Table 11.

The ERG considers that the pre-planned statistical approach used by the company is adequate and appropriate, but notes that awareness of amendments made to the statistical analysis plan following interim analysis 1 (IA1), including changes to definitions of outcomes, analysis populations and censoring rules for the analysis of BIRC-assessed PFS is required when directly comparing numerical results for BIRC-assessed PFS from IA1 and IA2 (Table 11).

Table 11 ERG summary and critique of statistical approaches used to analyse ALTA-1L trial data

Item	ERG assessment	Statistical approach	ERG comments
Were all analysis populations clearly defined and pre-specified?	Yes	The analysis populations are described in the CS (Section B.2.4.1, p39): ITT population, treated (safety) population, four populations according to presence of measurable or non-measurable CNS disease, crossover population and the PRO-ITT population.	The ERG is satisfied that the analysis populations are clearly defined and pre-specified (TSAP; Section 3.2)
Was an appropriate sample size calculation pre-specified?	Yes	The sample size calculation is described in the CS (Section 2.4.3, p40) and pre-specified in the TSAP (Section 3.1), assuming that 198 PFS events (progression, radiotherapy to the brain or death) will provide 90% power to detect a clinically meaningful 6-month improvement in PFS (HR=0.625). Two interim analyses (IA1 and IA2) were pre-specified (TSAP; Section 3.4.3.6) after approximately 50% and 75% of the total expected PFS events. A closed testing procedure for statistical testing of the key secondary endpoints (in rank order: confirmed ORR by BIRC, confirmed intracranial ORR by BIRC, intracranial PFS by BIRC and OS) is described in the CS (Section 2.4.2, p40) and pre-specified (TSAP; Section 3.5.2.1)	The ERG is satisfied that the sample size calculations and approach to statistical testing and interim analyses are appropriate
Were all protocol amendments carried out prior to analysis?	Yes	A list of all amendments made to the original trial protocol and TSAP, and the rationale for these amendments are outlined within the most recent versions of the trial protocol and statistical analysis plan. Amendments to the statistical approach were made between versions 2.0, 3.0 and 4.0 of the TSAP, including changes to definitions of outcomes, analysis populations and censoring rules for the analysis of BIRC-assessed PFS. The ERG notes that IA1 (date cut-off date 19 February 2018) would have been conducted according to version 2.0 of the TSAP (dated 18 February 2018)[55] and that clinical effectiveness results reported within the CS from IA2 (data cut-off date 28 June 2019) would have been conducted according to version 3.0 of the TSAP (dated 27 March 2018)[56]	The ERG considers that all protocol amendments are minor clarifications of wording or definitions and do not impact on any analyses. The ERG considers that the amendments made to the statistical approach are reasonable but notes that awareness of differences in the statistical approach and resulting changes to the definition of BIRC-assessed PFS is required when directly comparing numerical results from IA1 and IA2 for BIRC-assessed PFS
Were all primary and secondary efficacy outcomes pre-defined and analysed appropriately?	Yes	The primary and secondary efficacy outcomes are defined in the CS (Table 5, p31) and the statistical analysis approach for the primary outcome is briefly described in the CS (Section 2.4.2, p40). Outcome definitions and statistical analysis approaches are described in more detail in the TSAP: primary efficacy outcome (Section 3.4.2) and secondary efficacy outcomes (Section 3.5)	The ERG is satisfied that the primary and secondary efficacy outcome definitions and analysis approaches were pre-specified and are appropriate
Was the analysis approach for PROs appropriate and pre-specified?	Yes	The PRO was change from baseline in global health status or quality of life, collected using the EORTC QLQ-C30 questionnaire (version 3.0) and associated lung cancer module (LC13), measured in the PRO-ITT population (CS, Table 5 [p31] and Section 2.4.1 [p39])	The ERG is satisfied that the PRO outcome definitions and analysis approaches were pre-specified (TSAP; Section 3.5.3.5) and are appropriate

Item	ERG assessment	Statistical approach	ERG comments
Was the analysis approach for AEs appropriate and pre-specified?	Yes	AEs were assessed and graded using the NCI CTCAE version 4.0 classification system within the treated population. AEs are presented as numbers and percentages of patients experiencing events. No formal statistical analyses of AEs were conducted. TEAEs and TRAES in ≥10% of patients in either treatment arm or with ≥5% absolute difference in treatment arms (any Grade and Grade ≥3 events), as well as AEs of special interest, AEs leading to study drug discontinuation or dose reduction and SAEs are presented in the CS (Table 22, Table 23 and Section 2.10; pp72-77)	The ERG is satisfied that the analysis approach for AEs was pre-specified (TSAP, Section 3.7) and is appropriate. The ERG also notes that additional summary tables of TEAEs and SAEs in both the treated population and the crossover population are provided in the CSR (Section 12, pp134-190)
Were modelling assumptions (e.g. proportional hazards) assessed?	Yes	It was pre-specified that the primary efficacy outcome (BIRC-assessed PFS) and the secondary efficacy outcomes (intracranial PFS and OS) would be analysed using a Cox PH model (TSAP, Section 3.4.2 and Section 3.5). The company tested the PH assumption for BIRC-assessed PFS (CS; Figure 26), OS (CS; Figure 36),subgroup analyses of BIRC-assed PFS for patients with or without brain metastases (response to clarification question A4a) and treated or not treated with prior chemotherapy (response to clarification question A4b), investigator assessed PFS (response to clarification question A4c), intracranial PFS (response to clarification question A4d)and duration of response (response to clarification question A4e) using Schoenfeld's residual test and by plotting Schoenfeld residuals versus time and by plotting log (-log(PFS or OS)) versus log(time)	The ERG is satisfied from the testing of Schoenfeld residuals that there is no statistically significant evidence that the PH assumption was violated and that it is appropriate for the Cox PH model to be used and for HRs to be presented for ALTA-1L trial BIRC-assessed PFS (and subgroups of patients with and without brain metastases, and treated or not treated with prior chemotherapy), investigator assessed PFS, intracranial PFS, DoR and OS
Was a suitable approach employed for handling missing data?	Yes	Missing data were handled according to pre-specified imputation rules for all outcomes and also with censoring rules for time-to-event outcomes (CS, Section B2.4.4 and TSAP, Section 3.4.2 and Section 3.5)	The ERG is satisfied that all pre-specified methods for handling missing data are appropriate
Were all subgroup and sensitivity analyses pre-specified?	Yes	The ERG is satisfied that all of the subgroup analyses of the primary outcome defined (CS; Table 5, p32) and presented (CS; Section B 2.7) were pre-specified (TSAP; Section 3.4.3.8). One sensitivity analysis is presented in the CS for the primary outcome, with PFS based on investigator assessment	The ERG is satisfied that this sensitivity analysis was pre-specified (TSAP; Section 3.4.3.7). The ERG notes that other sensitivity analyses of the primary outcome and the secondary outcomes are described in the TSAP (Section 3.4.2 and Section 3.5) and results from these sensitivity analyses are presented in the CSR (Section 11.4)

AE=adverse event; BIRC=blinded independent review committee; CNS=central nervous system; CSR=clinical study report; CTCAE=common terminology criteria for adverse events; DoR=duration of response; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30; HR=hazard ratio; IA1=first interim analysis; IA2=second interim analysis; ITT=intention to treat; NCI=National Cancer Institute; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PH=proportional hazards; PRO=patient reported outcome; SAE=serious adverse event; TEAE=treatment-emergent adverse event; TRAE=treatment related adverse event; TSAP=trial statistical analysis plan
Source: Extracted from the CS, CSR of IA2,[52] most recent version of the trial protocol[53] and TSAP,[54] the company's response to the clarification letter and ERG comment

3.3 Efficacy results from the ALTA-1L trial

Two pre-specified interim analyses (IA1 and IA2) of the ALTA-1L trial have been conducted.

IA1 was conducted following 99 BIRC-assessed PFS events (50% of 198 expected events) at a data cut-off date of 19 February 2018.[37] The median follow-up time for the primary outcome BIRC-assessed PFS at the time of IA1 was 11.0 months for brigatinib and 9.3 months for crizotinib. IA1 results showed that treatment with brigatinib was statistically significantly superior (at the 5% level) to crizotinib (hazard ratio [HR]=0.49, 95% confidence interval [CI]: 0.33 to 0.74, p=0.0007). Other results from IA1 are provided in the ALTA-1L trial journal publication.[37]

IA2 represents the latest available data to inform this submission. IA2 was conducted using data from the cut-off date of 28 June 2019, following 150 BIRC-assessed PFS events (75.7% of 198 expected events), and after a median follow-up of 24.9 months for brigatinib and 15.2 months for crizotinib. A summary of key efficacy results from IA2 are presented in this section.

The ERG considers that key efficacy results were consistent between IA1 and IA2 and that awareness of the amendments made to the statistical analysis plan following IA1 is required when directly comparing numerical results from IA1 and IA2 (see Table 11 of this ERG report for details of amendments made).

3.3.1 Primary efficacy outcome: BIRC-assessed progression-free survival

A summary of primary efficacy outcome (BIRC-assessed PFS) results and results from a sensitivity analysis of PFS based on investigator assessment is provided in Table 12.

At the time of IA2, 63 out of 137 patients (46%) in the brigatinib arm and 87 out of 138 patients (63%) in the crizotinib arm had experienced a PFS event. The majority of PFS events observed were disease progression (128 events, 85% of total events), 12 death events (8% of total events) and 10 events of radiotherapy for CNS lesions (7% of total events).

BIRC-assessed PFS was statistically significantly longer in the brigatinib arm compared to the crizotinib arm (median BIRC-assessed PFS was 24 months compared to 11 months; HR=0.49, 95% CI: 0.35 to 0.68; p<0.0001). Clinical advice to the ERG was that BIRC-assessed PFS gain of brigatinib over crizotinib is clinically meaningful.

The ERG notes that results for investigator-assessed PFS are mostly consistent with BIRC-assessed PFS results. There are minor differences in the numbers of disease progression, death and local radiotherapy events between BIRC assessment and investigator assessment,

and a larger difference in median PFS between brigatinib and crizotinib based on investigator assessment.

Table 12 Summary of BIRC and investigator assessed PFS (ITT population, IA2)

	BIRC-assessed PFS		Investigator-assessed PFS	
	Brigatinib (n=137)	**Crizotinib (n=138)**	**Brigatinib (n=137)**	**Crizotinib (n=138)**
Number of events: n (%)	63 (46.0)	87 (63.0)	59 (43.1)	92 (66.7)
Death: n (%)	7 (5.1)	5 (3.6)	8 (5.8)	4 (2.9)
Disease progression: n (%)	54 (39.4)	74 (53.6)	50 (36.5)	84 (60.9)
Local radiotherapy for CNS lesions: n (%)	2 (1.5)	8 (5.8)	1 (0.7)	4 (2.9)
Median PFS (95% CI)	23.984 (18.46 to NE)	11.006 (9.17 to 12.88)	29.437 (21.22 to NE)	9.232 (7.39 to 12.88)
HR (95% CI), p-value	0.489 (0.35 to 0.68), p<0.0001		0.434 (0.31 to 0.61), p<0.0001	
Log-rank p-value	p<0.0001		Not reported	

BIRC=blinded independent review committee; CI=confidence interval; CNS=central nervous system; IA2=second interim analysis HR=hazard ratio; NE=not estimable; PFS=progression-free survival
Source: Extracted and adapted from CS, Table 12

Subgroup analysis of BIRC-assessed progression-free survival

Subgroup analyses results of BIRC-assessed PFS according to the two randomisation stratification factors of the ALTA-1L trial (the presence of brain metastases at baseline and prior chemotherapy use for locally advanced or metastatic ALK-positive NSCLC) are presented in Table 13.

Table 13 Subgroup analyses by presence of brain metastases and prior chemotherapy of BIRC assessed PFS (subgroups of ITT population, IA2)

Subgroup (n)	Number of events (%)	Median PFS (95% CI), months	HR (95% CI), p-value
Brigatinib, brain metastases (n=40)[a]	20 (50.0)	23.951 (18.37 to NE)	0.249 (0.14 to 0.46), p<0.0001
Crizotinib, brain metastases (n=41)[a]	30 (73.2)	5.552 (3.84 to 9.40)	
Brigatinib, no brain metastases (n=97)[a]	43 (44.3)	24.016 (15.67 to NE)	0.649 (0.44 to 0.97), p=0.0333
Crizotinib, no brain metastases (n=97)[a]	57 (58.8)	13.010 (9.46 to 21.13)	
Brigatinib, prior chemotherapy (n=36)	16 (44.4)	24.016 (16.62 to NE)	0.438 (0.23 to 0.83), p=0.0120
Crizotinib, prior chemotherapy (n=37)	26 (70.3)	11.006 (7.16 to 21.16)	
Brigatinib, no prior chemotherapy (n=101)	47 (46.5)	23.951 (18.37 to NE)	0.519 (0.35 to 0.77), p=0.0010
Crizotinib, no prior chemotherapy (n=101)	61 (60.4)	10.842 (9.13 to 15.61)	

BIRC=blinded independent review committee; CI=confidence interval; IA2=second interim analysis HR=hazard ratio; NE=not estimable; PFS=progression-free survival
[a] Presence of brain metastases at baseline for stratification of randomisation assessed by investigator
Source: Extracted and adapted from CS, Table 20 and Table 21

Irrespective of the presence of brain metastases and prior chemotherapy use at baseline, BIRC-assessed PFS was statistically significantly longer in the brigatinib arm compared to the crizotinib arm.

Results from the other pre-specified subgroup analyses of BIRC-assessed PFS are provided in Figure 11 of the CS. BIRC-assessed PFS results for all pre-specified subgroups are consistent with the BIRC-assessed PFS results presented in Table 12 of this ERG report but the ERG notes that imprecision of these results, reflected in wide 95% CIs, should be considered when drawing conclusions about some subgroup results due to small sample sizes and imbalanced group sizes.

3.3.2 Key secondary efficacy outcome: overall survival

A summary of OS results is provided in Table 14. No statistically significant difference between ALTA-1L trial treatment arms was shown at the time of IA2 (HR=0.92, 95% CI: 0.57 to 1.47; p=0.7134).

Table 14 Summary of OS (ITT population, IA2)

	Brigatinib (n=137)	**Crizotinib (n=138)**
Number of deaths, n, (%)	33 (24.1)	37 (26.8)
Median (95% CI)	NE (NE to NE)	NE (NE to NE)
HR (95% CI), p value	0.916 (0.57 to 1.47), p=0.7134	
Log-rank p-value	p=0.7710	

CI=confidence interval; CNS=central nervous system; IA2=second interim analysis HR=hazard ratio; NE=not estimable; OS=overall survival
Source: Extracted and adapted from CS, Table 18

However, at the time of IA2, OS data were immature. Median OS had not been reached for either treatment arm. A total of 70 deaths had occurred (46.7% of approximately 150 OS events required for the final analysis of OS [trial protocol, Section 15.5.3 and Table 10]).[37] Furthermore, as noted by the company, the ALTA-1L trial OS data are confounded by the high proportion of patients in the crizotinib arm who received brigatinib on disease progression. In total, 61 patients from the crizotinib arm (44.2% of the 138 patients randomised to this arm, and 82.4% of the 74 patients in this arm who experienced disease progression) were recorded as “official switchers” according to the protocol definition of the crossover phase of the ALTA-1L trial (trial protocol, Section 11 and Table 4).[37] The company identified an additional 12 patients who switched from crizotinib to brigatinib and 11 patients who switched from brigatinib to crizotinib after their review of subsequent therapies (CS, Table 7). Therefore, “all switchers” included a total of 84 patients; 73 patients from the crizotinib arm (52.9%) of the 138 patients randomised to this arm and 98.6% of the 74 patients randomised to this arm who experienced disease progression and crossed over to brigatinib and 11 patients from the brigatinib arm; 8.8% of the 137 patients randomised to the brigatinib arm and 22.2% of the 54 patients who experienced disease progression in the brigatinib arm crossed over to crizotinib.

Adjustment of overall survival data to account for treatment crossover

To adjust for the confounding of the OS data at IA2 due to crossover, the company performed treatment switching analyses using Rank Preserving Structural Failure Time Model (RPSFTM) methods. The ERG agrees that, for this appraisal, the RPFSTM method is appropriate and seems to have been implemented correctly. Further details and an ERG critique of the methods used by the company to adjust for treatment crossover are provided in Appendix 9.2.1 to this ERG report.

Ten different OS HRs (with 95% CIs) generated by the company are presented in Figure 3. These show alternative treatment crossover adjustment scenarios, namely unadjusted results with no adjustment for switching, "official switchers" only adjusted for, and "all switchers" (including those identified as switchers from their concomitant medications added), with or without re-censoring and with standard or bootstrapped 95% CIs.

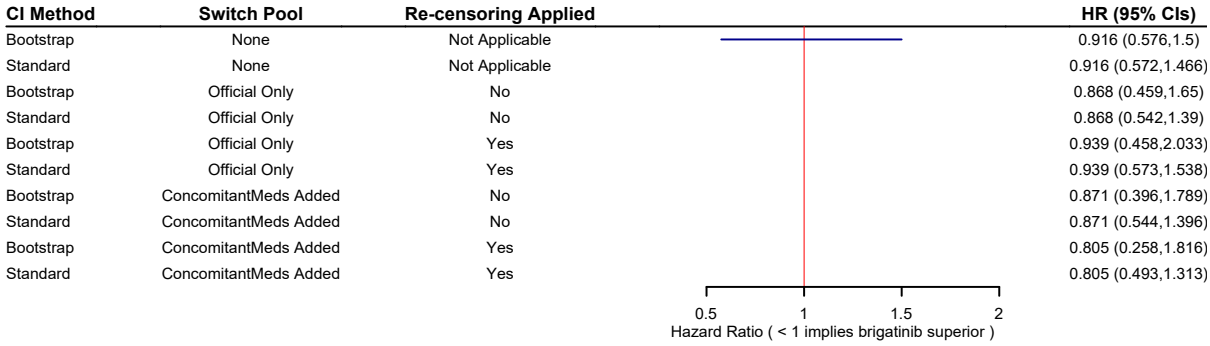

Figure 3 Brigatinib versus crizotinib OS HRs: results of alternative treatment switching adjustment scenarios

CI=confidence interval; HR=hazard ratio; OS=overall survival
Source: CS, Figure 42

The company noted that the 95% CIs for the alternative treatment switching adjustment scenarios are wide and include 1 (i.e., no statistically significant evidence that, at the 5% level, treatment with brigatinib is superior to crizotinib) for all estimates of the OS HR.

The company considered that the results from the analysis adjusted for "official switchers" only with re-censoring, which increased the HR estimate from 0.916 to 0.939 (i.e., in favour of crizotinib over brigatinib) were clinically implausible. The company notes that the change in OS HR estimates in other treatment crossover scenarios was not as large as they had anticipated. The company had expected that estimates of the OS HR from the ALTA-1L trial, when adjusted for treatment crossover, would align with the latest OS HR from the ALEX trial (HR=0.69, 95% CI: 0.47 to 1.02, estimated at a median follow up of 37.8 months for alectinib and 23.0 months for crizotinib).[51] The company suggested that these results, that they considered were counterintuitive, could be due to the available ALTA-1L trial OS data being

too immature, or the number of patients in the crizotinib arm who did not switch treatment being too small to allow robust RPSFTM analyses. The company concluded that the RPSFTM methods had failed to account for the bias introduced by crossover in the ALTA-1L trial.

The ERG agrees that the limitations highlighted by the company are likely to have impacted on the robustness of the RPSFTM adjusted results. The ERG also notes that the counterintuitive increase in the size of the HR for some of the alternative treatment switching adjustment scenario estimates may have resulted from loss of information within the limited number of observed OS events due to re-censoring.[57]

In addition, the ERG does not consider that it is appropriate to assume that RPSFTM adjusted OS HRs from the ALTA-1L trial, estimated using immature OS data, would align with the latest OS HR from the ALEX trial. The ERG considers that it is more appropriate to compare the RPSFTM adjusted OS HRs from the ALTA-1L trial with the earlier published OS HR from the ALEX trial (HR 0.76, 95% CI 0.48 to 1.20), estimated at a similar median follow up time to IA2 of the ALTA-1L trial (i.e., 18.6 months for alectinib and 17.6 months for crizotinib). The ERG considers that the RPSFTM adjusted HRs for "all switchers" from the ALTA-1L trial (HR 0.805 and HR 0.871) are more closely aligned with the earlier OS HR of the ALEX trial.[39]

Considering all the limitations of the treatment crossover adjustment approaches outlined in Appendix 7.1.2 to this ERG report, the ERG considers that the best available adjusted OS estimate from the ALTA-1L trial at the time of IA2 is the OS HR with RPSFTM adjustment for "all switchers", without re-censoring, and presented with bootstrapped 95% CIs (HR 0.871, 95% CI: 0.396 to 1.789).

The ERG emphasises, however, that due to the immaturity of the OS data from the ALTA-1L trial, definitive conclusions regarding the magnitude and precision of the relative OS effect of brigatinib versus crizotinib, with or without adjustment for treatment switching, cannot be reached. As the data from the ALTA-1L trial become more mature, the uncertainty around the OS benefit of brigatinib versus crizotinib may reduce as the impact of crossover becomes more accurately estimated as more OS events occur.

3.3.3 Key secondary efficacy outcome: intracranial PFS

A summary of BIRC-assessed intracranial PFS results is provided in Table 15.

At the time of IA2, BIRC-assessed intracranial PFS was statistically significantly longer in the brigatinib arm than in the crizotinib arm (treated population), and also within the subgroup of patients who had brain metastases at baseline as assessed by the BIRC.

[redacted]

Table 15 Summary of BIRC-assessed intracranial PFS results (treated population and subgroups of ITT population, IA2)

Subgroup (n)	Number of events (%)	Median intracranial PFS (95% CI), months	HR (95% CI), p-value
Brigatinib, treated population (n=136)	40 (29.41)	32.28 (29.51 to NE)	0.55 (0.36 to 0.84), p=0.005
Crizotinib, treated population (n=137)	51 (37.2)	24.0 (12.96 to NE)	
Brigatinib, brain metastases (n=47)[a]	21 (44.7)	23.95 (12.91 to NE)	0.31 (0.17 to 0.56), p<0.0001
Crizotinib, brain metastases (n=49)[a]	32 (65.3)	5.59 (3.71 to 7.52)	
Brigatinib, no brain metastases (n=90)[a]	[redacted]	[redacted]	[redacted]
Crizotinib, no brain metastases (n=89)[a]	[redacted]	[redacted]	

[a] Presence of any brain metastases assessed by BIRC
BIRC=blinded independent review committee; CI=confidence interval; IA2=second interim analysis HR=hazard ratio; NE=not estimable; PFS=progression-free survival
Source: Extracted and adapted from CS, Table 15; CSR of IA2 of the ALTA-1L trial;[52] Table 11.q, ALTA-1L trial data on file[58]

3.3.4 Other secondary efficacy outcomes

Overall response rate and duration of response

At the time of IA2, confirmed ORR as assessed by the BIRC was statistically significantly higher in the brigatinib arm (73.7%, 95% CI: 65.52 to 80.87) compared with the crizotinib arm (61.6%, 95% CI: 52.94 to 69.74); associated odds ratio (OR) 1.73 (95% CI: 1.04 to 2.88; p=0.0342). The median duration of response (DoR) among responders in the brigatinib arm was not reached (56.4% of patients with a confirmed response were censored). Among responders in the crizotinib arm, the median DoR was 13.83 months (95% CI: 9.30 to 20.80 months). Further ORR and DoR results can be found in the CS (Section B.2.6.3.1 and B.2.6.3.2 respectively).

Intracranial overall response rate and duration of response

For patients with measurable, non-measurable, or any brain metastases at the time of IA2, confirmed intracranial ORR as assessed by BIRC was statistically significantly higher in the brigatinib arm compared to the crizotinib arm (CS, Table 16); DoR results for patients with measurable or any brain metastases are presented in the CS (Table 17).

The ERG notes that the ORs of intracranial ORR are large and 95% CIs are very wide due to the relatively small numbers of patients included in these analyses with measurable (n=41), non-measurable (n=55) or any brain metastases (n=96), and even smaller numbers of confirmed responses (n=39 confirmed intracranial responses in total). The ERG considers the magnitude of treatment effect of brigatinib over crizotinib for intracranial ORR outcomes is very uncertain.

3.4 Patient reported outcomes from the ALTA-1L trial

HRQoL data were collected during the ALTA-1L trial using the European Organisation for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30 questionnaire [v.0])[59] and the EORTC lung cancer module (QLQ-LC13 [v3.0]).[60] HRQoL was assessed at screening, on day 1 of cycle 1 (28 days per cycle), on day 1 of cycle 2, and every 4 weeks thereafter. Assessments were repeated at the end of treatment and 30 days after the last dose was taken.[52]

The EORTC QLQ-C30 questionnaire is cancer-specific and consists of five functional scales (physical, role, cognitive, emotional and social functioning), three symptom scales (fatigue, pain, and nausea and vomiting) and a HRQoL scale. The company also included six single-item scales (dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties). The QLQ-LC13[60] is used to assess lung cancer symptoms, treatment-related AEs and use of pain medication.

The ALTA-1L trial HRQoL data were mapped from the EORTC QLQ-C30 to the EuroQoL 5-dimension 3-level utility values and these utility values were used to inform the generation of the utility estimates used in the company model. The company reports (CS, p79) that the mapping process resulted in some of the statistically significant results from the EORTC QLQ-C30 and LC13 questionnaires no longer being significant.

3.4.1 Summary of EORTC QLQ-C30 and QLQ-LC13 data

HRQoL data were analysed for the patient reported outcomes (PRO)-intention-to-treat (ITT) population. To be included in the PRO-ITT population, patients in the ITT population were required to have provided a baseline global health status/quality of life (QoL) score and at least one post-baseline global health status/QoL assessment score (CS, p39). As a result, evaluable data were available from 131/137 (95.6%) patients in the brigatinib arm and from 131/138 (94.9%) patients in the crizotinib arm.

Global health quality of life and functioning scores

The company reported statistically significant improvements in the emotional and cognitive functioning scale scores with brigatinib compared to crizotinib (CS, Figure 8). Although the global health status scores and the remaining functional scale scores (physical, role, and social functioning) from the EORTC QLQ-C30 displayed trends in favour of brigatinib, compared to crizotinib none of the differences were statistically significant (CS, Figure 8).

The median time to worsening in global health status/QoL score was statistically significantly longer for patients treated with brigatinib compared with patients treated with crizotinib (Table 16).

Symptom scores

From the eight symptoms measured in the EORTC QLQ-C30 questionnaire, statistically significant differences in favour of brigatinib compared to crizotinib were reported for fatigue, nausea and vomiting, appetite loss and constipation (CS, Figure 9). There were no statistically significant differences between the brigatinib and crizotinib treatment arms for pain, dyspnoea, insomnia and diarrhoea.

Table 16 Time to worsening in the PRO-ITT population based on EORTC QLQ-C30

Scale	Median time to worsening (95% CI), months		Hazard Ratio (95% CI)	Log-rank p-value
	Brigatinib (n=131)	Crizotinib (n=131)		
Global health status/QoL[a]	26.74 (8.34 to NE)	8.31 (5.68 to 13.54)	0.70 (0.49 to 1.00)	0.0485
Functioning				
Physical	NE (13.86 to NE)	10.32 (6.51 to 17.54)	0.67 (0.47 to 0.97)	0.0505
Role	10.15 (4.30 to 21.16)	6.47 (3.88 to 9.46)	0.84 (0.61 to 1.17)	0.3562
Emotional	NE (22.18 to NE)	10.09 (7.62 to 14.78)	0.56 (0.38 to 0.81)	0.0021
Cognitive	9.30 (4.67 to 16.16)	4.47 (3.35 to 8.31)	0.75 (0.54 to 1.02)	0.0663
Social	27.20 (14.32 to NE)	4.76 (2.92 to 12.71)	0.59 (0.42 to 0.85)	0.0043
Symptoms				
Fatigue	15.64 (7.52 to NE)	4.76 (3.25 to 8.64)	0.67 (0.48 to 0.93)	0.0129
Nausea and vomiting	12.02 (3.98 to NE)	2.83 (1.87 to 5.59)	0.55 (0.40 to 0.76)	0.0002
Pain	12.06 (6.37 to 23.20)	8.08 (5.65 to 11.63)	0.82 (0.59 to 1.15)	0.3008
Dyspnoea	28.58 (10.18 to NE)	16.76 (10.15 to NE)	0.98 (0.67 to 1.43)	0.8391
Insomnia	NE (18.63 to NE)	22.11 (12.68 to NE)	0.91 (0.61 to 1.35)	0.7362
Appetite loss	NE (17.48 to NE)	9.23 (6.28 to 24.90)	0.62 (0.43 to 0.90)	0.0092
Constipation	11.99 (6.47 to NE)	2.83 (1.87 to 3.88)	0.52 (0.38 to 0.73)	<0.0001
Diarrhoea	2.07 (1.87 to 3.75)	2.79 (1.91 to 3.75)	1.00 (0.75 to 1.34)	0.9682
Other				
Financial difficulties	NE (24.94 to NE)	NE (19.35 to NE)	1.04 (0.67 to 1.62)	0.8333

Green highlighted cells represent statistically significant results in favour of brigatinib over crizotinib and red highlighted cells represent statistically non-significant results.
[a] The company defined clinically meaningful time to worsening in QoL score (0 to 100) as a decrease of ≥10 points from a patient's baseline QoL score
EORTC=European Organisation for Research and Treatment of Cancer; NE=not estimable; QLQ=Quality of Life Questionnaire; QoL=quality of life
Source: Adapted from CS, Table 19

Duration of improvement in quality of life

The company defined an improvement in global health status/QoL (0 to 100) as an increase of ≥10 points from baseline score (CS, p58). The median duration of improvement in global health status/QoL was not reached for patients treated with brigatinib and the median duration of improvement for patients treated with crizotinib was 11.99 months (95% CI: 7.72 to 17.51). The company highlighted that patients treated with brigatinib maintained their improvement in global health status/QoL over the course of treatment (CS, Figure 10).

The company considers (CS, p160) that ALTA-1L trial HRQoL results demonstrate that treatment with brigatinib results in improved HRQoL compared with treatment with crizotinib. The ERG cautions that the ALTA-1L trial is an open-label trial and patient responses to the HRQoL questionnaires may be influenced by knowledge of their assigned treatment.

3.5 Safety and tolerability results from the ALTA-1L trial

3.5.1 Summary of safety and tolerability data presented by the company

Safety and tolerability data from the ALTA-1L trial are presented in the CS (Section B.2.10). AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0.[61]

The company defined a treatment-emergent adverse event (TEAE) as any AE that started or increased in severity on or after the first dose of study drug, and no later than 30 days after the last dose (CS, p72). Treatment-related AEs were those events where causality to either treatment with brigatinib or crizotinib was established by the investigator (CS, p72).

Additional information to that presented in the main CS, including the most common TEAEs of any causality leading to dose reduction and TEAE serious adverse events (SAEs), are presented in Appendix F of the CS (Tables 22 and 23, respectively).

3.5.2 The ALTA-1L trial adverse events

A summary of AEs from the ALTA-1L trial are shown in Table 17. The median duration of treatment exposure was greater in the brigatinib arm (24.3 months) compared with the crizotinib arm (8.4 months).

The rates of Grade 3 or Grade 4 TEAEs were greater in the brigatinib arm (66.2%) than in the crizotinib arm (53.3%). Compared with the crizotinib arm, a slightly higher proportion of patients in the brigatinib arm experienced TEAEs leading to treatment discontinuations (12.5% versus 8.8%). The proportion of patients experiencing TEAEs of any cause leading to dose reductions was also greater in the brigatinib arm (38.2%) compared with the crizotinib arm

(24.8%). The company considered (CS, p73) that this difference might be due to stricter protocol-mandated dose modifications for asymptomatic laboratory abnormalities for patients treated with brigatinib (e.g., increased blood and CPK levels) than for those treated with crizotinib (CS, p77). Similar proportions of patients treated with brigatinib and crizotinib experienced at least one SAE (33.1% versus 37.2%).

Table 17 Summary of adverse events in the ALTA-1L trial

	Brigatinib (n=136)	Crizotinib (n=137)
Duration of exposure, months (range)[a]	24.3 (0.1 to 34.6)	8.4 (0.1 to 36.0)
Dose intensity (mg/day)[b]	163.83 (36.9 to 180.0)	495.64 (215.5 to 500.0)
Median relative dose intensity (range)[c]	96.89% (23.7 to 136.8)	99.12% (43.1 to 100.0)
Patients with TEAEs, n (%)	135 (99.3)	137 (100.0)
Drug related, n (%)	124 (91.2)	131 (95.6)
Grade 3 or 4, n (%)	90 (66.2)	73 (53.3)
Leading to study drug discontinuation, n (%)	17 (12.5)	12 (8.8)
Leading to dose reduction, n (%)	52 (38.2)	34 (24.8)
Patients with at least one SAEs, n (%)	45 (33.1)	51 (37.2)
Deaths within 30 days after last dose or possibly related, n (%)	9 (6.6)	11 (8.0)

SAE=serious adverse event; TEAE=treatment-emergent adverse event
[a] Time (months) on study treatment = (last non-zero dose date-first dose date + 1) / 30.4375
[b] Total cumulative dose (mg) / time (days) on study treatment
[c] Total cumulative dose (mg) administered / total dose planned × 100%
Source: CS, Table 22

Treatment-emergent adverse events

The most common TEAEs experienced by ≥10% patients in either treatment arm, or with ≥5% absolute difference between arms, are presented in the CS (Table 23).

TEAEs of any grade that occurred with a >10% higher incidence in the brigatinib arm compared with the crizotinib arm were, blood creatine phosphokinase (CPK) increases (46.3% versus 16.8%), cough (34.6% versus 19.7%), hypertension (31.6% versus 8.0%), rash (14.7% versus 2.9%) and pruritus (18.4% versus 5.1%).

TEAEs of any grade that occurred with a >10% higher incidence in the crizotinib arm compared with the brigatinib arm were, nausea (58.4% versus 30.1%), increased alanine aminotransferase (ALT) (35.0% versus 21.3%), vomiting (43.8% versus 20.6%), constipation (41.6% versus 18.4%), decreased appetite (19.0% versus 8.8%), peripheral oedema (44.5% versus 6.6%), upper abdominal pain (17.5% versus 5.9%), increased creatinine (14.6% versus 3.7%), dysgeusia (13.9% versus 2.9%), photopsia (20.4% versus 0.7%), gastroesophageal reflux disease (10.9% versus 0.7%) and visual impairment (16.8% versus 0%).

The treatment-related TEAEs occurring in the brigatinib or crizotinib arms were increased CPK (44.1% versus 15.3%), hypertension (16.9% versus 1.5%), increased lipase (22.1% versus 11.7%), increased ALT (17.6% versus 32.8%), increased amylase (17.6% versus 6.6%), peripheral oedema (2.2.% versus 34.3%), nausea (22.8% versus 50.4%), vomiting (8.8% versus 29.9%), constipation (5.9% versus 23.4%), decreased neutrophil count (1.5% versus 10.2%) and visual impairment (0.0% versus 16.8%).

In the brigatinib arm, the most frequently reported Grade 3 to Grade 5 TEAEs were increased CPK (24.3%), increased lipase (14.0%), and hypertension (11.8%). In the crizotinib arm, the most frequently reported Grade 3 to Grade 5 TEAEs were increased ALT (10.2%), increased aspartate aminotransferase (6.6%) and increased lipase (6.6%).

The ERG notes that, overall, compared with the crizotinib arm, there were fewer AEs with an incidence of >10% in the brigatinib arm. Discontinuations due to AEs were similar in both arms of the trial. The company reports that patients treated with brigatinib experienced fewer gastrointestinal AEs and SAEs than patients treated with crizotinib but experienced a higher number of elevated CPK and hypertension events.

Adverse events of special interest and deaths

The company considered early onset pulmonary events (EOPE) to be AEs of special interest. In the CS, EOPEs were interstitial lung disease or pneumonitis of any grade occurring within 14 days after commencing treatment (CS, p74). EOPEs were observed in 2.9% of patients in the brigatinib arm and in no patients in the crizotinib arm. Brigatinib was discontinued in all patients with EOPEs (as stipulated in the trial protocol).

The company highlights (CS, p74) that despite similar exposure levels, the proportion of patients experiencing EOPEs in the ALTA-1L trial (2.9%) is only half of that observed in a phase II trial[62] of brigatinib in patients previously treated with crizotinib (6.4%). In addition, a lower frequency of EOPEs (1.6%) was experienced by patients in the crizotinib arm of the ALTA-1L trial who crossed over to brigatinib after disease progression. There were no deaths from EOPEs and all events had resolved or improved at the time of the latest safety report (CS, p74).

The incidence of AEs of any cause leading to death within 30 days after the last dose of study drug was similar in both brigatinib (n=9) and crizotinib arms (n=11). The company states that none of the deaths were considered to be related to treatment.

3.5.3 ERG adverse event conclusions

The safety data in the ALTA-1L trial were generally consistent with the known safety profile of brigatinib and no new safety concerns or risks were identified.

3.6 ERG critique of the indirect evidence

3.6.1 Studies included in the indirect comparison

In the absence of a head-to-head comparison of the efficacy and safety of brigatinib versus alectinib, the company carried out a series of ITCs.

As described in Section 3.2.1 of this ERG report, the company considered that only two trials (identified via the company's systematic literature search) were eligible for inclusion in the ITCs: the ALTA-1L trial and the ALEX trial.

A network diagram for the ITCs of brigatinib versus alectinib is shown in Figure 4.

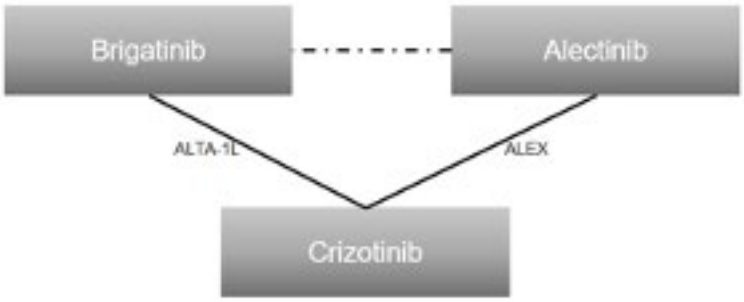

Figure 4 Network diagram of indirect comparison of brigatinib and alectinib

Key study and baseline participant characteristics of the ALTA-1L trial and the ALEX trial, as well as differences in the trial designs and methods are summarised in Section 3.2.1 of this ERG report. Quality assessments of the ALTA-1L trial and of the ALEX trial are provided in Section 3.2.3 of this ERG report. The ERG agrees with the company assessments and considers that the ALTA-1L trial and the ALEX trial are good quality trials.

3.6.2 Methodological approach to the indirect comparison

As described in Section 3.2.1 of this ERG report, the key differences, at baseline, between the ALTA-1L trial and the ALEX trial populations were the proportions of patients with brain metastases (a lower proportion in the ALTA-1L trial than in the ALEX trial) and the proportions who had received prior chemotherapy for locally advanced or metastatic NSCLC (not permitted in the ALEX trial). To account for these differences, matching-adjusted indirect comparison (MAIC) methods[63] were used by the company to compare the efficacy of brigatinib

versus alectinib. For the outcomes of BIRC-assessed PFS, OS and investigator-assessed PFS, the company presented:

(i) anchored MAICs (using the common treatment arm of crizotinib as an anchor)

(ii) unanchored MAICs (these ignore the crizotinib arms of the ALTA-1L and ALEX trials and compare data from the brigatinib arm of the ALTA-1L trial with data from the alectinib arm of the ALEX trial as if these two sets of data were from single arm trials)

(iii) an unweighted ITC (no population adjustment and using the methods described by Bucher et al[64] as a reference).

MAICs were conducted using individual participant data (IPD) from IA2 of the ALTA-1L trial and aggregate data from the ALEX trial. HRs from the ALEX trial were used in the anchored MAICs and the unweighted Bucher ITCs, while digitised Kaplan-Meier (K-M) data were used in the unanchored MAICs. A summary of the data included in the company ITCs is provided in Table 18. As ALEX trial data from different timepoints were used to inform the ITCs, the ERG considers that this adds to ITC uncertainty.

Table 18 Summary of data from the ALTA-1L and ALEX trials used in the ITCs

Trial		Outcome		
		OS	BIRC PFS	Investigator PFS
ALTA-1L (Brigatinib *vs* Crizotinib)	HR (95% CI)	0.92 (0.57 to 1.47)	0.49 (0.35 to 0.68)	0.43 (0.31 to 0.61)
	Median follow-up (data source)	24.9 months (IPD of IA2)		
ALEX (Alectinib *vs* Crizotinib)	HR (95% CI)	0.69 (0.47 to 1.02)	0.50 (0.36 to 0.70)	0.43 (0.32 to 0.58)
	Median follow-up (source of aggregate HR)	37.8 months (Text of Mok 2019[51])	18.6 months (Figure S1 of Peters 2017[39])	37.8 months (Figure 1 of Mok 2019[51])
	Median follow-up (source of KM data)	27.8 months (Figure 5 of Camidge 2018[50])		

BIRC=blinded independent review committee; CI=confidence interval; HR=hazard ratio; IA2=second interim analysis; IPD=individual participant data; K-M=Kaplan-Meier; OS=overall survival; PFS=progression-free survival
Source: Extracted and adapted from CS, Appendix D, Table 15, Table 16, Table 17

The ERG critique of the company approach to the ITCs is provided in Appendix 9.2.2 to this ERG report. In summary, the ERG considers that, in principle, given the observed differences in populations of the ALTA-1L trial and the ALEX trial, undertaking population-adjusted indirect comparisons was appropriate. The ERG also considers that it was appropriate to present an unweighted Bucher ITC of brigatinib versus alectinib, without population adjustment, to serve as a reference and to present ITC results using unadjusted OS data and RPSFTM adjusted

OS data. The ERG considers that the anchored MAICs and unweighted Bucher ITC methods seem to be correctly implemented.

The ERG considers that unanchored MAIC results should not be used for decision making as they rely on the strong assumption that all effect modifiers and prognostic factors have been accounted for and the company was not able to demonstrate that this assumption was valid for their unanchored MAICs.

The ERG agrees with the company that the company ITC methods cannot account for all of the differences between the ALTA-1L and ALEX trials (for example, different definitions of a PFS event and different follow-up times) and that these differences should be considered when interpreting ITC results.

3.6.3 Results from the company's indirect comparisons

Results from the company's anchored MAICs, unanchored MAICs and unweighted Bucher ITCs (reference) for OS (without adjustments for treatment switching), BIRC-assessed PFS and investigator assessed PFS are provided in Table 19.

Additional OS results from the company unweighted Bucher ITCs and anchored MAICs using data adjusted for different treatment crossover scenarios using RPSFTM methods (see Section 3.3.2 of this ERG report) are shown in Figure 5.

The company considered that the only prognostic factor that differed between the ALTA-1L and ALEX trial was proportions of patients in the crizotinib arm with baseline brain metastases. Further, the company highlighted that patients in the crizotinib arm of the ALTA-1L trial were permitted to switch and receive brigatinib, whilst treatment switching was not permitted in the ALEX trial. The company, therefore, carried out unanchored MAICs to explore the effect of comparing brigatinib versus alectinib as if the data were from two single arm trials. The ERG and the company acknowledge the limitations associated with unanchored MAICs (for example, that this approach breaks intra-trial randomisation), and is generally less preferred than anchored alternatives (CS, p72). The ERG also notes that the assumption underpinning an unanchored MAICs is that all effect modifiers and prognostic factors are accounted for. Failure to meet this assumption leads to unreliable unanchored MAIC results. The company was unable to demonstrate that this assumption was valid and the ERG, therefore, considers that results from the company's unanchored MAICs should not be used to inform decision making (see Appendix 9.2.2, Table 37 for further details).

Table 19 Results from the anchored MAICs, unanchored MAIC and unweighted Bucher ITCs for OS, BIRC-assessed PFS and investigator assessed PFS

Method	HR (95% CI) for brigatinib vs alectinib[a]		
	OS	BIRC PFS	Investigator PFS
Unweighted Bucher ITC	1.359 (0.741 to 2.494)	1.04 (0.652 to 1.66)	1.046 (0.669 to 1.636)
Anchored MAIC	1.21 (0.654 to 2.238)	0.969 (0.607 to 1.545)	0.965 (0.615 to 1.515)
Unanchored MAIC	0.832 (0.522 to 1.325)	0.974 (0.686 to 1.383)	0.969 (0.680 to 1.381)

[a] HR<1 implies brigatinib superior
BIRC=blinded independent review committee; CI=confidence interval; HR=hazard ratio; ITC=indirect treatment comparison; MAIC=matched adjusted indirect comparison; OS=overall survival; PFS=progression-free survival
Source: Extracted and adapted from the CS; Figure 17; Figure 18; Figure 19

The anchored MAICs and the unweighted Bucher ITCs generated similar results for BIRC-assessed PFS and investigator assessed PFS. These HRs were close to 1, indicating no statistically significant evidence, at the 5% level, that treatment with brigatinib is superior to treatment with alectinib. The ERG considers that the best available PFS estimate for the comparison of the efficacy of brigatinib versus alectinib, is the BIRC-assessed PFS HR generated by the anchored MAIC (HR 0.969; 95% CI: 0.607 to 1.545).

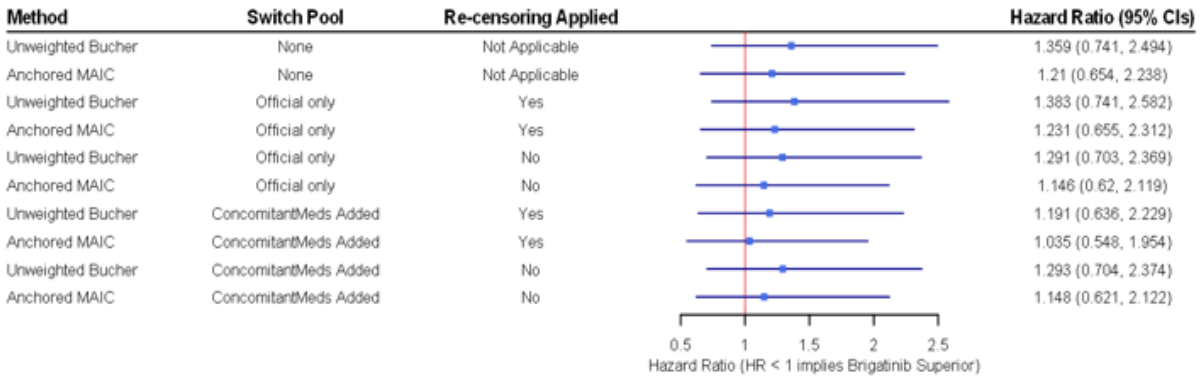

Figure 5 Brigatinib versus alectinib OS HRs: results from the anchored MAICs and unweighted Bucher ITCs with alternative treatment crossover scenarios

CI=confidence interval; HR=hazard ratio; ITC=indirect treatment comparison; MAIC=matched adjusted indirect comparison; OS=overall survival
Source: CS, Figure 20

The company OS ITC HR results ranged between 0.832 and 1.359, and the 95% CIs were wider than those for the PFS outcomes. The ERG considers this additional uncertainty likely reflects the immaturity of OS data from the ALTA-1L trial (as discussed in Section 3.3.2 of this ERG report). Furthermore, as noted in Table 18, the timepoints of ALEX trial data (and therefore the numerical estimates of OS for patients treated with alectinib used in the OS ITCs) are markedly different, which is also likely to have contributed to the differences in results generated by the OS ITCs.

The company considers that RPSFTM adjusted results (which show a deterioration of treatment effect of brigatinib versus alectinib compared to unadjusted results) are counterintuitive (CS, Section 2.9.1). The ERG considers that the brigatinib versus alectinib comparisons (estimated via population adjusted or unweighted indirect comparisons) are associated with more uncertainty than the direct comparison of brigatinib versus crizotinib; these comparisons were informed by the ALTA-1L trial data and therefore it is not straightforward to judge whether an increase or decrease in indirect OS HR following adjustment for treatment crossover is counterintuitive or not.

As discussed in Section 3.3.2 of this ERG report, the ERG considers that the best available OS estimate for the comparison of the efficacy of brigatinib versus crizotinib, at the time of IA2, is the OS HR with RPSFTM adjustment for "all switchers", without re-censoring and presented with bootstrapped 95% CIs (HR 0.871; 95% CI: 0.396 to 1.789). In line with this, whilst the ERG considers that all the company OS ITCs are unreliable, the best available OS estimate for the comparison of the efficacy of brigatinib versus alectinib is the OS HR generated by the anchored MAIC with RPSFTM adjustment for "all switchers", without re-censoring (HR 1.148; 95% CI: 0.621 to 2.122).

3.6.4 Additional indirect comparisons conducted by the ERG

Inclusion of the ALESIA trial

As noted in Table 5 of this ERG report, the ERG does not agree with the reasons provided by the company for excluding the ALESIA trial[42] from their ITCs. The ERG considers that the comparison of alectinib versus crizotinib within the ALESIA trial provides relevant efficacy evidence that can be used to inform indirect comparison of the effectiveness of brigatinib versus alectinib. The ERG has, therefore, carried out unweighted Bucher ITCs that include efficacy results from the ALTA-1L, ALEX and ALESIA trials; see Appendix 9.3 to this ERG report for further details.

Although the ERG considers that the best available PFS and OS estimates were generated by the company anchored MAICs, without access to the IPD (and data relating to prognostic factors/treatment effect modifiers) from the ALTA-1L trial, the ERG was unable to replicate or perform anchored MAICs.

The ERG unweighted Bucher ITC results for BIRC-assessed PFS and investigator assessed PFS following the inclusion of the ALESIA trial are similar to the company unweighted Bucher ITCs including only the ALTA-1L and ALEX trials (no statistically significant evidence that, at the 5% significance level, treatment with brigatinib is superior to alectinib, with HRs close to 1).

The ERG replicated the company unweighted Bucher OS ITC analyses (ALTA-1L and ALEX trial data) and carried out fixed effect (FE) and random effect (RE) OS unweighted Bucher ITCs (ALTA-1L, ALEX and ALESIA data). The HR results generated by all three of these analyses favour alectinib. However, the results using data from the two trials favour alectinib less than the results using data from the three trials (ERG replicated company unweighted Bucher OS ITC HR=1.33; ERG FE unweighted Bucher OS ITC HR=1.54; ERG RE unweighted Bucher OS ITC HR=1.910). The ERG highlights that the addition of data from the ALESIA trial increases uncertainty (the confidence intervals generated by the ERG FE and RE ITCs [three trials] were wider than the confidence intervals generated by the company unweighted Bucher ITCs [two trials]).

Inclusion of updated OS data from the ALEX trial

The ERG identified a report of an updated analyses of ALEX trial data (published in May 2020). The OS results from this analysis showed that treatment with alectinib was statistically significantly superior to treatment with crizotinib (HR=0.67, 95% CI: 0.48 to 0.98; p=0.0376).[40] BIRC-assessed and investigator-assessed PFS results from these analyses remained the same as previously published results (Table 18). The ERG acknowledges that, as the CS for this appraisal of brigatinib was sent to NICE in May 2020, the company was not able to include the updated ALEX trial OS data in their ITCs.

The ERG has included the updated alectinib versus crizotinib OS HR from the ALEX trial in additional unweighted Bucher ITCs (Appendix 9.3 to this ERG report); and results are very similar to the results company unweighted Bucher ITCs. Therefore, the ERG considers that if the company had been able to include the updated OS data from the ALEX trial in their ITCs, it is likely that results would have been similar and conclusions unchanged.

3.6.5 ERG conclusion of the indirect comparisons

The ITCs of PFS showed no statistically significant evidence that, at the 5% significance level, brigatinib is superior to alectinib, with all HRs close to 1. The ERG emphasises that due to the immaturity of the OS data from the ALTA-1L trial, reflected in the uncertainty of OS estimates provided by the different ITCs and the uncertainty around treatment switching adjustment scenarios, definitive conclusions regarding the relative OS effect of brigatinib versus alectinib (with or without adjustment for treatment switching) cannot be made.

3.7 Conclusions of the clinical effectiveness section

The company did not provide efficacy evidence for the comparison of brigatinib versus ceritinib (one of the comparators listed in the final scope issued by NICE). Market share data show that

use of ceritinib within the NHS is very low (0% to 2%)[47] and, therefore, the ERG supports the company and clinical expert views that ceritinib is not a relevant comparator.

3.7.1 Direct evidence

The ALTA-1L trial (source of evidence for the comparison of the effectiveness of brigatinib versus crizotinib) is a good quality trial. Clinical advice to the ERG is that the characteristics of the ALTA-1L trial population are generalisable to patients with ALK-positive NSCLC treated in the NHS.

ALTA-1L trial BIRC-assessed PFS was statistically significantly longer in the brigatinib arm compared to the crizotinib arm. The OS results from the ALTA-1L trial did not show (at the 5% significance level) that treatment with brigatinib was statistically significantly superior to treatment with crizotinib. However, OS data from the trial were immature (only 46.7% of the events required for the final analysis of OS had occurred). Further, OS results were confounded due to the high proportion of patients in the crizotinib arm who received brigatinib on disease progression or as a subsequent treatment. The company applied RPSFTM methods to adjust for treatment switching. Whilst these methods seem to have been implemented correctly, the available OS data were too immature to allow a robust analysis of the impact of crossover.

3.7.2 Indirect evidence

The company undertook a series of ITCs (anchored and unanchored MAICs and unweighted Bucher analyses) to generate evidence for the comparison of the effectiveness of brigatinib versus alectinib using data from the ALTA-1L and ALEX trials; anchored MAIC methods were used to account for population differences between the two trials but could not account for differences in study design. The ERG considers that undertaking population-adjusted anchored MAICs was appropriate and that presenting unweighted Bucher ITC results as a reference without population adjustment was also appropriate. The ERG considers that the anchored MAICs and unweighted Bucher ITC methods seem to be correctly implemented. The ERG considers that unanchored MAIC results should not be used for decision making as they rely on the strong assumption that all effect modifiers and prognostic factors have been accounted for and the company was not able to demonstrate that this assumption was valid for their unanchored MAICs.

The company carried out ITCs using PFS data; none of results demonstrated (at the 5% significance level) that treatment with brigatinib was statistically significantly superior to treatment with alectinib.

None of the results from the company's OS ITCs demonstrated (at the 5% significance level) that treatment with brigatinib was statistically significantly superior to treatment with alectinib., Due to the immaturity of the ALTA-1L trial data, and due to concerns regarding whether RPSFTM analyses were robust, the ERG does not consider that the results from any of the company's OS ITCs are reliable. Whilst all results are unreliable, the ERG considers that the best available OS estimate for the comparison of the efficacy of brigatinib versus alectinib is the OS HR generated by the anchored MAIC with RPSFTM adjustment for "all switchers", without re-censoring (HR 1.148; 95% CI: 0.621 to 2.122).

Clinical advice to the company and ERG was that brigatinib has a different, but comparable safety profile to alectinib.

4 COST EFFECTIVENESS EVIDENCE

This section provides a structured critique of the economic evidence submitted by the company in support of the use of brigatinib for the treatment of advanced or metastatic ALK-positive NSCLC in patients who have not previously received an ALK inhibitor. The two key components of the economic evidence presented in the CS are (i) a systematic review of the relevant literature and (ii) a report of the company's de novo economic evaluation. The company has provided a copy of the economic model, which was developed in Microsoft Excel.

4.1 Published cost effectiveness evidence

4.1.1 Objective of the company's literature searches

The company undertook systematic and targeted searches to identify studies that evaluated the cost effectiveness of treatment with brigatinib in adults with ALK-positive NSCLC in the first-line setting.

4.1.2 Company's literature searches

The searches were carried out in May 2018 and were updated in May 2019. Relevant electronic databases (MEDLINE, Embase, EconLit, NHS Economic Evaluation Database [NHS EED], Database of Abstracts and Review of Effects [DARE], and the Health Technology Assessment (HTA) database) were searched. The search terms used included combinations of keywords and medical subject headings.

Websites of key conferences, including those held by the American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO), European Lung Cancer Conference (ELCC), British Thoracic Oncology Group (BTOG), the World Conference on Lung Cancer (WCLC) and the Professional Society for Health Economics and Outcomes Research (ISPOR) were searched to identify relevant abstracts that had been published during the 3 years prior to the database searches. In addition, the websites of international HTA agencies were searched to identify appraisals or assessments of relevant therapies for ALK positive NSCLC.

Full details of the methods used by the company to identify and select cost effectiveness evidence are presented in the CS, Appendix G.

4.1.3 Eligibility criteria used in study selection

The eligibility criteria were designed to identify cost effectiveness models that had been developed for adults with advanced ALK-positive NSCLC previously untreated with a TKI.

Two researchers independently screened all publications according to title and abstract content. Any discrepancies in terms of inclusion/exclusion decisions between the researchers were resolved by a third reviewer. The same process was repeated for the full-length articles selected during the title and abstract screening process.

4.1.4 Findings from the company's cost effectiveness review

The company's selection strategy identified 30 publications: 16 partition-survival models, 10 state transition models, three budget impact models, and a study of unclear design. These publications included the NICE technology appraisals of alectinib (TA536),[31] ceritinib (TA500)[32] and crizotinib (TA406)[30] for the treatment of ALK-positive NSCLC in the first-line setting. However, none of these studies evaluated the cost effectiveness of treatment with brigatinib in adults with ALK positive NSCLC in the first-line setting.

4.1.5 ERG comments

The ERG is satisfied that the company's cost effectiveness literature searches were comprehensive and that study selection was undertaken using an appropriate process.

4.2 ERG summary of the company's submitted economic evaluation

The company developed a de novo economic model to compare the cost effectiveness of brigatinib versus crizotinib and brigatinib versus alectinib in England and Wales for the treatment of ALK-positive advanced NSCLC in adult patients naïve to ALK inhibitors. The primary outputs from the company model were ICERs per QALY gained. The company has also produced results from a cost comparison/cost minimisation of treatment with brigatinib and alectinib. The assumption underpinning this comparison is that the efficacy of alectinib is equal to that of brigatinib. The company stated that the statistically insignificant OS and PFS

results from its ITCs (Section 3.6.3) further support the assumption of equivalence between brigatinib and alectinib.

4.2.1 NICE Reference Case checklist and Drummond checklist

Table 20 NICE Reference case checklist completed by ERG

Attribute	Reference case	Does the de novo economic evaluation match the reference case?
Defining the decision problem	The scope developed by NICE	Yes
Comparator(s)	As listed in the scope developed by NICE	Partly. The company analyses only include crizotinib and alectinib; ceritinib was not included in the analyses
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and PSS	Yes
Type of economic evaluation	Cost utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes
Synthesis of evidence on outcomes	Based on systematic review	Partly. Data were primarily taken from the ALTA-1L trial and the company ITCs; the ERG has concerns about the reliability of the results from the company ITCs
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	Yes. Patient responses to the EORTC-QLQ-C30 were mapped onto EQ-5D-3L scores
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Evidence on resource use and costs	Costs should relate to the NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes
Discounting	The same annual rate for both costs and health effects (3.5%)	Yes

EORTC-QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30; EQ-5D-3L=EuroQol 5-dimensions 3-level questionnaire NHS=National Health Service; NMA=network meta-analysis; PSS=personal social services; QALY=quality adjusted life year

Source: NICE Guide to the Methods of Technology Appraisal[36]

Table 21 Critical appraisal checklist for the economic analysis completed by the ERG

Question	Critical appraisal	ERG comment
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	Partly	Effectiveness was only established for brigatinib and crizotinib. The results from the company's ITCs were too uncertain to establish the effectiveness of alectinib
Were all the important and relevant costs and consequences for each alternative identified?	Yes	
Were costs and consequences measured accurately in appropriate physical units?	Yes	
Were the cost and consequences valued credibly?	Partly	There is insufficient evidence to justify that the costs and QALYs associated with being in the PD-no-CNS health state and PD-CNS health state are different
Were costs and consequences adjusted for differential timing?	Yes	
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	
Did the presentation and discussion of study results include all issues of concern to users?	Yes	

NMA=network meta-analysis; PD-CNS=progressed disease with concurrent central nervous system progression; PD-no-CNS=progressed disease without concurrent central nervous system progression
Source: Drummond and Jefferson (1996)[65] and ERG comment

4.2.2 Population

The modelled population is adult patients with ALK-positive advanced NSCLC that has not been previously treated with an ALK inhibitor. This population is consistent with the ALTA-1L trial population and the population described in the final scope[35] issued by NICE. The starting age of the modelled cohort was 58.2 years and 45.4% of the population were male. These characteristics reflect the baseline patient characteristics of the ALTA-1L trial population.

4.2.3 Model structure

The company model structure (an area-under-the-curve partitioned survival model) is shown in Figure 6. It reflects the model structure used to inform the recent NICE appraisal of alectinib for untreated ALK-positive advanced NSCLC (TA536[31]). The company considered that patients with CNS progression (defined as the time from randomisation to the first occurrence

of disease progression in the CNS) incur a higher cost and have a lower HRQoL than those without CNS progression. The company, therefore, created a model that comprised four mutually exclusive health states: progression-free (PF), non-CNS progression (PD-no-CNS), CNS progression (PD-CNS) and death.

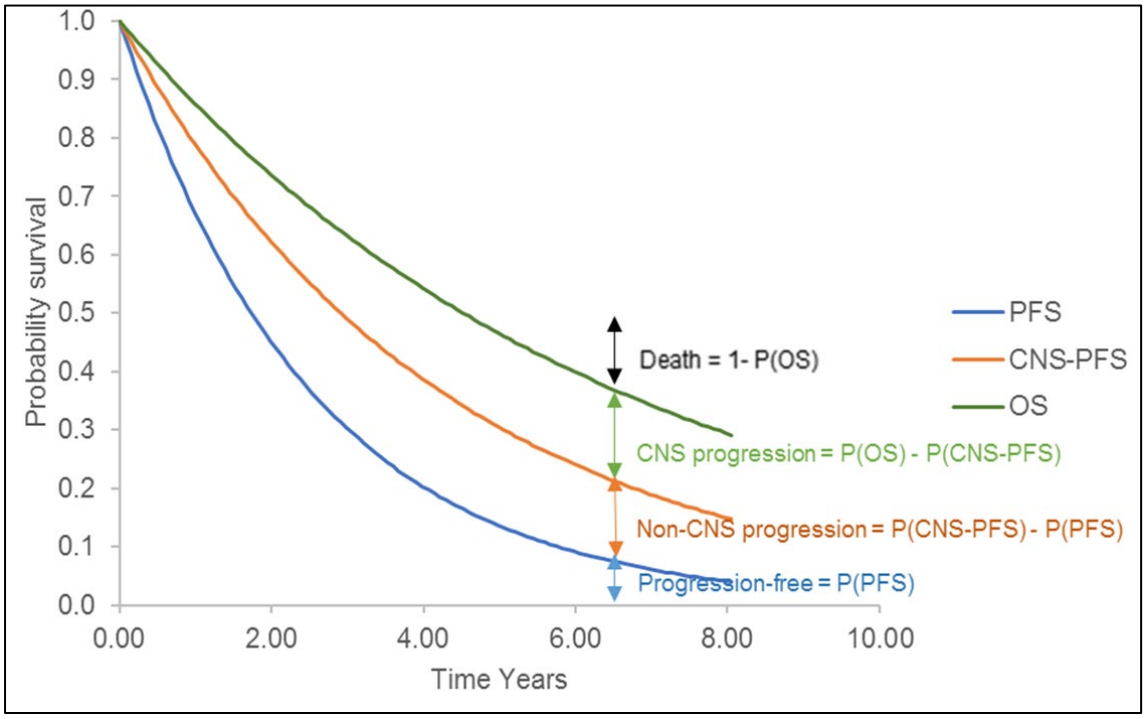

Figure 6 Structure of the company model

CNS=central nervous system; PD-CNS=progressed disease with concurrent central nervous system progression; PD-no-CNS=progressed disease without concurrent central nervous system progression; OS=overall survival; PFS=progression-free survival
Source: CS, Figure 24

4.2.4 Interventions and comparators

The intervention was brigatinib. The company considered two of the three comparators listed in the final scope[35] issued by NICE, namely crizotinib and alectinib. Ceritinib is also listed as a comparator in the final scope[35] issued by NICE. However, treatment with ceritinib was not included in the company model as clinical advice to the company, and market share data from April 2019 to January 2020,[47] suggested that the use of ceritinib as a first-line treatment for NHS patients with ALK-positive NSCLC was negligible.

The modelled doses of the first-line treatments included in the company model are provided in Table 22.

Table 22 Intervention and comparator treatment doses

	Method of administration	Modelled dose until disease progression	Source
Brigatinib	Oral	90mg once daily for the first 7 days and then 180mg once daily	SmPC[33] (and ALTA-1L trial)
Crizotinib	Oral	250mg twice daily	SmPC[66] (and ALTA-1L trial)
Alectinib	Oral	600mg twice daily	SmPC[45]

SmPC=Summary of Product Characteristics
Source: CS Table 41

4.2.5 Perspective, time horizon and discounting

The company stated that costs were considered from the perspective of the NHS and PSS. The model cycle length was 28 days and a half-cycle correction was applied. The model time horizon was set at 30 years and costs and outcomes were discounted at 3.5% per annum.

4.2.6 Treatment effectiveness and extrapolation

Brigatinib and crizotinib

The company fitted parametric distributions to ALTA-1L trial (IA2 analysis) OS, PFS BIRC and adjusted intracranial PFS K-M data to model the experience of patients treated with brigatinib and crizotinib. The intracranial PFS data were adjusted to align intracranial PFS outcomes with PFS BIRC outcomes, i.e., to remove events identified by the modified RECIST criteria that were not identified by the standard RECIST criteria. The adjusted and unadjusted intracranial PFS data were similar (CS, Figure 33).

The process used by the company to identify distributions to reflect patient experience was as follows:

- assess whether hazards were proportional (to inform whether to use stratified or independent parametric models for each treatment arm)
- fit parametric distributions (exponential, Weibull, Gompertz, gamma, log-normal and generalised gamma) to K-M data from each arm of the ALTA-1L trial
- assess fit of the parametric distributions using Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) statistics, comparison with the K-M data and experts' judgement on long-term clinical plausibility.

In the company base case, the distributions used to represent the model OS, PFS BIRC and adjusted intracranial PFS experience of patients receiving brigatinib and crizotinib were all exponential distributions.

Patients in the crizotinib arm of the ALTA-1L trial were permitted to receive brigatinib on disease progression (73 patients [61 as per trial protocol + 12 as concomitant medication], 52.9%). This is in line with current NHS practice (TA571[38]). The company considered that this might underestimate the relative OS advantage obtained from treatment with brigatinib and

explored the impact of treatment switching on base case cost effectiveness results using scenario analyses.

Modelling survival for patients receiving alectinib

To obtain survival estimates for patients treated with alectinib, the company applied HRs to brigatinib survival estimates obtained from the exponential function that was fitted to the ALTA-1L trial. The OS and PFS BIRC HRs used by the company were generated by the company's unanchored MAIC analyses. Intracranial PFS data were not publicly available from the ALEX trial and, therefore, it was not possible for the company to carry out an ITC for this outcome. The company, therefore, assumed that the adjusted intracranial PFS HR was equivalent to the BIRC-assessed PFS HR. The HRs used in the company base case are presented in Table 23.

Table 23 Hazard ratios used by the company to adjust brigatinib survival estimates to represent the survival of patients receiving alectinib

	Company unanchored MAIC HRs (95% CI)
OS	0.832 (0.522 to 1.325)
PFS BIRC	0.974 (0.686 to 1.383)
Adjusted intracranial PFS	0.974 (0.686 to 1.383)

BIRC=blinded independent review committee; CI=confidence interval; HR=hazard ratio; OS=overall survival; PFS=progression-free survival; MAIC=matched adjusted indirect comparison
Source: CS, Section B.3.3.7

4.2.7 Adverse events

Grade 3+ AEs occurring in ≥3% of patients in the brigatinib and crizotinib arms of the ALTA-1L trial,[49] and the alectinib arm of the ALEX trial,[39] were used to represent the experience of patients treated with brigatinib, crizotinib and alectinib respectively. The company assumed that, for all treatments, AEs only occurred whilst patients were receiving first-line treatment and that they lasted for one model cycle (28-days). The AE rates that were used in the model are presented in the CS (Table 37).

4.2.8 Health-related quality of life

Patients in the ALTA-1L trial completed the EORTC-QLQ-C30[59] at days 1, 8, and 15 of the first 28-day cycle and then every 4 weeks until (and including at) treatment discontinuation, and then 30 days post-treatment discontinuation. Patient responses to the EORTC-QLQ-C30 were mapped onto EQ-5D-3L scores using the Longworth et al[67] algorithm.

A regression equation that used baseline EQ-5D-3L score, Grade ≥3 AEs, treatment response (complete response, partial response, stable disease and progressed disease) as covariates was then used to estimate pre-progression (0.793) and post-progression (0.624) health state utility values, and a Grade ≥3 AE utility decrement (-0.037) (see Table 24).

The company highlighted that since HRQoL data were only collected within the ALTA-1L trial until 30 days after the last dose of first-line ALK inhibitor, the data used to calculate the post-progression utility value did not reflect patient experience during progression. The company, therefore, applied multipliers obtained from published studies to their post-progression utility values generated by the regression model. The following multipliers were used:

- 75.4% (95% CI: 73.9% to 76.8%) to reflect CNS progression (Roughley et al[68])
- 90.2% (95% CI: 88.5% to 91.9%) to reflect receipt of chemotherapy (Blackhall et al[69])
- 70.3% (95% CI: 69.0% to 71.6%)to reflect receipt of BSC (Nafees et al[70]).

The company stated that applying multipliers from external data sources was in line with NICE DSU TSD 12.[71] The health state utility values used in the company model are shown in Table 24.

Table 24 Utility values used in the company model

	Health states	Utility value (95% CI)	Source
Utility Values	Pre-progression	0.793 (0.774 to 0.812)	Mapped utility values from the ALTA-1L trial
	Progressed disease	0.624 (0.582 to 0.665)	
	CNS Progressed*		
	Brigatinib	0.543 (0.528 to **0.558**)*	Calculation based on mapped utility values from the ALTA-1L trial and multipliers from the literature
	Crizotinib	0.529 (0.511 to **0.550**)*#	
	Alectinib	0.539 (0.523 to **0.554**)*	
	Non-CNS Progressed*		
	Brigatinib	0.552 (0.536 to **0.567**)*	Calculation based on mapped utility values from the ALTA-1L trial and multipliers from the literature
	Crizotinib	0.568 (0.542 to **0.593**)*#	
	Alectinib	0.550 (0.533 to **0.566**)*	
Utility decrements	≥1 Grade 3+ AE	-0.037 (-0.046 to -0.029)	Mapped utility values from the ALTA-1L trial
	Age	-0.0003 (NA)	Ara et al[72]

*=mean values are reported in the table whilst upper bound values (**in bold**) were used in the model; #=values in the company model differ from those in the company submission, reported values in the table are those used in the company model
AE=adverse event; BSC=best supportive care; CNS=central nervous system NA=not available
Source: CS, Table 40

4.2.9 Resource use and costs

The cost categories included in the company model were:

- first-line treatment acquisition and administration costs
- subsequent treatment acquisition and administration costs
- health state resource use costs
- concomitant drug costs
- AE treatment costs.

First-line treatment acquisition and administration costs

Brigatinib, crizotinib and alectinib have been made available to the NHS at confidential PAS discount prices; however, the PAS discounts for crizotinib and alectinib are not known to the company.

The company model includes the option to account for dose interruption or reduction using a relative dose intensity (RDI) multiplier. The RDI multipliers for brigatinib (85.51%) and crizotinib (91.73%) were derived from ALTA-1L trial data, and the value for alectinib (95.60%) was obtained from the NICE STA of alectinib (TA536[31]). In the base case, the company assumed that the NHS would be able to save half of the costs associated with the RDIs; this assumption reflects a model amendment made by the ERG responsible for appraising the evidence for NICE TA571[38] (treatment with brigatinib after crizotinib for ALK-positive advanced NSCLC), which was supported by the NICE AC for that appraisal. Therefore, the actual RDIs used in the company model for brigatinib, crizotinib and alectinib were 92.76%, 97.80% and 95.87% respectively.

Brigatinib, crizotinib and alectinib are all administered orally. The company applied a £9 drug dispensing cost per cycle to account for pharmacist time (12 minutes). Details of the intervention and comparator drug acquisition costs are presented in Table 25.

Table 25 Drug acquisition costs used in the company model

Drug	Dosage	Pack information (units per pack)	Model cycle	Cost per pack (Source)	RDI (Source)	Cost per 28-day cycle
Brigatinib	90mg once daily for the first 7 days and then 180mg once daily	90mg (28 tablets)	Cycle 1: day 1 to 7	[redacted] (Takeda UK)	92.76% (ALTA-1L trial)	[redacted]
Brigatinib		180mg (28 tablets)	Cycle 1: day 8 to 28	[redacted] (Takeda UK)		[redacted]
Brigatinib		180mg (28 tablets)	Subsequent cycles			[redacted]
Crizotinib	250mg twice daily	250mg (60 capsules)	All cycles	£4,689 (BNF 2020[73])	97.80% (ALTA-1L trial)	£4,195
Alectinib	600mg twice daily	200mg (224 capsules)	All cycles	£5,032 (BNF 2020[73])	95.87% (TA536[31])	£4,921

BNF=British National Formulary; mg=milligram; RDI=relative dose intensity
Source: CS, Table 41

Subsequent treatment drug acquisition and treatment costs

Modelled treatment following brigatinib and alectinib was based on clinical expert opinion and assumptions used in the NICE STA of alectinib (TA536[31]). The proportions of patients receiving first-line crizotinib, who subsequently received brigatinib or ceritinib were obtained from the company's analysis of UK market share data (averages across sales from November

2019 to February 2020),[47] whilst the sources of estimates for other treatments were expert opinion and TA536.[31]

Subsequent ALK inhibitors (i.e., brigatinib and ceritinib) and nintedanib are oral therapies. These treatments were modelled to incur an administration cost of £9 per cycle to account for pharmacist time. The per cycle administration cost associated with subsequent treatment with an immunotherapy (atezolizumab) or chemotherapy was the NHS Reference Cost associated with administration of more complex parenteral therapy (£306.90 NHS Reference code: SB13Z[74]).

Company model subsequent treatment (acquisition and administration) costs per cycle are provided in Table 26.

Table 26 Per cycle subsequent treatment and administration costs

Subsequent treatment	First-line treatment					
	Brigatinib		Crizotinib		Alectinib	
	%	Cost	%	Cost	%	Cost
ALK inhibitor	0%	£0	84%	[redacted]	0%	£0
Immunotherapy	5%	£32	5%	£25	5%	£42
VEGF-R (nintedanib)	5%	£5	5%	£4	5%	£7
Chemotherapy	50%	£154	30%#	£49	50%	£205
BSC	100%	£438	100%	£350	100%	£427
Total		£628		[redacted]		£681
Source of estimates	TA536[31] and expert opinion		Market share information (ALK inhibitors), TA536 and expert opinion		TA536[31] and expert opinion	

#=value in the CS (30%) differs from the value (20%) used in the company model, reported values in the table are those used in the company model; ALK=anaplastic lymphoma kinase; BSC=best supportive care; VEGF-R=vascular endothelial growth factor
Source: CS, Table 45 and Table 50

Resource use by health state

In the company model, patient resource use varied depending on first-line treatment status (i.e., on- or off-treatment), and CNS progression status (i.e., with or without CNS progression). A summary of model resource use and costs is provided in Table 27.

In the base case, the company assumed that patients were treated until progression and, therefore, on-treatment related to the PF-health state and off-treatment related to the PD health state. Resource use inputs used to inform TA536[31] were validated during two advisory boards organised by the company (one in February 2019 and the other in January 2020).

The company calculated the PF and PD-no-CNS health states costs per cycle to be £290 and £452, respectively. Compared to the PD-no-CNS health state, patients in the PD-CNS health state incurred an additional cost for the management of CNS progression. The types and

levels of resource use required to manage CNS progression were obtained from TA536.[31] Further, clinical advice to the company was that 10% of patients would require steroid therapy, 50% would require stereotactic radiotherapy (SRS), 5% would require whole brain radiotherapy (WBRT) and 5% would require surgical resection. The company applied a one-off cost of £11,979 to account for SRS, WBRT and surgical resection to new patients entering the PD-CNS health state. A per cycle cost of £1.84 for steroid therapy was also applied to all patients in the PD-CNS health state. Full details of the health state cost calculations are provided in the CS (Section B.3.5.3).

Table 27 Model resource use and costs

Item	Unit cost	Source	Progression-free health state		Post-progression health states	
			Freq per month	% of patients	Freq per month	% of patients
First cycle*						
Oncology outpx	£244.84	Ref cost (2018/19): WF01B[74]	1.00	100%	0.00	0%
Full blood test	£2.79	Ref cost (2018/19): DAPS05[74]	1.00	100%	0.00	0%
Biochemistry	£1.10	Ref cost (2018/19): DAPS04[74]	1.00	100%	0.00	0%
Total per cycle*				**£229**		**£0**
Subsequent cycles*						
Oncology outpx	£147.97	Ref cost (2018/19): WF01C[74]	0.75	100%	1.25	100%
GP visit	£39.00	PSSRU (2019/19): 9.22 minutes consultation[75]	1.00	10%	1.00	50%
Cancer nurse	£98.74	Ref cost (2018/19): N10AF[74]	1.00	50%	1.50	80%
Full blood test	£2.79	Ref cost (2018/19): DAPS05[74]	1.00	100%	1.50	100%
Biochemistry	£1.10	Ref cost (2018/19): DAPS04[74]	1.00	100%	1.50	100%
CT scan	£88.81	Ref cost (2018/19): weighted average of RD20A-C, RD21A-C and RD22Z[74]	0.50	100%	0.75	100%
MRI	£217.49	Ref cost (2018/19): RD03Z[74]	0.20	50%	0.50	80%
X-ray	£30.59	Ref cost (2018/19): DAPF[74]	0.30	50%	0.50	60%
ECG	£76.10	Ref cost (2018/19): RD51A[74]	1.00	100%	0.00	0%
Total per cycle*				**£290**		**£452**

*=A month is 30.43 days and cycle length is 28 days so cost per month is lower than cost per cycle.
CT=computerised tomography; ECG=electro-cardiogram; Freq=frequency; GP=general practitioner; MRI=magnetic resonance imaging; Outpx=outpatient; PSSRU=Personal Social Services Research Unit; Ref cost=National Health Service Reference Costs
Source: Extracted from CS, Table 42, Table 43 and Table 44

Adverse event costs

Unit costs obtained from the 2018/2019 NHS Schedule of Reference Costs[74] and TA536[31] (see CS, Table 52) were applied to the AE rates that were used in the model (see CS, Table 37). The company estimated the per cycle cost of treating AEs associated with brigatinib, crizotinib and alectinib were £10.08, 18.03 and £4.15, respectively. The model did not include any costs associated with treating AEs associated with subsequent treatments.

Other costs

Concomitant medications received by ≥10% of patients in the ALTA-1L trial were costed and these costs were applied every cycle during the PF health state. The cost of concomitant medications for patients treated with brigatinib was £85.67 and that for patients treated with crizotinib was £111.11. The cost of concomitant medications for patients treated with alectinib was assumed to be the same as that for patients treated with brigatinib. The company also applied a one-off end of life/terminal care cost of £1,772[75] 8 weeks before death to account for palliative/terminal care costs.

5 COST EFFECTIVENESS RESULTS

5.1 Company base case analysis

The company pairwise base case ICERs per QALY gained are shown in Table 28 and fully incremental analysis is shown in Table 29. The company used the confidential PAS discount price when costing treatment with brigatinib. List prices were used for all other treatments.

Table 28 Base case pairwise cost effectiveness results versus brigatinib (brigatinib PAS price)

Treatment	Total cost	Total LYG	Total QALYs	Incremental			Incremental cost per QALY gained
				Cost	LYG	QALYs	
Brigatinib	[redacted]	5.868	[redacted]				
Crizotinib	[redacted]	5.610	[redacted]	[redacted]	0.26	[redacted]	Dominated by brigatinib
Alectinib	[redacted]	5.072	[redacted]	[redacted]	0.80	[redacted]	Dominated by brigatinib

LYG=life years gained; PAS=Patient Access Scheme; QALY=quality adjusted life year
Source: CS, Table 55

Table 29 Base case fully incremental cost effectiveness results (brigatinib PAS price)

Treatment	Total cost	Total QALYs	Incremental		Incremental cost per QALY gained
			Cost	QALYs	
Brigatinib	[redacted]	[redacted]			
Crizotinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by brigatinib
Alectinib*	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by brigatinib

LYG=life years gained; PAS=Patient Access Scheme; QALY=quality adjusted life year
*=alectinib is compared with brigatinib in fully incremental analysis since crizotinib is already dominated by brigatinib
Source: ERG calculations

The company also presented results from a cost comparison analysis (brigatinib versus alectinib). This analysis relied on assumption that the effectiveness (OS, PFS and intracranial PFS) of these two treatments was the same (Table 30).

Table 30 Base case cost comparison of brigatinib versus alectinib (brigatinib PAS price)

Treatment	Total cost	Incremental cost
Brigatinib	[redacted]	
Alectinib	[redacted]	-£104,579

PAS=Patient Access Scheme
*=Total cost for alectinib in the cost comparison analysis is different to the total cost for alectinib cost in the cost effectiveness analysis because the effectiveness of alectinib is equivalent to the effectiveness of brigatinib in the cost comparison analysis
Source: CS, Table 57

5.2 Deterministic sensitivity analyses

Results from the company's deterministic one-way sensitivity analyses (OWSAs) for the comparison of treatment with brigatinib versus crizotinib showed that using the upper and lower bound costs of subsequent treatments for patients receiving crizotinib had the greatest impact on the magnitude of the company base case cost effectiveness results (Figure 7).

For treatment with brigatinib versus alectinib, using the upper and lower bound 95% CI of the BIRC-assessed PFS HR had the greatest impact on the magnitude of the company base case cost effectiveness results (Figure 8).

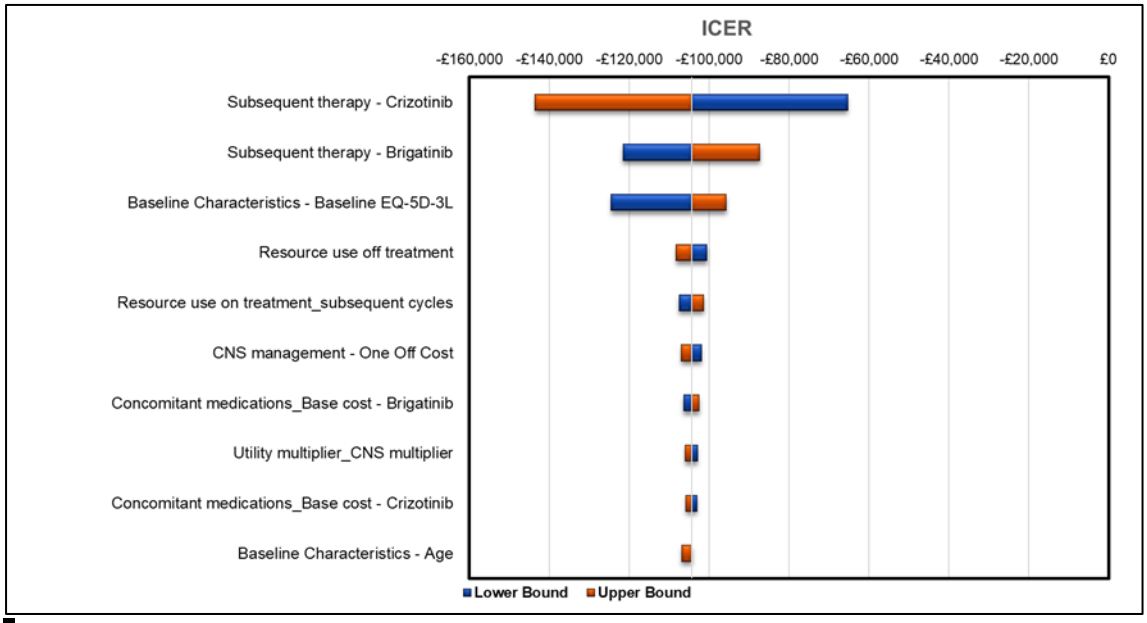

Figure 7 Tornado diagram showing OWSA results for the comparison of treatment with brigatinib versus crizotinib

CNS=central nervous system; EQ-5D-3L=EuroQol-5 Dimensions-3 Levels; ICER=incremental cost effectiveness ratio
Source: CS, Figure 53

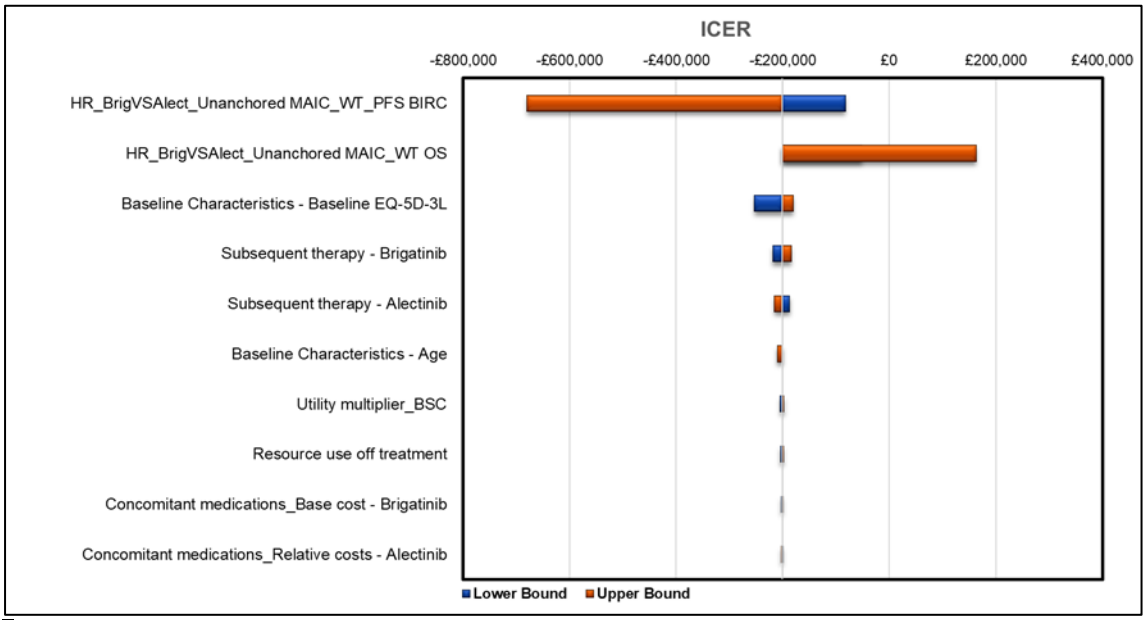

Figure 8 Tornado diagram showing OWSA results for the comparison of treatment with brigatinib versus alectinib

BrigVSAlect=brigatinib versus alectinib; BSC=best supportive care; EQ-5D-3L=EuroQol-5 Dimensions-3 Levels; HR=hazard ratio; ICER=incremental cost effectiveness ratio; MAIC=matched-adjusted indirect comparison; OS=overall survival
Source: CS, Figure 55

5.3 Probabilistic sensitivity analyses

The company carried out a probabilistic sensitivity analysis (PSA). Results (means from 10,000 iterations) are reproduced in Table 31. Using the PAS discounted price of brigatinib, treatment with brigatinib dominated treatment with crizotinib and alectinib. The company estimated that the probability of brigatinib being a cost effective treatment option at a willingness-to-pay threshold of £30,000 per QALY gained was 100% (see CS, Figure 52).

Table 31 Probabilistic cost effectiveness results (brigatinib PAS price)

Treatment	Total cost	Total LYG	Total QALYs	Incremental			Incremental cost per QALY gained
				Cost	LYG	QALYs	
Brigatinib	[redacted]	[redacted]	[redacted]				
Crizotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by brigatinib
Alectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by brigatinib

LYG=life years gained; QALY=quality adjusted life year
Source: Company model

5.4 Scenario analyses

The company explored 61 alternative scenarios (CS, Table 63) for the comparison of treatment with brigatinib versus crizotinib and brigatinib versus alectinib. Treatment with brigatinib was the preferred option in all of the scenarios.

5.5 Model validation

The company stated that they sought advice from clinical experts during the model development process (advisory boards in February 2019 and January 2020). Additionally, the model was quality assured through the NICE PRIMA review process[76] and through external quality checking processes.

6 ERG CRITIQUE OF THE COMPANY MODEL

6.1 Overview

The ERG commends the company for producing a model that is easy to understand and, except for a discrepancy between the utility values presented in the CS and those used in the model, accurately represents the model structure and parameter values described in the CS.

The company has presented ICERs per QALY gained for the comparison of the cost effectiveness of brigatinib versus crizotinib, and for the comparison of brigatinib versus alectinib. The company has also carried out a cost minimisation analysis comparing the cost of brigatinib with the cost of alectinib. The ERG highlights that as alectinib has now been recommended by NICE as a treatment option for patients with ALK-positive advanced NSCLC that has not been previously treated with an ALK-inhibitor, alectinib rather than crizotinib is now standard of care in the NHS. Hence, a comparison of the cost effectiveness of brigatinib versus crizotinib is not relevant when determining whether brigatinib is a cost effective option for patients treated in the NHS.

The main driver of uncertainty around model cost effectiveness results is the validity of the OS estimates used in the model. The company has used ALTA-1L trial OS K-M data as the basis for estimating OS for patients treated with brigatinib and crizotinib. To obtain OS estimates for patients treated with alectinib, the company has applied the HR generated by their unanchored MAIC to their brigatinib OS estimates. As outlined in Section 3.6.3 (further details provided in Appendix 9.2.2), the ERG does not consider that unanchored MAIC estimates are suitable for decision making. The ERG also identified four other areas of concern:

- Using PFS to model time on treatment
- Modelling utility values
- Partitioning of the progressed disease health state
- Assumption that the effects of treatment with brigatinib, and with alectinib, last for a lifetime.

At IA2 (28 June 2019), only 70 deaths had occurred in the ALTA-1L trial. This represents 25% of the trial population and 46.7% of the approximately 150 OS events required for the final analysis of ALTA-1L trial OS data (trial protocol,[37] Section 15.5.3 and Table 10). Given the immaturity of the ALTA-1L trial OS data and the uncertainty around the results from the company's ITCs, it is not possible to generate robust OS estimates. Robust OS data are required to generate robust cost effectiveness results; the ERG has, therefore, not identified a preferred ICER per QALY gained. Summary details of the ERG's critique of the main aspects of the company model are provided in Table 32.

Table 32 ERG company model economic critique summary

Aspect considered	ERG comment	Section of ERG report (if appropriate)
Population	• The ERG is satisfied that the population in the model is consistent with the population described in the final scope issued by NICE and the ALTA-1L trial except for prior use of chemotherapy • There are key differences between the ALTA-1L trial and the ALEX trial populations that are important for the comparison of brigatinib versus alectinib	6.1 and 6.1.1
OS	• The company base case brigatinib and crizotinib OS estimates were chosen using appropriate methods • The ALTA-1L trial data are immature and have not shown that brigatinib and crizotinib are statistically significantly different; however, the company has modelled a difference in OS • Alectinib OS estimates were generated by applying the OS HR result from the unanchored MAIC ITC (using data from the ALTA-1L and ALEX trials) to the company brigatinib OS estimates • Only the company unanchored OS MAIC showed that brigatinib was numerically superior to alectinib (this difference was not statistically significant) • The ERG considered that the unanchored MAIC is associated with strong assumptions that are not suitable for decision making	6.1.1
PFS	• The company base case brigatinib and crizotinib PFS estimates were chosen using appropriate methods • The ERG does not have any concerns about how the company generated PFS estimates for patients treated with alectinib	NA
Intracranial PFS	• The company base case brigatinib and crizotinib intracranial PFS estimates were chosen using appropriate methods • There are other specific types of extrapulmonary progression that may also incur very specific costs and QALYs, which have not been explored by the company • The implication of partitioning PD health state on OS has also not been explored	6.1.4
ToT	• The company used PFS to model ToT for brigatinib, crizotinib and alectinib • The company did not explore the use of ToT K-M data from the ALTA-1L trial to represent treatment duration for patients treated with brigatinib, crizotinib and alectinib	6.1.3
Resource use	• The ERG does not have any concerns about how the company modelled resource use	NA
Utility values	• The methods used by the company to estimate the utility values used in the company model are in line with the NICE Reference Case • The model is populated by upper bound rather than mean utility values • The evidence base for the CNS multiplier is weak	6.1.2 and 6.1.4
AE costs	• The ERG does not have concerns about how the company has modelled costs associated with AEs	NA
PSA	• The ERG does not have any concerns about how the company's PSA was conducted	NA

AE=adverse event; CNS=central nervous system; ERG=Evidence Review Group; HR=hazard ratio; HRQoL=health-related quality of life; ITC=indirect treatment comparison; MAIC=matched adjusted indirect comparison; NA=not applicable; OS=overall survival; PD=progressed disease; PFS=progression-free survival; PSA=probabilistic sensitivity analysis; QALY=quality adjusted life year; ToT=time on treatment

6.1.1 Modelling overall survival

Brigatinib versus crizotinib

Data from the ALTA-1L trial (brigatinib versus crizotinib) showed that the difference between the trial arms is not statistically significant (HR=0.92; 95% CI: 0.57 to 1.47). Since the ALTA-1L trial protocol permitted patients in the crizotinib arm to crossover and receive brigatinib on disease progression, the lack of a statistically significant difference in OS may, at least in part, be due to crossover. The ERG agrees with the company that the OS data from ALTA-1L trial are too immature for it to be possible to statistically account for the effect of crossover (46.7% mature). The ERG also supports the company decision to populate their model with OS data that had not been adjusted for crossover (rather than adjusted OS data) as using adjusted data would only have introduced further uncertainty into model results.

The company extrapolated ALTA-1L trial brigatinib OS K-M data using an exponential function and ALTA-1L trial crizotinib OS K-M data using a different exponential function. The ERG considers that, as trial OS results did not demonstrate that the effectiveness of brigatinib and crizotinib was statistically significantly different, a difference should not have been modelled. The ERG has, therefore, generated model results using the same (brigatinib) OS estimates for patients treated with brigatinib and for patients treated with crizotinib. It is important to stress that the ERG does not consider that the available evidence supports the conclusion that OS for the two treatments are the same; this scenario illustrates the impact on cost effectiveness of not modelling an OS advantage for brigatinib over crizotinib when there is insufficient evidence to demonstrate that such an advantage exists. Implementing this alternative scenario resulted in brigatinib remaining dominant by being [redacted] cheaper and generating more QALYs ([redacted]) than crizotinib.

Brigatinib versus alectinib

The ALEX trial is an RCT that compared the clinical effectiveness of alectinib versus crizotinib. In the absence of direct evidence, the company conducted ITCs using data derived from the ALTA-1L and the ALEX trials. Results from only one of the company's OS ITCs (the unanchored MAIC) showed that treatment with brigatinib was numerically, but not statistically significantly, superior to alectinib. Other company OS ITCs numerically favoured alectinib, although these results were not statistically significant. Whilst the company chose to use results from their unanchored MAIC to estimate OS for patients treated with alectinib, neither the company nor the ERG has confidence in the results from any of the company's OS ITCs. Further, the ERG considers that if results from the company OS ITCs do not provide robust point estimates, then it follows that the confidence intervals around the point estimates are also not robust. Whilst, the ERG has not undertaken any scenario analyses using alternative

OS HRs, using the 11 different OS ITC HR result options available in the company model, the base case ICERs for the comparison of brigatinib versus alectinib range from £147,222 (incremental cost and QALY= [redacted] and [redacted] QALYs respectively; ITC approach=unadjusted Bucher, "official switchers", with re-censoring) to £1,520,162 (incremental cost and QALY= [redacted] and [redacted] QALYs respectively; ITC approach=anchored MAIC, "all switchers", with re-censoring).

Recognising the weaknesses of the ITC evidence (Section 3.6.3; further details provided in Appendix 9.2.2), the company undertook a cost minimisation analysis. The company considered that the cost minimisation analysis should be the primary analysis for decision making. The company's argument that a cost minimisation approach is appropriate, rests on two claims:

- Clinical advice to the company was that brigatinib and alectinib are similar
- The wide overlapping confidence intervals for brigatinib versus alectinib for the outcomes considered in the company ITCs show there is no difference in these outcomes.

Whilst the ERG does not dispute the first argument presented by the company, the company ITCs have not demonstrated, at the 5% level, that brigatinib is statistically significantly superior to alectinib. This is not the same as providing statistical evidence that there is no difference between the two treatments (or that brigatinib is non-inferior to alectinib). Wide confidence intervals cannot be interpreted as evidence of similarity between treatments but rather can only be interpreted as a measure of uncertainty.

Failure to assess equivalence or non-inferiority before undertaking a cost minimisation analysis introduces the risk that an inferior treatment to standard of care could be preferred on price alone, without properly assessing the trade-off associated with any differences in efficacy. As conclusions about non-inferiority and superiority are conclusions about the relative effectiveness of treatments, the same level of confidence in the evidence is required irrespective of choice of economic evaluation method employed (i.e., a cost utility or cost minimisation analysis).

During clarification, the ERG asked the company to carry out a non-inferiority test of brigatinib versus alectinib (question A15 of the clarification letter), in order to provide statistical evidence that brigatinib was non-inferior to alectinib for PFS and OS. The company did not carry out this test and provided the following reasons in their response to the clarification letter:

- It is difficult to reject the hypothesis that brigatinib is non-inferior to alectinib because neither the ALTA-1L trial nor the ALEX trial were designed to conduct non-inferiority assessments, and both of the trials have relatively small sample sizes
- There are differences between ALTA-1L and ALEX trial population that cannot be accounted for in a non-inferiority test
- There is no Decision Support Unit guidance on setting a non-inferiority margin and that the margin would likely be wide.

The ERG recognises that non-inferiority testing of brigatinib versus alectinib would be difficult to carry out using available data. However, without a non-inferiority test result, there is no statistical evidence to support the conclusion that brigatinib and alectinib are sufficiently similar to justify carrying out a cost minimisation analysis.

The ERG considers that any assessment of the cost effectiveness of brigatinib versus alectinib can only be speculative at this time. As the data from the ALTA-1L trial become more mature, the uncertainty around the OS benefit of brigatinib versus crizotinib may reduce as the impact of crossover becomes more accurately estimated as more OS events occur. This would mean that the anchored MAIC adjusted for crossover may provide a more robust assessment of the comparative assessment of the effectiveness of brigatinib versus alectinib.

6.1.2 Model utility values

The ERG identified errors in the algorithms used to generate utility values in the company model. The company base case incremental QALYs resulting from using the upper bound and mean utility values are shown in Table 33. Irrespective of which utility values are used in the model, brigatinib dominates crizotinib (incremental cost=[redacted]; incremental QALYs=[redacted]) and dominates alectinib (incremental cost=[redacted]; incremental QALYs=[redacted]).

Table 33 Incremental QALYs resulting from using different utility estimates

Comparison	Incremental QALYs	
	Upper bound values	Mean values
Brigatinib versus crizotinib	[redacted]	[redacted]
Brigatinib versus alectinib	[redacted]	[redacted]

QALY=quality adjusted life year
Source: Values generated using the company model

6.1.3 Time on treatment

The company has used PFS as a proxy for ToT, i.e., has assumed that patients receiving brigatinib, crizotinib and alectinib are treated until disease progression. The ERG notes that data from the ALTA-1L trial show that this approach underestimates the cost of treatment with brigatinib and overestimates the cost of treatment with crizotinib (see Figure 9).

The ERG has modelled ToT for patients treated with brigatinib and crizotinib by using ToT K-M data up to 24 months followed by an exponential function. As ToT K-M data were not available for patients treated with alectinib, the ERG used brigatinib ToT estimates to represent the experience of patients treated with alectinib.

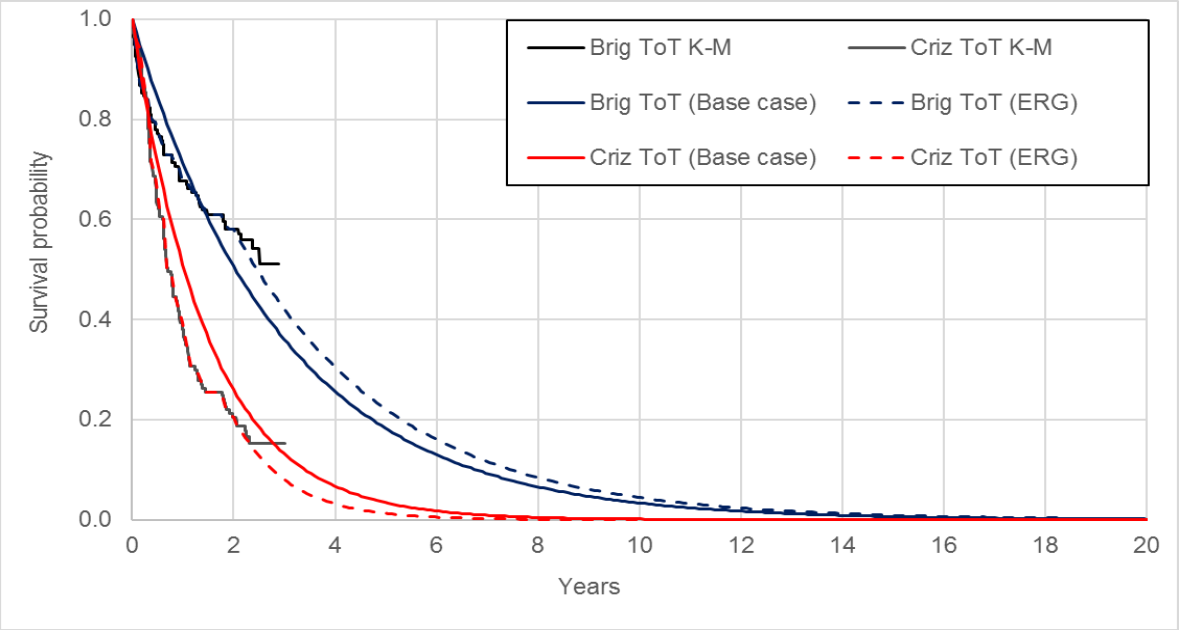

Figure 9 Progression-free survival and time on treatment curves for brigatinib and crizotinib: from company base model and from the ALTA-1L trial with appended exponential function

Brig=brigatinib; criz=crizotinib; ERG=evidence review group; K-M=Kaplan-Meier; PFS=progression-free survival; ToT=time on treatment
Source: Constructed from data in the company model

When ALTA-1L trial ToT K-M data were extrapolated and used to model ToT for patients treated with brigatinib and crizotinib, incremental results showed that treatment with brigatinib remained cost saving ([redacted]) and more effective ([redacted] QALYs) than crizotinib, i.e., brigatinib remained the dominant treatment.

When ALTA-1L trial ToT data were extrapolated and used to model ToT for patients treated with brigatinib and alectinib, incremental results showed that treatment with brigatinib remained cost saving ([redacted]) and more effective ([redacted] QALYs) than alectinib, i.e., brigatinib remained the dominant treatment.

6.1.4 Partitioning progressed disease

The company has partitioned the PD health state into a PD-no-CNS health state and a PD-CNS health state to reflect their assumption that costs and HRQoL differ between patients with and without CNS progression. Whilst it is clinically plausible that patients with CNS progression have a lower HRQoL and incur more costs than those without, the company has

not explored other specific types of extrapulmonary progression (e.g. bone metastasis) that may also incur very specific costs and QALYs. Further, the company has not explored the impact of CNS progression on OS. The ERG considers that if PFS is partitioned, then OS should also be partitioned.

In addition, the ERG considers that the utility values chosen by the company to represent the experience of patients in the PD-CNS health state are not robust. The company has assumed that CNS progression leads to a 75.4% (the CNS multiplier) reduction in HRQoL (CS, Section B.3.4.6). This assumption is based on data included in an abstract[68] that reported results from a cross-sectional survey of patients with metastatic NSCLC in France and Germany. These data showed that the EQ-5D score (mean score=0.52; n=29) for patients with brain metastases was lower than that for patients with contralateral lung metastasis (mean score=0.69; n=111). In addition to the small number of patients with brain metastases reported in the survey, the ERG notes that treatment-related AEs, comorbidities and age i.e., factors that may be responsible for the observed difference in HRQoL, were not reported. The limited information available from the abstract[68] precludes further investigation of the reliability of the CNS multiplier used by the company.

The ERG considers that there is insufficient evidence to partition the PD health state, or to apply robust utility weights to the PD-CNS health state.

When the effect of partitioning was removed from the company model, treatment with brigatinib still dominated crizotinib (incremental cost=[redacted]; incremental QALYs=[redacted]) and alectinib (incremental cost=[redacted]; incremental QALYs=[redacted]).

6.1.5 Lifetime duration of treatment effect

In the company base case, the mortality, disease progression and CNS progression rates for patients treated with brigatinib were lower than the same rates for patients treated with crizotinib or alectinib for the whole model time horizon. To explore the impact of relaxing this assumption, the company carried out scenarios in which the treatment effect of brigatinib and alectinib waned such that mortality rates associated with all three treatments became equal to that of crizotinib before the end of the model time horizon. The ERG considers that the OS treatment waning scenarios carried out by the company were flawed as PFS and intracranial PFS treatment effects were not waned.

There is considerable uncertainty around the best way to estimate the duration of treatment effect. This cannot be resolved using data from the ALTA-1L trial, the ALEX trial or other published studies. Even if the duration of treatment could be estimated, further uncertainty

remains around the appropriate approach to implementing treatment waning within a partitioned survival model. Given the subjectivity around modelling treatment effect waning, the ERG has run two scenarios where OS, PFS and intracranial PFS HRs for patients treated with brigatinib and alectinib become equal after 3 years and 5 years. The results from these two scenarios showed that treatment with brigatinib continued to dominate crizotinib and alectinib by being cheaper (incremental cost: 3-year waning=[redacted]; 5-year waning=[redacted]) and more effective (incremental QALYs: 3-year waning= [redacted]; 5-year waning=[redacted]). Brigatinib also dominated alectinib with incremental costs of [redacted] (3-year waning) and [redacted] (5-year waning) and incremental QALYs of [redacted] and [redacted].

6.2 Impact on the ICER of additional clinical and economic analyses by the ERG

The ERG corrected the utility value error and then carried out the following scenarios:

- S1: In the comparison of brigatinib versus crizotinib, set OS estimates for crizotinib to be the same as the OS estimates for brigatinib (obtained from exponential function fitted to OS data from the ALTA-1L trial). The OS HR for the comparison of brigatinib versus alectinib was too uncertain to be considered in an ERG scenario analysis

- S2: Model duration of treatment by appending exponential functions to ALTA-1L trial brigatinib and crizotinib ToT K-M data (brigatinib estimates used to represent the experience of patients receiving alectinib)

- S3: Remove CNS-based partitioning of PFS

- S4: Set the effect of treatment waning on OS, PFS and intracranial PFS to apply to all patients who had been treated with brigatinib and were alive at 3 years

- S5: Set the effect of treatment waning on OS, PFS and intracranial PFS to apply to all patients who had been treated with brigatinib and were alive at 5 years.

Details of how the ERG implemented the scenarios in the company model are presented in Appendix 9.4 of this ERG report). The cost effectiveness results from these scenarios are provided in Table 34 (brigatinib versus crizotinib) and Table 35 (brigatinib versus alectinib). These results have been generated using the PAS price for brigatinib and list prices for all other drugs. Results using the discounts for all drugs are provided in a confidential appendix.

Table 34 ERG scenarios for the comparison of brigatinib versus crizotinib (confidential PAS discount for brigatinib)

Scenarios	Brigatinib			Crizotinib			Incremental			*ICER*
	Cost	Life Years	QALYs	Cost	Life Years	QALYs	Cost	Life Years	QALYs	£/QALY
A. Company base case	[redacted]	***5.868***	[redacted]	***£179,660***	***5.610***	[redacted]	[redacted]	***0.258***	[redacted]	***Brigatinib dominates***
B. Corrected company base case	[redacted]	***5.868***	[redacted]	***£179,660***	***5.610***	[redacted]	[redacted]	***0.258***	[redacted]	***Brigatinib dominates***
S1) Use of brigatinib OS estimates for crizotinib OS estimates	[redacted]	5.868	[redacted]	£182,713	5.868	[redacted]	[redacted]	0.000	[redacted]	Brigatinib dominates
S2) Use ToT to model treatment duration for brigatinib and crizotinib	[redacted]	5.868	[redacted]	£162,158	5.610	[redacted]	[redacted]	0.258	[redacted]	Brigatinib dominates
S3) Remove partitioning of PD health state	[redacted]	5.868	[redacted]	£173,256	5.610	[redacted]	[redacted]	0.258	[redacted]	Brigatinib dominates
S4) 3-year duration of treatment effect (OS, PFS and intracranial PFS)	[redacted]	5.716	[redacted]	£179,660	5.610	[redacted]	[redacted]	0.105	[redacted]	Brigatinib dominates
S5) 5-year duration of treatment effect (OS, PFS and intracranial PFS)	[redacted]	5.761	[redacted]	£179,660	5.610	[redacted]	[redacted]	0.151	[redacted]	Brigatinib dominates

ICER=incremental cost effectiveness ratio; OS=overall survival; PAS=patient access scheme; PFS=progression-free survival; PD=progressed disease; ToT=time on treatment; QALY=quality adjusted life year

Table 35 ERG scenarios for the comparison of brigatinib versus alectinib (confidential PAS discount for brigatinib)

Scenarios	Brigatinib			Alectinib			Incremental			*ICER*
	Cost	Life Years	QALYs	Cost	Life Years	QALYs	Cost	Life Years	QALYs	£/QALY
A. Company base case	[redacted]	***5.868***	[redacted]	***£222,160***	***5.072***	***3.424***	[redacted]	***0.796***	[redacted]	***Brigatinib dominates***
B. Corrected company base case	[redacted]	***5.868***	[redacted]	***£222,160***	***5.072***	***3.334***	[redacted]	***0.796***	[redacted]	***Brigatinib dominates***
S1) Use of brigatinib OS estimates for crizotinib OS estimates	-	-	-	-	-	-	-	-	-	-
S2) Use ERG brigatinib ToT estimates to model treatment duration for brigatinib and alectinib	[redacted]	5.868	[redacted]	£237,637	5.072	3.422	[redacted]	0.796	[redacted]	Brigatinib dominates
S3) Remove partitioning of PD health state	[redacted]	5.868	[redacted]	£221,006	5.072	3.430	[redacted]	0.796	[redacted]	Brigatinib dominates
S4) 3-year duration of treatment effect (OS, PFS and intracranial PFS)	[redacted]	5.716	[redacted]	£206,534	5.366	3.484	[redacted]	0.349	[redacted]	Brigatinib dominates
S5) 5-year duration of treatment effect (OS, PFS and intracranial PFS)	[redacted]	5.761	[redacted]	£215,996	5.268	3.482	[redacted]	0.494	[redacted]	Brigatinib dominates

ERG=Evidence Review Group; ICER=incremental cost effectiveness ratio; OS=overall survival; PAS=patient access scheme; PFS=progression-free survival; PD=progressed disease; ToT=time on treatment; QALY=quality adjusted life year

6.3 Conclusions of the cost effectiveness section

Brigatinib vs crizotinib

The ERG agrees with the company that the most relevant cost effectiveness comparison is brigatinib versus alectinib, as alectinib is the standard of care in the NHS. The ALTA-1L trial crizotinib results are confounded by crossover (RPFSTM adjustments are considered unreliable). The ERG has not, therefore, generated a preferred ICER per QALY gained.

Brigatinib vs alectinib

Given the immaturity of the company OS data and the unreliability of the results from the company's ITCs, the ERG considers that it is not possible to generate robust OS estimates or generate robust cost effectiveness results. The ERG has not, therefore, generated a preferred ICER per QALY gained.

The ERG considers that the cost minimisation analysis results presented by the company should not be used to inform decision making as the company has not established that the effectiveness of brigatinib is equal or non-inferior to the effectiveness of alectinib.

7 END OF LIFE CRITERIA

A technology meets NICE End of Life criteria if (i) the treatment is indicated for patients with a short life expectancy, normally less than 24 months and (ii) there is sufficient evidence to indicate that the treatment offers an extension to life, normally of a least an additional 3 months compared with current NHS treatment.

The ERG considers that the company has (appropriately) not put forward a case for brigatinib to be considered under NICE's End of Life treatment criteria. The median OS was not reached at 24 months in either the brigatinib or crizotinib arms of the ALTA-1L trial. Further, the results from the ALTA-1L trial have not shown that brigatinib statistically significantly improves life expectancy versus crizotinib. The results from the company's OS ITCs are too uncertain for the company and the ERG to conclude that brigatinib improves OS versus alectinib.

8 REFERENCES

1. Cancer Research UK. Lung cancer statistics. Published date: 02 April 2020; Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer. Accessed June 2020.
2. Royal College of Physicians. National Lung Cancer Audit Annual report 2018 (for the audit period 2017). Published date: May 2019; Available from: https://www.rcplondon.ac.uk/projects/outputs/nlca-annual-report-2018. Accessed June 2020.
3. Cancer Research UK. Lung Cancer: Symptoms of advanced cancer. Published date: 21 November 2019; Available from: https://www.cancerresearchuk.org/about-cancer/lung-cancer/advanced/symptoms. Accessed June 2020.
4. NIH National Cancer Institute. Non-small cell lung cancer treatment (PDQ®)–Health professional version. Published date: 7 May 2020; Available from: https://www.cancer.gov/types/lung/hp/non-small-cell-lung-treatment-pdq. Accessed June 2020.
5. National Comprehensive Cancer Network (NCCN). Non-small cell lung cancer. NCCN Clinical Practice Guidelines in Oncology. 2020; Available from: https://www.nccn.org/professionals/physician_gls/default.aspx. Accessed June 2020.
6. Gainor JF, Varghese AM, Ou S-HI, Kabraji S, Awad MM, Katayama R*, et al.* ALK rearrangements are mutually exclusive with mutations in EGFR or KRAS: an analysis of 1,683 patients with non-small cell lung cancer. Clin Cancer Res. 2013; 19:4273-81.
7. Wong DW-S, Leung EL-H, So KK-T, Tam IY-S, Sihoe AD-L, Cheng L-C*, et al.* The EML4-ALK fusion gene is involved in various histologic types of lung cancers from nonsmokers with wild-type EGFR and KRAS. Cancer. 2009; 115:1723-33.
8. Koivunen JP, Mermel C, Zejnullahu K, Murphy C, Lifshits E, Holmes AJ*, et al.* EML4-ALK fusion gene and efficacy of an ALK kinase inhibitor in lung cancer. Clin Cancer Res. 2008; 14:4275-83.
9. Gubens M, Wong W, Wu N, Chu L, Schulze K, Illei P. Real-world patient characteristics, testing, and treatment patterns of ALK+ NSCLC. J Thorac Oncol; IASLC 18th World Conference on Lung Cancer, Yokohama, Japan. 2017. p. P1.01-008.
10. Tao H, Cai Y, Shi L, Tang J, Liu Z, Wang Z*, et al.* Analysis of clinical characteristics and prognosis of patients with anaplastic lymphoma kinase-positive and surgically resected lung adenocarcinoma. Thorac Cancer. 2017; 8:8-15.
11. Chia PL, Mitchell P, Dobrovic A, John T. Prevalence and natural history of ALK positive non-small-cell lung cancer and the clinical impact of targeted therapy with ALK inhibitors. Clin Epidemiol. 2014; 6:423-32.
12. Koh Y, Kim D, Kim T, Lee S-H, Jeon Y, Chung D*, et al.* Clinicopathologic characteristics and outcomes of patients with anaplastic lymphoma kinase-positive advanced pulmonary adenocarcinoma. J Thorac Oncol. 2011; 6 (5):905-12.
13. Subramanian J, Morgensztern D, Goodgame B, Baggstrom M, Gao F, Piccirillo J*, et al.* Distinctive characteristics of non-small cell lung cancer (NSCLC) in the young: A surveillance, epidemiology, and end results (SEER) analysis. J Thorac Oncol. 2010; 5:23-8.
14. Rangachari D, Yamaguchi N, VanderLaan PA, Folch E, Mahadevan A, Floyd SR*, et al.* Brain metastases in patients with EGFR-mutated or ALK-rearranged non-small-cell lung cancers. Lung Cancer. 2015; 88:108-11.
15. Guérin A, Sasane M, Zhang J, Culver KW, Dea K, Nitulescu R*, et al.* Brain metastases in patients with ALK+ non-small cell lung cancer: clinical symptoms, treatment patterns and economic burden. J Med Econ. 2015; 18:312-22.
16. Kuijpers C, Hendriks LEL, Derks JL, Dingemans AC, van Lindert ASR, van den Heuvel MM*, et al.* Association of molecular status and metastatic organs at diagnosis

in patients with stage IV non-squamous non-small cell lung cancer. Lung Cancer. 2018; 121:76-81.
17. Martín C, Cardona AF, Zatarain-Barrón ZL, Ruiz-Patiño A, Castillo O, Oblitas G*, et al.* Real-world treatment patterns, survival, and prediction of CNS progression in ALK-positive non-small-cell lung cancer patients treated with first-line crizotinib in Latin America oncology practices. Oncology. 2018; 94:297-305.
18. Johung KL, Yeh N, Desai NB, Williams TM, Lautenschlaeger T, Arvold ND*, et al.* Extended survival and prognostic factors for patients with ALK-rearranged non-small-cell lung cancer and brain metastasis. J Clin Oncol. 2016; 34:123-9.
19. Sperduto PW, Kased N, Roberge D, Xu Z, Shanley R, Luo X*, et al.* Summary report on the graded prognostic assessment: an accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases. J Clin Oncol. 2012; 30:419-25.
20. Zhang I, Zaorsky NG, Palmer JD, Mehra R, Lu B. Targeting brain metastases in ALK-rearranged non-small-cell lung cancer. Lancet Oncol. 2015; 16:e510-e21.
21. Mezquita L, Planchard D. The role of brigatinib in crizotinib-resistant non-small cell lung cancer. Cancer Manag Res. 2018; 10:123-30.
22. National Institute for Health and Care Excellence (NICE). Medtech innovation briefing: HTG EdgeSeq ALKPlus Assay EU for ALK status testing in non-small-cell lung cancer. Published date: 7 November 2017; Available from: www.nice.org.uk/advice/mib128. Accessed June 2020.
23. 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:v1-v27.
24. Royal College of Physicians. Spotlight audit on molecular testing in advanced lung cancer 2019 (for diagnoses in 2017). Published date: 7 January 2020; Available from: https://www.rcplondon.ac.uk/projects/outputs/spotlight-audit-molecular-testing-advanced-lung-cancer-2019-diagnoses-2017. Accessed June 2020.
25. Gandhi L, Rodríguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F*, et al.* Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med. 2018; 378:2078-92.
26. National Institute for Health and Care Excellence (NICE). Crizotinib for previously treated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer. Technology appraisal guidance 422 [TA422]. Published date: 21 December 2016; Available from: https://www.nice.org.uk/guidance/ta422. Accessed June 2020.
27. National Institute for Health and Care Excellence. Brigatinib for treating ALK-positive non-small-cell lung cancer after crizotinib [ID1328]. Final appraisal document. Published date: February 2019; Available from: https://www.nice.org.uk/guidance/gid-ta10268/documents/final-appraisal-determination-document. Accessed June 2020.
28. Peters S, Zimmermann S. Management of resistance to first-line anaplastic lymphoma kinase tyrosine kinase inhibitor therapy. Curr Treat Options Oncol. 2018; 19:37.
29. Itchins M, Chia PL, Hayes SA, Howell VM, Gill AJ, Cooper WA*, et al.* Treatment of ALK-rearranged non-small cell lung cancer: A review of the landscape and approach to emerging patterns of treatment resistance in the Australian context. Asia Pac J Clin Oncol. 2017; 13 Suppl 3:3-13.
30. National Institute for Health and Care Excellence (NICE). Crizotinib for untreated anaplastic lymphoma kinase-positive advanced non small-cell lung cancer. Technology appraisal guidance [TA406] Published date: 28 September 2016; Available from: https://www.nice.org.uk/guidance/ta406. Accessed June 2020.
31. National Institute for Health and Care Excellence (NICE). Alectinib for untreated ALK-positive advanced non-small-cell lung cancer. Technology appraisal guidance [TA536] Published date: 08 August 2018; Available from: https://www.nice.org.uk/guidance/ta536. Accessed June 2020.

32. National Institute for Health and Care Excellence (NICE). Ceritinib for untreated ALK-positive nonsmall-cell lung cancer. Technology appraisal guidance [TA500]. Published date: 24 January 20182018; Available from: https://www.nice.org.uk/guidance/ta500. Accessed June 2020.
33. Takeda Pharmaceuticals Inc. Summary of Product Characteristics: Alunbrig. 2018. Published date: 24 April 2020; Available from: https://www.medicines.org.uk/emc/product/9691/smpc#. Accessed June 2020.
34. Howlader N, Noone A, Krapcho M, Miller D, Brest A, Yu M*, et al.* SEER Cancer Statistics Review, 1975-2016. Published date: April 2020; Available from: https://seer.cancer.gov/csr/1975_2016/. Accessed June 2020.
35. National Institute for Health and Care Excellence. Brigatinib for ALK-positive advanced non-small-cell lung cancer that has not been previously treated with an ALK inhibitor. Final scope. Published 05 May 2020; Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10351/documents. Accessed June 2020.
36. National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013. Published date: 04 April 2013; Available from: https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781. Accessed June 2020.
37. Camidge DR, Kim HR, Ahn MJ, Yang JC, Han JY, Lee JS*, et al.* Brigatinib versus crizotinib in ALK-positive non-small-cell lung cancer. N Engl J Med. 2018; 379:2027-39.
38. National Institute for Health and Care Excellence (NICE). Brigatinib for treating ALK-positive advanced non-small-cell lung cancer after crizotinib. Technology appraisal guidance [TA571]. Published date: 20 March 2019; Available from: https://www.nice.org.uk/guidance/ta571. Accessed June 2020.
39. Peters S, Camidge D, Shaw A, Gadgeel S, Ahn J, Kim D*, et al.* Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. N Engl J Med. 2017; 377:829-38.
40. Mok T, Camidge DR, Gadgeel SM, Rosell R, Dziadziuszko R, Kim DW*, et al.* Updated overall survival and final progression-free survival data for patients with treatment-naive advanced ALK-positive non-small-cell lung cancer in the ALEX study. Ann Oncol. 2020; S0923-7534:39796-9.
41. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD*, et al.* The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011; 343.
42. Zhou C, Kim S-W, Reungwetwattana T, Zhou J, Zhang Y, He J*, et al.* Alectinib versus crizotinib in untreated Asian patients with anaplastic lymphoma kinase-positive non-small-cell lung cancer (ALESIA): a randomised phase 3 study. Lancet Respir Med. 2019; 7:437-46.
43. Hida T, Nokihara H, Kondo M, Kim YH, Azuma K, Seto T*, et al.* Alectinib versus crizotinib in patients with ALK-positive non-small-cell lung cancer (J-ALEX): an open-label, randomised phase 3 trial. Lancet. 2017; 390:29-39.
44. Soria JC, Tan DSW, Chiari R, Wu YL, Paz-Ares L, Wolf J*, et al.* First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study. Lancet. 2017; 389:917-29.
45. Roche Registration GmbH. Annex I Summary of product characteristics Alecensa 150 mg hard capsules. Published date: 19 June 2020; Available from: https://www.ema.europa.eu/en/documents/product-information/alecensa-epar-product-information_en.pdf. Accessed June 2020
46. National Institute for Health and Care Excellence (NICE). Alectinib for untreated anaplastic lymphoma kinase positive advanced nonsmall-cell lung cancer [ID925]. Committee Papers [TA536]. Published date: 28 June 2018; Available from:

https://www.nice.org.uk/guidance/ta536/documents/committee-papers Accessed June 2020.
47. Takeda UK Ltd. Data on file: UK/DOF/BRIG/20/004. Data on File in support of the following claim: Brigatinib market share data (Mar 2019-Feb 2020)2020.
48. ClinicalTrialsRegister.eu. 2013-004133-33: Randomized, multicenter, phase III, open-label study of alectinib versus crizotinib in treatment-naive anaplastic lymphoma kinase-positive advanced non−small cell lung cancer. Published date: 23 February 2018; Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2013-004133-33/results Accessed July 2020.
49. Camidge R, Kim HR, Ahn MJ, Yang JCH, Han JY, Hochmair MJ*, et al.* Brigatinib vs crizotinib in patients with ALK inhibitor naive advanced ALK+ NSCLC: updated results from the phase III ALTA-1L trial. ESMO Asia Congress 2019; Singapore. Ann Oncol. 2019; 30 (Suppl 9):ix183-ix202.
50. Camidge DR, Peters S, Mok T, Gadgeel SM, Cheema PK, Pavlakis N*, et al.* Updated efficacy and safety data from the global phase III ALEX study of alectinib(AL) versus crizotinib(CZ) in untreated advanced ALK+ NSCLC. J Clin Oncol. 2018; 36:9043.
51. Mok T, Shaw AT, Camidge DR, Gadgeel SM, Rosell R, Dziadziuszko R*, et al.* Final PFS, updated OS and safety data from the randomised phase III ALEX study of alectinib (ALC) versus crizotinib (CRZ) in untreated advanced ALK+ NSCLC. ESMO 2019 Barcelona, Spain. Ann Oncol. 2019; 30 (Suppl 5):v602-v660.
52. Takeda UK Ltd. Data on file: AP26113-13-301 Clinical Study Report (Interim Analysis 2, 9 December 2019). 2019.
53. Takeda UK Ltd. Data on file: AP26113-13-301 Clinical Study Protocol (version 3.0, 17 May 2018). 2018.
54. Takeda UK Ltd. Data on file: AP26113-13-301 Statistical Analysis Plan (version 4.0, 19 August 2019). 2019.
55. Takeda UK Ltd. Data on file: AP26113-13-301 Statistical Analysis Plan (version 2.0, 18 February 2018). 2018
56. Takeda UK Ltd. Data on file: AP26113-13-301 Statistical Analysis Plan (version 3.0, 27 March 2018). 2018.
57. Latimer N, White I, Abrams K, Siebert U. Causal inference for long-term survival in randomised trials with treatment switching: should re-censoring be applied when estimating counterfactual survival times? Stat Methods Med Res. 2019; 28:2475-93.
58. Takeda UK Ltd. Data on file: UK/DOF/BRIG/20/003 in support of the following claim: Intracranial PFS in the ITT population for brigatinib versus crizotinib. 2020.
59. European Organisation for Research and Treatment of Cancer. EORTC QLQ-C30 reference values. Published July 2008; Available from: https://www.eortc.org/app/uploads/sites/2/2018/02/reference_values_manual2008.pdf. Accessed June 2020.
60. Bergman B, Aaronson NK, Ahmedzai S, Kaasa S, Sullivan M. The EORTC QLQ-LC13: a modular supplement to the EORTC Core Quality of Life Questionnaire (QLQ-C30) for use in lung cancer clinical trials. EORTC Study Group on Quality of Life. Eur J Cancer. 1994; 30a:635-42.
61. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Published date: 14 June 2010; Available from: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_40. Accessed June 2020.
62. Kim D-W, Tiseo M, Ahn M-J, Reckamp K, Hansen K, Kim S-W*, et al.* Brigatinib in patients with crizotinib-refractory anaplastic lymphoma kinase–positive non–small-cell lung cancer: A randomized, multicenter phase II trial. J Clin Oncol. 2017; 35:1-9.
63. Phillippo DM, Ades AE, Dias S, Palmer S, Abrams KR, Welton NJ. NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submissions to NICE. Published date: December 2016; Available from: http://www.nicedsu.org.uk Accessed June 2020.

64. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect comparisons in meta-analysis of randomised controlled trials. J Clin Epi. 1997; 50:683-91.
65. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. BMJ. 1996; 313:275-83.
66. Pfizer Limited. Summary of product characteristics (SmPC) Xalkori (crizotinib) 200 mg hard capsules. Published date: 12 December 2019: European Medicines Agency (EMA),; Available from: https://www.medicines.org.uk/emc/product/2857/smpc. Accessed June 2020.
67. Longworth L, Yang Y, Young T, Mulhern B, Hernandez Alava M, Mukuria C*, et al.* Use of generic and condition-specific measures of health-related quality of life in NICE decision-making: a systematic review, statistical modelling and survey. Health Technol Assess. 2014; 18:1-224.
68. 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.
69. Blackhall F, Ross Camidge D, Shaw AT, Soria JC, Solomon BJ, Mok T*, et al.* Final results of the large-scale multinational trial PROFILE 1005: efficacy and safety of crizotinib in previously treated patients with advanced/metastatic ALK-positive non-small-cell lung cancer. ESMO open. 2017; 2:e000219.
70. Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non small cell lung cancer. Health Qual Life Outcomes. 2008; 6:84.
71. Ara R, Wailoo A. NICE DSU Technical Support Document 12: The use of health state utility values in decision models. Published date: July 2011; Available from: http://nicedsu.org.uk/wp-content/uploads/2016/03/TSD12-Utilities-in-modelling-FINAL.pdf. Accessed June 2020.
72. Ara R, Brazier J. Using health state utility values from the general population to approximate baselines in decision analytic models when condition-specific data are not available. Value Health. 2011; 14:539-45.
73. British National Formulary (BNF). Medicines Complete. Published date: 17 June 2020; Available from: https://www.medicinescomplete.com/mc/bnf/64/. Accessed June 2020.
74. Department of Health and Social Care. NHS Reference Costs 2018/19. Published date: 10 February 2020; Available from: https://improvement.nhs.uk/resources/national-cost-collection/. Accessed June 2020.
75. Curtis L. Unit Costs of Health and Social Care 2018/19. Published date: December 2019; Available from: https://www.pssru.ac.uk/project-pages/unit-costs/. Accessed June 2020.
76. National Institute for Health and Care Excellence (NICE). PReliminary Independent Model Advice (PRIMA). Published date: 20 March 2020; Available from: https://www.nice.org.uk/about/what-we-do/life-sciences/scientific-advice/prima. Accessed June 2020.
77. Latimer N, Abrams K. NICE DSU Technical Support Document 16: Adjusting survival time estimates in the presence of treatment switching. Published date: July 2014; Available from: http://www.nicedsu.org.uk Accessed June 2020.
78. White I, Babiker A, Walker S, Darbyshire J. Randomization-based methods for correcting for treatment changes: examples from the Concorde trial. Stat Med. 1999; 18:2617-34.
79. Miladinovic B, Chaimani A, Hozo I, Djulbegovic B. Indirect treatment comparison. Stata J. 2014; 14:76-86.

9 APPENDIX

9.1 Appendix 1: Additional evidence presented by the company

9.1.1 Summary of clinical evidence: comparators

Table 36 Baseline patient characteristics for the ALEX trial (ITT population)

Baseline characteristic	Alectinib (N=152)	Crizotinib (N=151)
Age, years		
Mean (SD)	56.3 (12.0)	53.8 (13.5)
Median (range)	58.0 (25-88)	54.0 (18-91)
Sex, N (%)		
Female	84 (55)	87 (58)
Race, N (%)		
Asian	69 (45)	69 (46)
Non-Asian	83 (55)	82 (54)
Brain metastasis at baseline, N (%)		
	64 (42)	58 (38)
Prior chemotherapy for locally advanced/metastatic disease, N (%)		
	0 (0)	0 (0)
Prior whole-brain radiotherapy, N (%)		
	17 (11.2)	16 (10.6)
ECOG performance status, N (%)		
0 or 1	142 (93)	141 (93)
2	10 (7)	10 (7)
Cigarette smoking history, N (%)		
Never	84 (61.3)	75 (54.3)
Former	50 (36.5)	56 (40.6)
Current	3 (2.2)	7 (5.1)
Current stage of disease, N (%)		
IIIB	4 (3)	6 (4)
IV	148 (97)	145 (96)

ECOG=Eastern Cooperative Oncology Group; SD=standard deviation
Source: Adapted from Peters 2017[39]

9.2 Appendix 2: ERG critiques of company methodological approaches

9.2.1 Adjustment of OS data to account for treatment cross-over in the ALTA-1L trial

To adjust for the confounding of the OS data at IA2 due to crossover, the company performed treatment switching analyses using Rank Preserving Structural Failure Time Model (RPSFTM) methods. A summary and an ERG assessment of the company approach is provided in Table 37.

Table 37 ERG summary and critique of statistical approaches used to account for treatment cross-over in the ALTA-1L trial

Item	ERG assessment	Approach	ERG comments
Were treatment switchers clearly defined?	Yes (as 'official switchers' and as 'all switchers')	61 patients from the crizotinib arm (44.2% of the 138 patients randomised to the crizotinib arm and 82.4% of the 74 patients who experienced disease progression on the crizotinib arm) were recorded as "official switchers" according to the protocol definition of the crossover phase of the ALTA-1L trial (trial protocol, Section 11 and Table 4).[37] The company identified an additional 12 patients who switched from crizotinib to brigatinib and 11 patients who switched from brigatinib to crizotinib after considering subsequent therapies (CS, Table 7). Therefore, "all switchers" included a total of 84 patients, 52.9% of the 138 patients randomised to the crizotinib arm and 98.6% of the 74 patients who experienced disease progression on the crizotinib arm crossed over to brigatinib and 8.8% of the 137 patients randomised to the brigatinib arm and 22.2% of the 54 patients who experienced disease progression on the brigatinib arm crossed over to crizotinib. The company has presented RPSFTM adjusted OS HRs for "official switchers" and also for "all switchers."	The ERG agrees it is appropriate to present results for both sets of "switchers" and considers that OS HRs which are adjusted for "all switchers" are the most comprehensive when considering all crossover between brigatinib and crizotinib. The ERG notes that the RPSFTM OS HRs are adjusted only for switching between brigatinib and crizotinib and these adjusted OS HRs do not account for other subsequent treatments received by patients (including any additional treatments received by "official switchers" in the ALTA-1L trial (CS, Table 7).
Was an appropriate method used?	Yes	In Appendix L to the CS (Section L.1.1.1), the company outlines the rationale for choosing RPSFTM out of the four treatment switching adjustment methods described in DSU TSD 16:[77] The four methods described in TSD 16[77] are RPSFTM, Inverse Probability of Censoring Weights, Two Stage Method (following progression), and Iterative Parameter Estimation approach.	The ERG agrees that, for this appraisal, the RPFSTM method is the most appropriate of the four methods considered and that the company has implemented the RPSFTM method appropriately (Appendix L to the CS, Section L.1.1.2 and response to clarification question A9)

Item	ERG assessment	Approach	ERG comments
	Yes	The company implemented the RPSFTM method with and without re-censoring. It has been shown that censoring of counterfactual survival times (i.e., the survival times that would have been observed in the absence of treatment switching) estimated via RPSFTM methods may be related to prognostic factors and are informative.[77,78] Therefore, re-censoring of counterfactual survival times at an earlier time point related to the magnitude of treatment effect (i.e., the larger the treatment effect, the earlier the re-censoring time-point) avoids informative censoring. However, if the re-censoring time is less than the event time, that patient has their survival time recensored and their event is no longer observed. This leads to a loss of longer-term survival information which is likely to be detrimental to extrapolation of survival data in the context of an economic model.[77]	The ERG considers it was appropriate for the company to implement the RPSFTM with and without re-censoring. Given the limited available OS data available from the ALTA-1L, the ERG considers that the RPSFTM adjusted OS HRs without re-censoring are the most appropriate for decision making, to avoid any information loss from an already limited number of OS events due to re-censoring.[57] However, the ERG notes that any potential bias associated with informative censoring should be carefully considered when using RPSFTM adjusted OS HRs without re-censoring.
Were modelling assumptions assessed and shown to be valid?	Yes	RPSFTM is a randomisation-based method.[77] In other words, RPSFTM methods require the assumption that the only difference between randomised groups is the treatment received.	The ERG is satisfied that this assumption is met for the ALTA-1L trial with patient characteristics of the brigatinib and crizotinib groups balanced by randomisation.
	No	RPSFTM methods also assume a "common treatment effect";[77] in other words, the relative treatment effect is the same for all participants with respect to time on treatment, regardless of whether the treatment was received or was received following treatment crossover. The company states that this assumption "remains unvalidated" (Appendix L to the CS, Section L.1.1.2) and acknowledges that this assumption may be "flawed" and may contribute to counterintuitive results (CS, Section B.3.3.5.2).	The ERG acknowledges this assumption is difficult to formally test using OS data. Clinical advice to the ERG is that this "common treatment effect" assumption is unlikely to hold for brigatinib and crizotinib.
	Yes	RPSFTM methods can be applied based on one of two assumptions:[77] "on treatment" assumption, where it is assumed that treatment effect is only received while a patient is "on" treatment and that the treatment effect disappears as soon as treatment is discontinued or alternatively, a "treatment group" assumption, where it is assumed that a continued or lagged treatment effect may be present following discontinuation of treatment. The company confirmed in their response to question A12 of the clarification letter, that they used the "treatment group" assumption to allow for patients who switched to other non-trial treatments to be included within follow-up to maximise the length of survival data.	The ERG considers that the "treatment group" assumption used by the company is practical and reasonable given limited OS data available. However, clinical advice to the ERG is that an "on treatment" assumption would be more representative of the comparison of brigatinib versus crizotinib.

Item	ERG assessment	Approach	ERG comments
Were results presented appropriately?	Yes	The company presented results for all analyses conducted (CS, Figure 42). In addition to standard 95% CIs, the company has presented OS HRs with bootstrapped 95% CIs to account for uncertainty introduced to the estimation of OS HRs following RPSFTM adjustments.	The ERG considers that all relevant results are presented. The ERG agrees that it was appropriate to present standard and bootstrapped 95% CIs and prefers the bootstrapped 95% CIs.

CI=confidence interval; DSU=decision support unit; HR=hazard ratio; OS=overall survival; RPSFTM=rank preserving structure failure time model; TSD=technical support document
Source: Extracted from the CS; Section B.3.3.5.2, Appendix L Section L1.1.1 and Section L1.1.2, the company's response to the clarification letter, TSD 16[77] and ERG comment

9.2.2 Indirect comparison of brigatinib versus alectinib

In the absence of a head-to-head comparison of the efficacy and safety of brigatinib versus alectinib, the company carried out a series of indirect treatment comparison (ITCs). A summary and an ERG assessment of the company approach is provided in Table 38.

Table 38 ERG summary and critique of statistical approaches used for the ITCs

Item	ERG assessment	Approach	ERG comments
Was an appropriate method used?	Yes	For the outcomes of BIRC-assessed PFS, OS and investigator-assessed PFS, the company used population-adjusted methods[63] (anchored and unanchored MAICs) to inform a comparison of brigatinib versus alectinib. The company also present an unweighted Bucher ITC[64], without population adjustment, as a reference. Given the high rate of treatment crossover following progression among patients in the ALTA-1L trial, primarily from the crizotinib arm, and the differences between the ALTA-1L and ALEX trials with regard to permitted treatment crossover (CS, Table 7), the company performed ITCs using unadjusted OS data from the ALTA-1L trial, as well as with OS data adjusted for crossover using RPSFTM methods (see Section 3.3.2 of this ERG report).	The ERG considers that the company has described their complex statistical approach to the ITCs comprehensively and clearly. The ERG agrees that, in principle, given the observed differences in populations of the ALTA-1L trial and the ALEX trial, undertaking population-adjusted indirect comparisons was appropriate. The ERG also agrees that it was appropriate to present an unweighted Bucher ITC of brigatinib versus alectinib, without population adjustment, to serve as a reference and to present ITC results using unadjusted OS data and RPSFTM adjusted OS data
Were all relevant prognostic factors and effect modifiers identified appropriately?	Yes	Population-adjusted methods outlined in TSD18[63] include the identification of all relevant prognostic factors (i.e., factors which influence absolute outcomes) and effect modifiers (i.e., factors which influence relative comparisons), ideally supported by prior literature and/or clinical expert opinion, rather than factors based solely on the data of the trials included in the ITC. The prognostic factors identified by the company were gender, age, ever smoked, Asian, baseline brain metastases, prior chemotherapy and ECOG score. These factors were identified from previous NICE STA submissions (TA536[31] and TA571[38]) and validated by a clinical advisory board. The company identified the effect modifiers for inclusion in the anchored MAIC by examining statistically significant interactions between each identified prognostic factor and treatment (brigatinib or crizotinib) from analyses of ALTA-1L trial BIRC-assessed PFS, OS and investigator assessed PFS. Results indicated that the presence of baseline brain metastases was the only treatment effect modifier present for all outcomes (Appendix D to the CS; Table 18, Table 19, Table 20).	The ERG considers this approach was appropriate and clinical advice to the ERG is that all important prognostic factors were identified. The ERG agrees that the approach used by the company to identify effect modifiers was appropriate.

Item	ERG assessment	Approach	ERG comments
Were all relevant prognostic factors and effect modifiers interpreted appropriately?	No	Clinical advice to the company was that "due to the intracranial efficacy observed with brigatinib and alectinib, presence of brain metastases at baseline would be considered less prognostic for patients treated with these later generation ALK inhibitors" (CS, Section 2.9.1) and therefore the company noted that the proportions of patients with baseline brain metastases "influence the crizotinib arms only" (CS, Section B.2.9.2).	The ERG notes that, by definition, an effect modifier is assumed to influence the treatment effect estimate, and that the statistically significant interactions shown in Appendix D to the CS (Table 18, Table 19 and Table 20) demonstrate that the presence of baseline brain metastases influences the brigatinib versus crizotinib treatment effect estimates. The ERG considers that by performing an anchored MAIC controlling for baseline brain metastases, the company implicitly assumed that the presence of baseline brain metastases influences the treatment effect estimate of brigatinib compared to alectinib. If this were not the case, population-adjusted methods would not have been required and the unweighted Bucher ITC could have been used to inform the comparison of brigatinib and alectinib.
Were anchored MAICs implemented appropriately?	Yes	The company approach to the anchored MAICs is outlined in Appendix D to the CS, Section D.1.4.3 and response to clarification question A9	The ERG considers that the company has implemented the anchored MAIC methods appropriately. The ERG considers that the effective sample size of the anchored MAIC is similar to the effective sample size of the unweighted Bucher ITC and this indicates that the anchored MAIC weights were appropriate and there was sufficient overlap in the populations of the ALTA-1L and ALEX trials.
Were unanchored MAICs implemented appropriately?	No	The company performed unanchored MAICs with the objective of avoiding "the bias introduced through the crizotinib anchor related to baseline brain metastases and treatment switching" (Appendix D to the CS, Section D.1.4.4). Unanchored MAICs are associated with a very strong assumption that absolute outcomes can be predicted from the included covariates; in other words, all effect modifiers and prognostic factors are accounted for and that failure to meet this assumption leads to an unknown amount of bias in the unanchored estimate.[63] The company was unable to provide a likely range of bias associated with the unanchored estimate (response to question A10 of the clarification letter).	The ERG acknowledges the limitations of the ALTA-1L trial treatment switching adjusted OS analysis (see Section 3.3.2 of this ERG report). Furthermore, as noted in the critique of the anchored MAICs, the ERG considers that baseline brain metastases should also be considered as a relevant effect modifier for the comparison of brigatinib versus alectinib. The ERG acknowledges that methods for quantifying bias associated with unanchored MAICs are limited (Appendix C of TSD 18,[63]). However, the ERG considers that the unanchored estimates cannot be assumed to be any more reliable than the unweighted Bucher ITC estimates and considers that the unanchored estimates are not suitable for decision making.

Item	ERG assessment	Approach	ERG comments
Were results presented appropriately?		The company presented results for all analyses conducted (CS; Figure 17; Figure 18; Figure 19; Figure 20). The company considered (Appendix L to the CS, Section L.1.1.2) that it was too computationally demanding to extend the bootstrapping algorithm used in their treatment switching analyses to the anchored MAIC analyses. Hence, the 95% CIs around the anchored MAIC results for brigatinib versus alectinib when adjusted OS data were incorporated, are likely to be too narrow.	The ERG considers that all relevant results are presented. The ERG acknowledges the computational demands of treatment switching analyses and MAIC analyses and notes that this limitation should be taken into consideration when interpreting the 95% CIs of the OS HRs from the MAICs.

BIRC=blinded independent review committee; CI=confidence interval; DSU=decision support unit; ECOG=eastern cooperative oncology group; HR=hazard ratio; ITC=indirect treatment comparison; MAIC=matching adjusted indirect comparison; OS=overall survival; PFS=progression free survival; RPSFTM=rank preserving structure failure time model; TSD=technical support document
Source: Extracted from the CS; Section 2.9.1 and Section 2.9.2, Appendix D Section D1.4.3 and Section D1.4.4, Appendix L Section L1.1.2, the company's response to the clarification letter, TSD 16[77] and ERG comment

9.3 Appendix 3: Additional considerations for the indirect comparisons

Inclusion of the ALESIA trial

As described in Section 3.2.1 of this ERG report, the company excluded two trials (the J-ALEX and the ALESIA trial), which compared alectinib versus crizotinib within Asian populations only, from their ITCs as they considered that results from Asian populations were not generalisable to UK practice (CS, Section B.2.2). The company elaborated in response to question A8 of the clarification letter, that the J-ALEX and ALESIA trials were excluded from the economic model that informed the NICE appraisal of alectinib[31] due to "differences in the patient population and dosing", and that the J-ALEX and ALESIA trials were not considered "pivotal evidence" for the European marketing authorisation of alectinib.

The ERG agrees that it was appropriate to exclude the J-ALEX trial from the ITCs as the dose of alectinib in this trial was lower than the European licensed dose.[33] However, the ERG notes that the European marketing authorisation for alectinib was granted in February 2017 and that the CS of alectinib was completed in October 2017. The ALESIA trial was still recruiting patients in May 2017 and was published in April 2019.[42] Hence, results from the ALESIA trial would not have been available at the time of the European marketing authorisation submission or economic modelling within the alectinib submission[31] and therefore, could not have been 'excluded' from either submission.

The ERG notes that results from the ALEX trial, which enrolled 45.8% participants from countries in Asia and only 1% of patients from the UK[39] were considered by the company to be relevant to the UK population. Furthermore, it is stated within the European Public Assessment Report for brigatinib (Section 2.3.4) that:

"It is considered possible to extrapolate efficacy in the Asian population to the European mainly white population, as brigatinib is a specific targeted treatment for ALK+ NSCLC."

The ERG, therefore, considers that if it is appropriate to 'extrapolate' the alectinib (a targeted treatment for ALK+NSCLC) results from the ALEX trial then it is also appropriate to 'extrapolate' the results from the ALESIA trial and, therefore, results from the ALESIA trial should have been included in the company's ITCs.

The ERG has performed ITCs to explore the impact that the inclusion of results from the ALESIA trial have on the ITCs. The ERG extracted aggregate HRs for OS, BIRC-assessed PFS and investigator assessed PFS from the ALESIA trial publication[42] and combined these results with aggregate HRs from the ALTA-1L and ALEX trials in unweighted Bucher ITCs. Without access to the IPD (and data relating to prognostic factors and effect modifiers) from

the ALTA-1L trial, the ERG was unable to replicate or perform MAICs with or without the inclusion of the ALESIA trial.

The data included in the unweighted Bucher ITCs performed by the ERG are provided in Table 39.

Table 39 Data used in the additional ERG indirect comparison

HR (95% CI)	ALTA-1L	ALEX	ALESIA
	Brigatinib vs crizotinib	Alectinib vs crizotinib	
OS	0.92 (0.57 to 1.47)	0.69 (0.47 to 1.02)[a]	0.28 (0.12 to 0.68)
BIRC PFS	0.49 (0.35 to 0.68)	0.50 (0.36 to 0.70)	0.37 (0.22 to 0.61)
Investigator PFS	0.43 (0.31 to 0.61)	0.43 (0.32 to 0.58)	0.22 (0.13 to 0.38)

[a] An updated OS analysis of the ALEX trial was identified by the ERG (HR=0.67, 95% CI:0.48 to 0.98; p=0.0376).[40] These data were published too late to be included within the company ITCs but are included in the ERG ITCs.
BIRC=blinded independent review committee; CI=confidence interval; HR=hazard ratio; OS=overall survival; PFS=progression-free survival
Source: Extracted and adapted from CS; Appendix D, Table 17 and the ALESIA trial publication[42]

Summaries of trial design and patient baseline characteristics of the ALESIA trial are provided in Appendix D to the CS (Section D.1.17; Table 8, Table 9, Table 10). The ERG notes that although the countries from which participants were recruited were different, the ALESIA and ALEX trials were similar in terms of trial design (specifically, prior treatment, treatment crossover not permitted, investigator assessed PFS as the primary outcome). Further, similar proportions of patients in these trials had brain metastases at baseline.

Despite the broad similarities between the ALESIA and ALEX trials, except for the countries from which the participants were recruited, the ERG notes that compared with results from the ALEX trial, all ALESIA trial HRs favoured alectinib (Table 39). The ERG also notes that the ALESIA trial OS data were immature and that treatment crossover was not permitted, but that patients were able to "receive any available treatment after discontinuation from study treatment." [42] Also, the ALESIA trial PFS results (BIRC-assessed and investigator assessed) were reported earlier than originally planned (after a median follow-up time of 16.2 months in the alectinib group and 15.0 months in the crizotinib group) due to results being "better than expected" reported in the ALEX trial.[39] The ERG considers that the time point at which the results were reported for the ALESIA trial may (at least in part) explain the difference in results compared to the ALEX trial (median follow-up time of 37.8 months).

The ERG performed unweighted Bucher ITCs using the 'indirect' command in Stata Software version 14.1.[79] The ERG firstly replicated the unweighted Bucher ITCs performed by the company (including only aggregate data from the ALTA-1L and ALEX trials) and subsequently performed unweighted Bucher ITCs that also included aggregate results from the ALESIA trial. As, following the addition of the ALESIA trial, two trials contributed to the alectinib versus

crizotinib link of the network, the ERG has presented fixed effect (FE) and random effect (RE) unweighted Bucher ITC results to take account of variability between the ALEX and ALESIA trials. Results from the ERG's unweighted Bucher ITCs are provided in Table 40.

The ERG notes that the results from the ERG unweighted Bucher ITCs are slightly different to the results from the company's unweighted Bucher ITCs. This is likely to be due to the use of different sources of data (the company used IPD from the ALTA-1L trial, while the ERG used aggregate HRs to two decimal places) and different statistical software (the company performed all ITC analyses using R software and the ERG used Stata statistical software). The ERG is not concerned by these slight differences in results. The ERG also notes that the ERG unweighted Bucher ITC results are very similar when including OS data used in the company ITC for the ALEX trial and when including recently updated OS data from the ALEX trial).[40] Therefore, the ERG considers that if the company had been able to include the updated OS data from the ALEX trial in their ITCs, it is likely that results would have been similar and conclusions unchanged.

Table 40 Company and ERG unweighted Bucher ITC results

HR (95% CI)[a]	ALTA-1L and ALEX trials		ALTA-1L, ALEX and ALESIA trials	
	Company ITC	ERG ITC	ERG FE ITC	ERG RE ITC
OS	1.359 (0.741 to 2.494)	1.334 (0.722 to 2.465)	1.544 (0.856 to 2.784)	1.910 (0.714 to 5.110)
OS (updated OS data from the ALEX trial)	NA	1.373 (0.751 to 2.511)	1.572 (0.876 to 2.821)	1.930 (0.741 to 5.024)
BIRC PFS	1.04 (0.652 to 1.66)	0.980 (0.612 to 1.568)	1.076 (0.700 to 1.656)	1.076 (0.700 to 1.656)
Investigator PFS	1.046 (0.699 to 1.636)	1.000 (0.644 to 1.544)	1.167 (0.754 to 1.807)	1.342 (0.641 to 2.813)

a. HR<1 favours brigatinib
BIRC=blinded independent review committee; CI=confidence interval; FE=fixed effects; HR=hazard ratio; ITC=indirect treatment comparison; MAIC=matched adjusted indirect comparison; NA=not applicable; OS=overall survival; PFS=progression-free survival; RE=random effects
Source: Extracted and adapted from CS (Figure 17, Figure 18 and Figure 19) and ERG analyses

The ERG notes that the unweighted Bucher ITC result for BIRC-assessed PFS following the inclusion of the ALESIA trial is very similar to the unweighted Bucher ITC including only the ALTA-1L and ALEX trials (no statistically significant evidence that, at the 5% level, treatment with brigatinib is superior alectinib, with HRs close to 1). Compared to brigatinib, investigator-assessed PFS HRs are more in favour of alectinib, particularly within the RE ITC. It is likely that this result is due to the difference in HR of investigator-assessed PFS observed in the ALESIA trial compared to the ALTA-1L and ALEX trials (Table 39).

Following the inclusion of the ALESIA trial data, the OS HR increases in favour of alectinib from around 1.33 to between 1.54 (FE unweighted Bucher ITC) and 1.91 (RE unweighted Bucher ITC). Furthermore, following inclusion of the ALESIA trial data compared to the ITCs of the ALEX-1L trial and the ALEX trial, 95% CIs are even wider around the OS HR, particularly from the RE unweighted Bucher ITC. This further indicates the uncertainty associated with the OS estimates when this additional evidence from the ALESIA trial is incorporated.

The additional unweighted Bucher ITC analyses performed by the ERG have limitations. They were performed using slightly different data sources and different statistical software to the analyses performed by the company. Although the ERG considers that the best available PFS and OS estimates were generated by the company anchored MAICs, without access to the IPD (and data relating to prognostic factors and effect modifiers) from the ALTA-1L trial, the ERG was unable to replicate or perform anchored MAICs. Therefore, it should be emphasised that unweighted Bucher ITC results presented in this section do not account for any differences in populations between the ALTA-1L, ALEX and ALESIA trials and do not adjust for treatment crossover in the ALTA-1L trial or any other trial design differences across the trials.

Despite these limitations, these additional analyses performed by the ERG, further highlight that substantial uncertainty surrounds the relative OS effect of brigatinib compared to alectinib.

9.4 Appendix 4: Revisions made by the ERG to the company's model

Revisions are activated by a logic switch. Logic switches are indicated by named range variables Mod_*letter* where *letter* = A to G. A menu of revisions and Mod names appears below and on the 'ERG switches' worksheet in the ERG amended model.

Instructions for modifying the company model

1. Paste the following table into A2:E9 of a new sheet named 'ERG switches' and **name the switches with the modification names**

Revision #	Modification name	Switch	Description	Instructions
Corrected base case	Mod_A	0	Use mean utility value	Choose (0 to 1)
S0	Mod_G	0	Cost minimisation switch (Company)	Choose (0 to 1)
S1	Mod_C	0	Use brigatinib OS to model crizotinib OS	Choose (0 to 1)
S2	Mod_B	0	Use ToT for treatment duration for brigatinib, crizotinib and alectinib	Choose (0 to 1)
S3	Mod_F	0	Remove CNS multiplier and additional cost	Choose (0 to 1)
S4 & S5	Mod_D	0	Wane brigatinib and alectinib OS at 38 years	Choose (0 to 30) years
S4 & S5	Mod_E	0	Wane brigatinib and alectinib PFS and intracranial PFS at 38 years	Choose (0 to 30) years

PFS=progression-free survival; OS=overall survival; ToT=time on treatment

Note: Set Mod_D and MoD_E switches to 3 (i.e. wane OS, PFS and intracranial PFS after year 3) to implement ERG's scenario 4; Set Mod_D and MoD_E switches to 5 (i.e. wane OS, PFS and intracranial PFS after year 5) to implement ERG's scenario 5

2. For each sheet given in the 'Sheet' column below:
    - copy formulae from the 'Modified formulae' column in the table below
    - paste formulae into the cells referred to in the 'Cells' column in the table below

ERG revision number	Modification name	Sheet(s)	Cells	Modified formulae
Corrected base case	Mod_A	HRQL	E19	=IF(Mod_A=0, T15+p_Base_EQ5D*T16,I15+p_Base_EQ5D*I16)
	Mod_A	HRQL	E20	=Utility_PFS+IF(Mod_A=0,T18,I18)
S0	Mod_G	Model Controls	E50	=IF(Mod_G=0,IF(AlectComp=CostComparison,1,VLOOKUP("HR_"&"BrigVSAlect_"&ITCmethod_alectinib&"_"&"WT"&"_"&ITC_PFSmeasure,Table_HazardRatios,14,FALSE)),1)
S0	Mod_G	Model Controls	E52	=IF(mod_g=0,IF(F8=CostComparison,1,VLOOKUP("HR_"&"BrigVSAlect_"&ITCmethod_alectinib&"_"&"WT"&IF(ITCmethod_alectinib="Unanchored MAIC","",IF(Tx_Switch_Option="No adjustment","_No switch","_"&Tx_Switch_Option))&" OS",Table_HazardRatios,14,FALSE)),1)
S1	Mod_C	Crizotinib	L15:L537	=IF(Mod_C=0,OS!R9,OS!Q9)

S2	Mod_B	Brigatinib	W15:W537	=IF(F15>tm.horzn,"",
				IF(Mod_B=1, IF(E15<=24,VLOOKUP(E15,KM!$DR$11:$DX$107,4,TRUE),EXP(-(-LN(W14)+0.0246678))),
				IF(ToT_method=ToT_equal_to_PFS,R15,
				IF(ToT_method=ToT_one_PP,IF(R15+(SUM(U15:V15)*(1/$V$12))>P15,P15,R15+(SUM(U15:V15)*(1/$V$12))),
				IF(ToT_method=ToT_two_PP,IF(R15+(SUM(U15:V15)*(2/$V$12))>P15,P15,R15+(SUM(U15:V15)*(2/$V$12))),
				IF(ToT_method=ToT_three_PP,IF(R15+(SUM(U15:V15)*(3/$V$12))>P15,P15,R15+(SUM(U15:V15)*(3/$V$12))),
				"ERROR"))))))

S2	Mod_B	Crizotinib	W15:W537	=IF(F15>tm.horzn,"",
				IF(Mod_B=1, IF(E15<=24,VLOOKUP(E15,KM!$DY$11:$EB$107,4,TRUE),EXP(-(-LN(W14)+0.0711486))),
				IF(ToT_method=ToT_equal_to_PFS,R15,
				IF(ToT_method=ToT_one_PP,IF(R15+(SUM(U15:V15)*(1/$V$12))>P15,P15,R15+(SUM(U15:V15)*(1/$V$12))),
				IF(ToT_method=ToT_two_PP,IF(R15+(SUM(U15:V15)*(2/$V$12))>P15,P15,R15+(SUM(U15:V15)*(2/$V$12))),
				IF(ToT_method=ToT_three_PP,IF(R15+(SUM(U15:V15)*(3/$V$12))>P15,P15,R15+(SUM(U15:V15)*(3/$V$12))),
				"ERROR"))))))

ERG revision number	Modification name	Sheet(s)	Cells	Modified formulae
	Mod_B	Alectinib	W15:W537	=IF(F15>tm.horzn,"", IF(Mod_B=1, IF(E15<=24,VLOOKUP(E15,KM!$DR$11:$DX$107,4,TRUE),EXP(-(-LN(W14)+0.0246678))), IF(AlectComp=CostComparison,Brigatinib!W15, IF(ToT_method=ToT_equal_to_PFS,R15, IF(ToT_method=ToT_one_PP,IF(R15+(SUM(U15:V15)*(1/$V$12))>P15,P15,R15+(SUM(U15:V15)*(1/$V$12))), IF(ToT_method=ToT_two_PP,IF(R15+(SUM(U15:V15)*(2/$V$12))>P15,P15,R15+(SUM(U15:V15)*(2/$V$12))), IF(ToT_method=ToT_three_PP,IF(R15+(SUM(U15:V15)*(3/$V$12))>P15,P15,R15+(SUM(U15:V15)*(3/$V$12))), R15)))))))
S3	Mod_F	HRQL	E31	=IF(Mod_F=0,0.52/0.69,1)
S3	Mod_F	Costs	E:113:F113	=IF(Mod_F=1,0,c_Stereotactic_radiotherapy*CNS_SRS*G109+c_WBRT*CNS_WBRT*G110+c_Surgical_resection*CNS_Surgical_resection)
S3	Mod_F	Costs	E:114:F114	=IF(Mod_F=1,0,P127*CNS_Steroids)
S4 & S5	Mod_D	Brigatinib	L15:L537	=IF(Mod_D=0, IF(TxWaningInclude=Yes,IF(F15>IF(TxWaningTime=list.txwaning5,5,IF(TxWaningTime=list.txwaning10,10,IF(TxWaningTime=list.txwaning20,20,"ERROR"))),L14*(Crizotinib!L15/Crizotinib!L14),OS!Q9),OS!Q9), IF(F15>Mod_D,L14*(Crizotinib!L15/Crizotinib!L14),OS!Q9))
S4 & S5	Mod_D	Alectinib	L15:L537	=IF(Mod_D=0, IF(TxWaningInclude=Yes,IF(F15>IF(TxWaningTime=list.txwaning5,5,IF(TxWaningTime=list.txwaning10,10,IF(TxWaningTime=list.txwaning20,20,"ERROR"))),L14*(Crizotinib!L15/Crizotinib!L14),OS!Q9^(1/$L$10)),OS!Q9^(1/$L$10)), IF(F15>Mod_D,L14*(Crizotinib!L15/Crizotinib!L14),OS!Q9^(1/$L$10)))
S4 & S5		Brigatinib	K15:K537	= IF(Mod_E=0,'CNS-PFS'!R9, IF(F15>Mod_E,K14*(Crizotinib!K15/Crizotinib!K14),'CNS-PFS'!R9))
S4 & S5		Alectinib	K15:K537	= IF(F15>tm.horzn,"", IF(Mod_E=0,('CNS-PFS'!R9)^(1/$K$10), IF(F15>Mod_E,K14*(Crizotinib!K15/Crizotinib!K14),('CNS-PFS'!R9)^(1/$K$10))))
& S5		Brigatinib	J15:J537	= IF(Mod_E=0,PFS!R9, IF(F15>Mod_E,J14*(Crizotinib!J15/Crizotinib!J14),PFS!R9))
S4 & S5		Alectinib	J15:J537	= IF(F15>tm.horzn,"", IF(Mod_E=0,(PFS!R9)^(1/$J$10), IF(F15>Mod_E,J14*(Crizotinib!J15/Crizotinib!J14),(PFS!R9)^(1/$J$10))))