NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Committee Papers

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SINGLE TECHNOLOGY APPRAISAL

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Contents:

The following documents are made available to consultees and commentators:

The **final scope and final stakeholder list** are available on the NICE website.

1. **Company submission** from **Takeda**

2. **Company response to NICE's request for clarification**

3. **Patient and professional groups and NHS organisation submission** from:
   a. ALK Positive UK
   b. Roy Castle Lung Cancer Foundation
   c. British Thoracic Oncology Group, on behalf of BTOG/RCP/RCR/ACP/NCRI

4. **Expert personal perspectives** from:
   a. Alastair Greystoke, Senior Lecturer and Honorary Consultant in Medical Oncology – clinical expert, nominated by Takeda

5. **Evidence Review Group report** prepared by **Liverpool Reviews and Implementation Group**

6. **Evidence Review Group – factual accuracy check**

7. **Technical report sent for engagement**

8. **Technical engagement response** from **Takeda**

9. **Technical engagement response from consultees and commentators:**
   a. ALK Positive UK
   b. Roche

10. **Evidence Review Group critique of company response to technical engagement** prepared by **Liverpool Reviews and Implementation Group**

11. **Analyses provided by the company, post committee meeting**

12. **Evidence Review Group critique of analyses provided by the company, post committee**

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Document B

Company evidence submission

May 2020

File name	Version	Contains confidential information	Date
Document B_ID1468_v1.0_CIC	1.0	Yes	15 May 2020

List of abbreviations

AE	Adverse event
AIC	Akaike information criteria
ALK	Anaplastic lymphoma kinase
ALK+	Anaplastic lymphoma kinase positive
ALTA-1L	ALK in Lung Cancer Trial of AP26113
AUC	Area under curve
BOR	Best overall response
BIC	Bayesian information criterion
BIRC	Blinded independent review committee
BSC	Best supportive care
CADTH	Canadian agency for drugs and technologies in health
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CiC	Commercial in confidence
CMs	Concomitant medication
CNS	Central nervous system
CR	Complete response
CRD	Centre for reviews and dissemination
CrI	Credible interval
CSR	Clinical study report
CTCAE	Common terminology criteria for adverse events
DLT	Dose limiting toxicity
DOR	Duration of response
DSU	Decision support unit
ECGs	Electrocardiograms
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EGFR	Epidermal growth factor receptor
EGP	Economic guidance panel
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30
EQ-5D	EuroQol 5-dimensions
ERG	Evidence review group
ESS	Effective sample size
FE	Fixed effect

HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IGF-1R	Insulin-like growth factor 1 receptor
INV	Investigator
IRC	Independent review committee
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IQR	Interquartile range
IPCW	Inverse probability of weight censoring
IPE	Iterative parameter estimation
KM	Kaplan-Meier
LYG	Life years gained
MAIC	Matching-adjusted indirect comparison
MMA	Marketing authorisation application
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
N	Number
NCI	National Cancer Institute (US)
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	Not reported
NSCLC	Non-small cell lung cancer
OR	Odds ratio
ORR	Objective response rate/ Overall response rate
OS	Overall survival
PD	Progressive disease
PF	Prognostic factor
PFS	Progression-free survival
PK	Pharmacokinetics
PR	Partial response
PRISMA	Preferred reporting items for systematic review and meta-analysis
PS	Performance status
PSS	Personal social services
QALYs	Quality adjusted life years
QD	Once daily
QoL	Quality of Life
RCT	Randomised controlled trial

RE	Random effect
RECIST	Response Evaluation Criteria in Solid Tumours
RP2D	Recommended phase 2 dose
RT-PCR	Reverse transcriptase polymerase chain reaction
RPSFTM	Rank preserving structural failure time model
SAE	Serious adverse event
SD	Stable disease
SLR	Systematic literature review
SMC	Scottish medicines consortium
SmPC	Summary of product characteristics
STC	Simulated treatment comparison
TEAE	Treatment emergent adverse event
TEM	Treatment effect modifier
TKI	Tyrosine kinase inhibitor
ToT	Time on treatment
TRAE	Treatment related adverse event
TSD	Technical support document
TTR	Time to response
UK	United Kingdom
v	Version

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List of tables and figures

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

B.1.1 Decision problem

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

A detailed outline of the decision problem is presented in Table 1, including rationale for any amendments.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with ALK-positive advanced NSCLC that has not been previously treated with an ALK inhibitor	Adults with ALK-positive advanced NSCLC that has not been previously treated with an ALK inhibitor	NA
Intervention	Brigatinib	Brigatinib	NA
Comparator(s)	• Alectinib • Ceritinib • Crizotinib	• Alectinib • Crizotinib	Based on analysis of the market and discussions with clinical experts, we have excluded ceritinib as a comparator for the following reasons: • Ceritinib use as a treatment option for ALK inhibitor naïve patients in the UK has been extremely limited since the positive NICE recommendation for alectinib in mid-2018. Market share data analysed on a moving quarterly basis shows that ceritinib market share has remained negligible over some time; from April 2019 to January 2020, ceritinib market share ranged between 0-2%. This clearly demonstrates that ceritinib is not a relevant frontline treatment that is used in the NHS. • This is consistent with the perspective of UK clinicians, who state that the use of ceritinib in new patients is negligible, due to tolerability and efficacy concerns. Rather, clinicians predominantly use alectinib and (to a much lesser extent) crizotinib in the frontline setting. Alectinib is now the standard of care in the frontline setting, with an estimated market share of 76% as of January 2020.[1] UK clinical experts agree that alectinib is superior to ceritinib (and crizotinib).This was recognised by NHS England in its written submission to NICE during the appraisal of brigatinib in the post-crizotinib setting: *"Alectinib is the main 1st line option currently used in NHS England for newly diagnosed patients on account of its better tolerability."*[2]

Outcomes	• Overall survival • Progression-free survival • Response rates • Adverse effects of treatment Health-related quality of life	• Overall survival • Progression-free survival • Response rates • Adverse effects of treatment Health-related quality of life	NA

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

B.1.2 Description of the technology being appraised

The technology being appraised is described in

Table **2**. See Appendix C for the summary of product characteristics (SmPC). Please note the EPAR was not available at time of submission.

Table 2: Description of the technology

Approved name and brand name	Brigatinib (Alunbrig®)
Mechanism of action	Brigatinib is a highly selective, potent, TKI which binds to and inhibits ALK and ALK fusion proteins as well as EGFR and mutant forms. Brigatinib has shown in vitro activity at clinically achievable concentrations against multiple kinases including ALK, c-ROS1, IGF-1R, and FLT-3 as well as EGFR deletion and point mutations. Brigatinib inhibits autophosphorylation of ALK and ALK-mediated phosphorylation of the downstream signalling proteins STAT3, AKT, ERK1/2, and S6 in in vitro and in vivo assays. The inhibition of ALK kinase and EGFR kinase disrupts their signalling pathways and inhibits tumour cell growth. In addition to inhibiting in vitro proliferation of cell lines expressing EML4-ALK and NPM-ALK fusion proteins, brigatinib also demonstrated dose-dependent inhibition of EML4-ALK-positive NSCLC xenograft growth in mice.[3] Furthermore, brigatinib reduced tumour burden and prolonged survival in mice implanted intracranially with an ALK-driven tumour cell line.[4, 5]
Marketing authorisation/CE mark status	Brigatinib received marketing authorisation on 22 November 2018 for use as monotherapy for the treatment of adult patients with ALK-positive advanced NSCLC previously treated with crizotinib. On 1 April 2020, EMA granted an extension for the new indication of brigatinib as "monotherapy for the treatment of adult patients with ALK-positive advanced NSCLC previously not treated with an ALK inhibitor".
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Current indication is "Brigatinib as monotherapy for the treatment of adult patients with anaplastic lymphoma kinase positive advanced non-small cell lung cancer previously not treated with an ALK inhibitor".
Method of administration and dosage	Oral, 90mg once daily for the initial 7 days then, 180mg once daily.
Additional tests or investigations	None. ALK testing is routinely undertaken in the NHS during diagnosis of NSCLC.
List price and average cost of a course of treatment	List price is £4,900 applicable both to 1) starter pack (i.e. 7 tablets at 90mg + 21 tablets at 180mg) and 2) 28-tablet pack at 180mg. The mean duration of treatment is 38.34 cycles (35.27 months).
Patient access scheme (if applicable)	As per the agreement with UK Department of Health and NHS England, a patient access scheme (PAS) in the form of a simple discount applies for all approved indications of brigatinib. The previous PAS for brigatinib (as per TA571) was a straight discount of [redacted] off the list price, which reduced net price to [redacted] per 28-tablet pack. A proposed PAS has been accepted by NHSE and PASLU for consideration in this appraisal, this increases the discount to [redacted] and reduces the net price to [redacted] per 28-tablet pack.

TKI, tyrosine kinase inhibitor; ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; ROS1, ROS protooncogene 1 receptor; IGF-1R, insulin-like growth factor-1 receptor; FLT-3, FMS-like tyrosine kinase; STAT, signal transducer and activator of transcription; ERK, extracellular signal-regulated kinases; EML, echinoderm microtubule associated

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

B.1.3.1 Disease overview

Lung cancer is the third most common cancer in the United Kingdom (UK)[6] with over 39,000 cases diagnosed in England and Wales in 2017.[7] It remains the leading cause of cancer-related mortality in the UK with an age standardised mortality rate of 61.4 per 100,000 persons.[7] Lung cancer is classified into two main groups; small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLC is the most common type accounting for approximately 88% of all lung cancer cases in England and Wales[7] and can be further subdivided into three major subtypes; squamous-cell carcinoma, adenocarcinoma and large cell carcinoma.[8]

Molecular assessments of NSCLC have shown that lung cancer is a highly heterogenous condition with various driver mutations of prognostic importance. These include, anaplastic lymphoma kinase (ALK), epidermal growth factor (EGFR), ROS proto-oncogene 1 (ROS1) rearrangements.[9] In a small proportion of people with NSCLC estimated to be between 3-5%, the growth of cancer cells is caused in part by the ALK gene translocations.[10-13] ALK rearrangement can occur in NSCLC of any histology but is predominantly found in tumours with adenocarcinoma histology.[14] Although the specific function of the ALK receptor tyrosine kinase is unknown, the signalling pathways are understood to be important for many cellular processes such as cell growth, maturity and proliferation.[15] ALK status testing is done through fluorescence in situ hybridisation (FISH) and immunohistochemistry (IHC). In the UK, the National Institute for Health and Care Excellence (NICE) recommends that biopsies are routinely tested for the ALK gene during diagnostic work-up for NSCLC.[16]

Clinical features of patients with ALK-positive NSCLC at the time of diagnosis include:

- Estimated median age of 49-52 years,[17-20],[19]14 years younger than that of the overall NSCLC population[18] (71 years at diagnosis[20]).
- No or light smoking history.[21]
- Advanced disease at the time of diagnosis.[18]
- Histology of adenocarcinomas, with few reports of squamous cell pathology.[18]

Due to the nature of the disease, ALK-positive patients tend to be younger with little or no smoking history and are often diagnosed in the advanced disease stages with no curative options. This is partly due to misperception of distinct characteristics of patients with ALK-positive NSCLC being low risk for lung cancer and the lack of apparent symptoms in the early stages.[17] Patients with ALK-positive NSCLC typically present with more metastatic sites than those with other disease subtypes.[22] Most present with inoperable tumours which have either spread to the lymph nodes and other organs in the chest (locally advanced, Stage IIIb) or, to other parts of the body (metastatic, Stage IV).[7] Outcomes for patients with metastatic disease are worse, real-world data from the 2017 National Lung Cancer Audit (NLCA) demonstrated

that the 1-year survival of patients with stage IIIB and IV disease is 15.5% in England and Wales.[7]

Common metastatic sites include the central nervous system (CNS), liver, pericardium, pleura and bone.[23] The CNS is a known and key sanctuary site for progression in advanced ALK-positive NSCLC due in part, to poor blood-brain barrier penetration of earlier treatments such as crizotinib and indeed chemotherapy.[24] Unfortunately, prognosis associated with brain metastasis remains poor, with reports of median overall survival (OS) between 3 and 14.8 months.[25] Real-world studies estimate that approximately 20-30% of patients have brain metastases at diagnosis.[26-30] Intracranial disease progression occurs in 20% of patients without prior CNS involvement and in up to 70% of patients with CNS involvement at diagnosis. The high rates of metastatic disease in the CNS, coupled with associated significant morbidity and mortality[31] mean that the overall efficacy, (i.e. whole body and intracranial outcomes), of an ALK inhibitor is a key determinant in selecting the most effective treatment.

Symptoms of lung cancer can include persistent cough, breathlessness, unexplained weight loss and ongoing chest infections. In the presence of brain or CNS metastases, patients may also experience confusion, drowsiness, weakness in the limbs and severe headaches.[32] As a result of the high symptom burden associated with NSCLC, caregiver burden in the context of psychological, emotional and financial strain is also a challenge.[33, 34] On average, caregivers are estimated to provide 29.5 hours of support each week. [35]

The identification of the ALK driver mutation has led to a major paradigm shift as targeted therapies can now be utilised in the clinical management of patients with ALK-positive NSCLC. Tyrosine kinase inhibitors (TKIs) work by blocking the action of the altered ALK gene challenging the action of molecules that enable abnormal cancer cell growth. Prior to 2011, patients with ALK-positive disease had few effective treatment options available and relatively poor prognosis.[21] Since that time, the sequential launches of crizotinib, ceritinib and alectinib have led to marked improvements in outcomes for patients with ALK-positive advanced NSCLC. However, each of these therapies is subject to limitations, particularly relating to tolerability (mainly ceritinib), emergence of resistance mutations (especially crizotinib), and effectiveness against CNS metastases (limited for crizotinib).[36-38] Despite the advances made with earlier TKIs such as crizotinib and ceritinib, the majority of patients progress within two years, with the brain being the most frequent site of relapse.[38] More recently developed ALK inhibitors such as brigatinib and alectinib have greater diffusion across the brain-blood barrier and are thus associated with much better CNS outcomes than crizotinib.[38] Although data on the optimal sequencing of ALK inhibitors is lacking, the availability of several improved ALK TKIs (e.g. brigatinib and alectinib) means that many patients can potentially have disease control for several years.[39-41] Therefore, the need for well-tolerated and convenient long-term therapies is becoming increasingly important. As previously stated, patients with ALK-positive disease tend to be younger (median age at diagnosis is between 49-52 years.[17]) than the overall NSCLC population (median age of 68 years[20]) and are hence, more likely to be of working age and have dependents. Consequently, the disease burden may be particularly difficult in this population.

Health-related quality of life (HRQoL) for patients diagnosed with ALK-positive NSCLC is severely impacted as demonstrated by a clinically meaningful reduction in mean global quality

of life (QoL) score (assessed by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30)). When compared with the general population, an approximate decrease of 20% is observed.[42, 43] For patients with progressive disease, a 17% reduction in EuroQol five-dimension (EQ-5D) score is reported compared with patients who are progression free[44]. In the presence of brain metastases in particular, a major decrease in quality of life is observed.[45, 46] One observational study found a greater decline over time in 18 of 20 evaluated HRQoL measures in patients with brain metastases than in patients without. Individuals with brain metastases were observed to experience deterioration of 28.1% within the first year compared with an improvement of 1.8% in patients without brain metastases.[47] Other studies have also associated brain metastases with increased mortality, severe morbidity[27, 48] and increased economic burden resulting from frequent hospital visits and inpatient stays, increased medical treatment, imaging and radiotherapy.[49-51]

Taking all of this into account, well-tolerated and convenient treatment options that are highly effective in delaying both systemic and intracranial progression are essential for patients with ALK-positive advanced NSCLC. As will be demonstrated in this submission, brigatinib offers a profile that meets these needs in the frontline setting.

B.1.3.2 Treatment pathway

NICE and ESMO guidelines on lung cancer recommend that ALK status testing should be undertaken for all people with non-squamous NSCLC at diagnosis, as the mutation is more common in this subgroup.[16, 52] There is NICE guidance that recommends the ALK inhibitors crizotinib, ceritinib and alectinib for the frontline treatment of ALK-positive advanced NSCLC in the UK (see Figure 1).[53-55]

Whilst chemotherapy with a platinum-doublet in combination with pembrolizumab is the gold standard for advanced NSCLC without an ALK rearrangement[56] the emergence of targeted therapies has resulted in the diminishing use of chemotherapy as the first treatment for ALK-positive advanced NSCLC. However, there are situations in clinical practice where some patients are still initially treated with chemotherapy. The National Lung Cancer Audit in 2017 showed that 90% of patients were tested, with a median time from biopsy to results of 17 days (IQR: 13-23 days). Among individuals who tested positive for the ALK mutation, only 58% received an ALK inhibitor as their first treatment[57] hence it is likely that many received chemotherapy first. Given that clinical practice has rapidly evolved, this estimate is likely to be more reflective of practice prior to the availability of alectinib and ceritinib (both subsequently recommended by NICE in 2018). However, expert opinion confirms that in current circumstances where a patient requires immediate treatment, and/or a result confirming the presence of an ALK mutation is unattainable or delayed, chemotherapy may be initiated as the first treatment. There is no existing evidence for frontline ALK inhibitor treatment with alectinib and ceritinib in patients who initially received chemotherapy. As such, crizotinib is the only ALK inhibitor recommended by NICE (TA422[58]) and funded by NHS England for use after initial treatment with chemotherapy based on clinical trial evidence for crizotinib in this setting. Given the known limitations of crizotinib, particularly in the CNS[39, 59] (see below), there is an unmet clinical need for a more effective and well-tolerated ALK inhibitor that can be used irrespective of whether or not patients have received prior chemotherapy. Due to the breadth of its evidence base, brigatinib is uniquely well positioned to address this unmet need.

Crizotinib was the first ALK inhibitor to be granted EMA approval in October 2012, and later in 2016 received positive NICE guidance for both untreated ALK-positive NSCLC (TA406[53]) and for ALK-positive NSCLC previously treated with chemotherapy (TA422[58]). While the superiority of crizotinib to traditional chemotherapy has been well documented,[39, 60-62] other studies have shown that patients treated with crizotinib often develop resistance. Disease progression generally occurs within one year from start of treatment with crizotinib, with the CNS often being the first and most common site of progression due to the known low CNS penetration of crizotinib.[39, 60, 63] This factor, combined with the availability of improved second-generation ALK inhibitors (see below), has resulted in a dramatic decline in the use of crizotinib as the first ALK inhibitor in the UK. The remaining low-level use of crizotinib as the first ALK inhibitor is limited to those patients who have had prior chemotherapy (based on TA422) and are therefore not eligible to receive alectinib.

The second-generation ALK inhibitors ceritinib[54] and alectinib[55] have demonstrated efficacy as frontline ALK inhibitors, although disease progression still ultimately occurs. Despite being recommended by NICE in January 2018[54], the use of ceritinib in the first-line setting has always been extremely limited, partly due to concerns about its tolerability profile and the subsequent availability of the more effective alectinib. The randomised ASCEND-4 trial of ceritinib vs. platinum-based chemotherapy reported that the most common adverse events (AEs) associated with ceritinib were diarrhoea, nausea and vomiting.[64] Clinical experts at a Takeda organised medical advisory board held in January 2020 were unanimous in the view that ceritinib use remains extremely limited in the UK (see Section B.3.10). This is corroborated by market data which indicates that the use of ceritinib as a first-line ALK inhibitor is now negligible with a UK market share of 1% in January.[1] Based on this lack of use, we consider ceritinib to be an irrelevant comparator to brigatinib in this appraisal.

Based on clinical input, alectinib which was recommended by NICE in June 2018[55] is now considered the standard of care in the UK for previously untreated patients with ALK-positive advanced NSCLC. This is also reflected in UK market data which showed that alectinib had a market share of 76% in January 2020. The dominance of alectinib is due to its superiority over crizotinib as demonstrated in the randomised head-to-head ALEX trial. In this trial, alectinib showed superior systemic and CNS efficacy compared to crizotinib in the front-line treatment of patients who have received no prior therapy.[40, 59, 65] However, patients still ultimately progress and some fail to tolerate alectinib. For example, half of patients treated with alectinib progressed within three years and clinically relevant AEs such as oedema, constipation, myalgia (including musculoskeletal pain) are observed.[66, 67] This highlights a continued unmet need for an additional frontline treatment option, such as brigatinib, that is highly effective (including in patients who have had prior chemotherapy), with a different but manageable safety profile and convenient dosing regimen.

While the main mechanism of action is the same for all of the ALK inhibitors, there are differences between them in terms of chemical and molecular structure, binding specificities to the ALK kinase, and kinase inhibition potency. These characteristics are reflected in variable safety profiles, varying efficacy in the presence of ALK mutations, and in their ability to penetrate the blood-brain barrier and thereby, target CNS metastases.[36, 37] Hence, all else

being equal, there is value in having a range of effective ALK inhibitors available, particularly in the frontline setting.

Brigatinib is a novel (next-generation) ALK inhibitor that binds to and inhibits ALK kinase and fusion proteins, as well as EGFR and mutant forms. Brigatinib has demonstrated promising efficacy and safety among Stage IIIB/IV ALK-positive NSCLC patients who are ALK inhibitor-naïve and previously treated with crizotinib. Based on data from two clinical trials, ALTA and Study-101,[68] brigatinib was recommended by NICE in February 2019 for ALK-positive advanced NSCLC in adults who have already received crizotinib.[2] Recently, results from a large Phase III, randomised controlled trial comparing brigatinib with crizotinib in patients previously untreated with an ALK inhibitor (ALK in Lung Cancer Trial of AP26113 [ALTA-1L]) indicate that brigatinib provides superior PFS and response compared to crizotinib. Notably, the magnitude of the relative PFS benefit appears to be similar to that seen with alectinib in its corresponding Phase III trial (ALEX) vs. crizotinib in untreated patients; this is supported by indirect treatment comparisons (ITCs) which indicate that brigatinib is at least as efficacious as alectinib. Therefore, it is anticipated that, at a minimum, brigatinib will provide similar benefits to alectinib in the frontline setting.

In addition, brigatinib has some dosing advantages compared to other ALK inhibitors. It is administered as a once-daily, single tablet treatment that can be taken with or without food,[3] thereby offering significant patient convenience advantages over the other ALK-inhibitors which require;

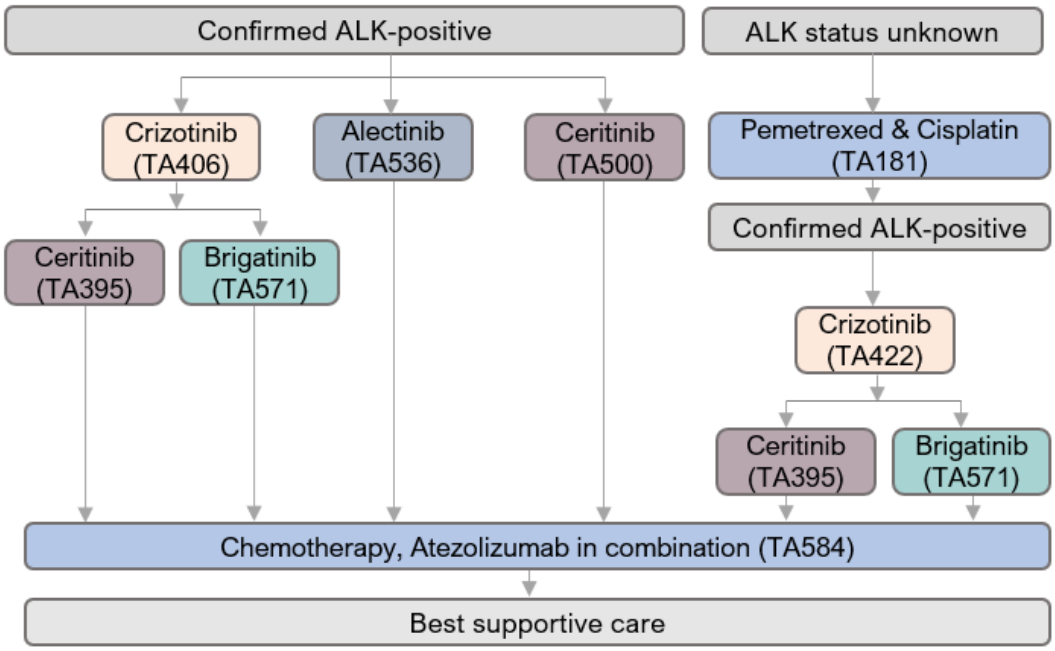
- either twice-daily dosing (alectinib and crizotinib) or,
- multiple capsules to be taken daily (alectinib and ceritinib, eight and three capsules daily, respectively) or,
- must be taken with food (alectinib and ceritinib).[66, 69]

Brigatinib is shown in Figure 2 in its proposed positioning within the UK treatment pathway, (i.e. first-line treatment of adult patients with ALK-positive advanced NSCLC that has not been previously treated with an ALK inhibitor).

B.1.4 Equality considerations

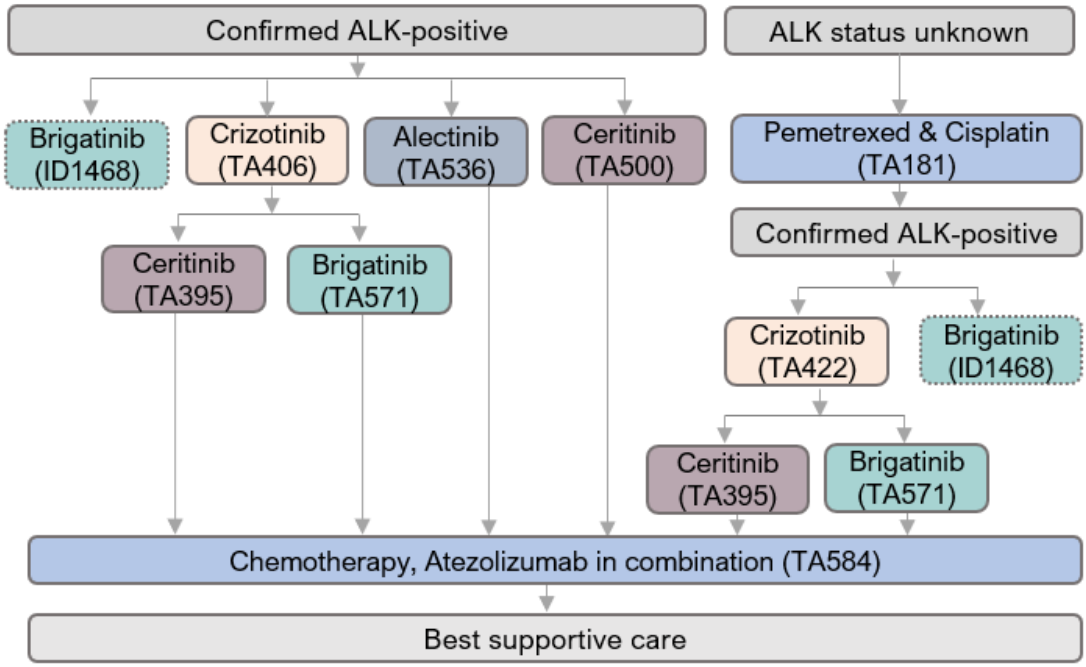
No equality issues have been identified.

Figure 1: Current treatment pathway for ALK-positive advanced NSCLC



ALK, anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer

Figure 2: Proposed treatment pathway for ALK-positive advanced NSCLC



ALK, anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify relevant information relating to the efficacy and safety of brigatinib and existing comparators available in the first-line treatment of ALK-positive advanced NSCLC. As per the final NICE scope, the comparators included in the search were alectinib, crizotinib and ceritinib.

The SLR was conducted using a rigorous approach following principles of systematic reviewing published in the Cochrane Handbook, the Centre for Reviews and Dissemination (CRD)[70, 71] to ensure that it meets the requirements of NICE and is suitable for any necessary updates.

All electronic databases were searched on 3 January 2020 (i.e. standard evidence sources used in UK HTA assessments). See Appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to brigatinib.

B.2.2 List of relevant clinical effectiveness evidence

The review resulted in the identification of eight randomised controlled trials (RCTs); one brigatinib trial (ALTA-1L), three alectinib trials (ALEX, J-ALEX, ALESIA), one ceritinib trial (ASCEND-4), and three crizotinib trials (PROFILE 1007, PROFILE 1014, PROFILE 1029). The ALTA-1L and ALEX trials are considered to contain relevant clinical effectiveness evidence for this appraisal, hence more detail is provided on these studies in this section.

The pivotal Phase III, ALTA-1L trial forms the primary evidence base underpinning the marketing authorisation for brigatinib and this submission. In ALTA-1L, patients were randomised 1:1 to receive either oral brigatinib or crizotinib. Therefore, ALTA-1L provides robust clinical evidence for the comparison of brigatinib vs. crizotinib.

As identified in the SLR, there are no head-to-head studies of brigatinib vs. the main comparator, alectinib. In the Phase III ALEX trial for alectinib, patients were randomised 1:1 to receive either oral alectinib or crizotinib. Hence, ITCs based on data from ALTA-1L and ALEX are utilised to determine the relative efficacy of brigatinib vs. alectinib (see Section B.2.9). The key outcomes for efficacy in the ALTA-1L and ALEX studies are summarised in Appendix D.1.1.8, Table 11 and a naïve comparison of the BIRC-assessed PFS Kaplan-Meier curves is presented in Figure 44.

J-ALEX and ALESIA were excluded from the ITCs as these studies are not representative of the UK population (Asian populations only).

Table 3: Clinical effectiveness evidence for brigatinib

Study	ALTA-1L (NCT02737501), Camidge *et. al* 2018[39]				
Study design	Randomised, phase III multi-centre, international, open-label comparative study. Stratification conducted according to presence of baseline brain metastases and completion of at least one full cycle of previous chemotherapy.				
Population	Adult patients with ALK-positive locally advanced or metastatic NSCLC who have not been previously treated with an ALK inhibitor.				
Intervention(s)	Brigatinib 90mg once daily for 7 days, then 180mg once daily				
Comparator(s)	Crizotinib 250mg orally twice daily				
Indicate if trial supports application for marketing authorisation	Yes	✓	**Indicate if trial used in the economic model**	Yes	✓
	No			No	
Rationale if trial not used in model	NA				
Reported outcomes specified in the decision problem	• **Overall survival (OS)** • **BIRC-assessed progression-free survival (PFS) as the primary outcome** • Response rates • **Adverse effects of treatment** • **Health-related quality of life (HRQoL)**				
All other reported outcomes	• Duration of response • Disease control rate • **Intracranial progression-free survival**				

Outcomes in bold were included in the economic model. ALK, anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer; NA, not applicable; BIRC, blinded independent review committee;

Table 4: Clinical effectiveness evidence for alectinib

Study	ALEX (NCT02075840), Peters *et. al* 2017[59]				
Study design	Randomised, phase III multi-centre, international, open-label comparative study. Stratification conducted according to ECOG performance, race and presence of CNS metastases at baseline.				
Population	Treatment naïve adult patients with ALK-positive advanced NSCLC				
Intervention(s)	Alectinib 600 mg, twice daily				
Comparator(s)	Crizotinib 250 mg, twice daily				
Indicate if trial supports application for marketing authorisation	Yes		**Indicate if trial used in the economic model**	Yes	✓
	No	✓		No	
Rationale if trial not used in model	NA				
Reported outcomes specified in the decision problem	• **Overall survival (OS)** • **Investigator-assessed progression-free survival (PFS) as the primary outcome** • Response rates • **Adverse effects of treatment** • **Health-related quality of life**				
All other reported outcomes	• Duration of response • Time to CNS progression				

Outcomes in bold were included in the economic model. ECOG, European Cooperative Oncology Group; CNS, central nervous system; ALK, anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer; NA, not applicable

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

This section details the study design and baseline characteristics associated with the ALTA-1L clinical trial, as well as providing a comparison of the study methodologies with the ALEX clinical trial. The discussion of the differences between the two trials forms the basis of the ITC feasibility discussion in Section B.2.9. The key outcomes for efficacy in the ALTA-1L and ALEX studies are summarised in Appendix D.1.1.8, Table 11 and a naïve comparison of the BIRC-assessed PFS Kaplan-Meier curves is presented in Figure 44.

B.2.3.1 ALTA-1L study design

ALTA-1L is a Phase III, open-label, multicentre, comparative, randomised, international study at 92 sites in 19 countries with a total enrolment of 275 patients. There were 36 UK patients enrolled in the ALTA-1L trial across six sites. Figure 3 depicts the trial design schematic.

At screening, disease assessment included imaging of the chest and abdomen (including adrenal glands) and imaging of the head, using appropriate radiological procedures. Eligible patients were required to have at least one measurable lesion per Response Evaluation Criteria in Solid Tumours (RECIST) version (v) 1.1. Disease assessment carried out by

computerised tomography (CT) and magnetic resonance imaging (MRI) (all imaging of the head was performed by MRI with contrast material) scans was performed at 8-week intervals after screening through to cycle 14 (28 days per cycle) after the initial dose of study drug, and every three cycles (12 weeks) thereafter, until the end of treatment. Imaging of chest, abdomen, and brain occurred at each assessment for all patients. More-frequent imaging was recommended at any time if clinically indicated; confirmation of complete response (CR) or partial response (PR) was to be performed at least four weeks after initial response. Two independent review committees, whose members were unaware of the trial drug assignments performed disease assessments; one for all disease according to RECIST v1.1 and the other exclusively for the evaluation of intracranial outcomes. Visits were scheduled to occur on days 1, 8, and 15 of the first 28-day cycle and then every four weeks, at treatment discontinuation and then 30 days post-treatment.

The design, eligibility criteria, outcomes and additional methodological information for ALTA-1L are presented in Table 5. The ALEX clinical trial, providing evidence for alectinib, is documented in three publications in the literature: Peters *et al.* 2017,[59] Camidge *et al.* 2018[65] and Mok *et al*. 2019.[40] The key features are summarised alongside the ALTA-1L trial in Table 5.

Figure 3: ALTA-1L trial design schematic

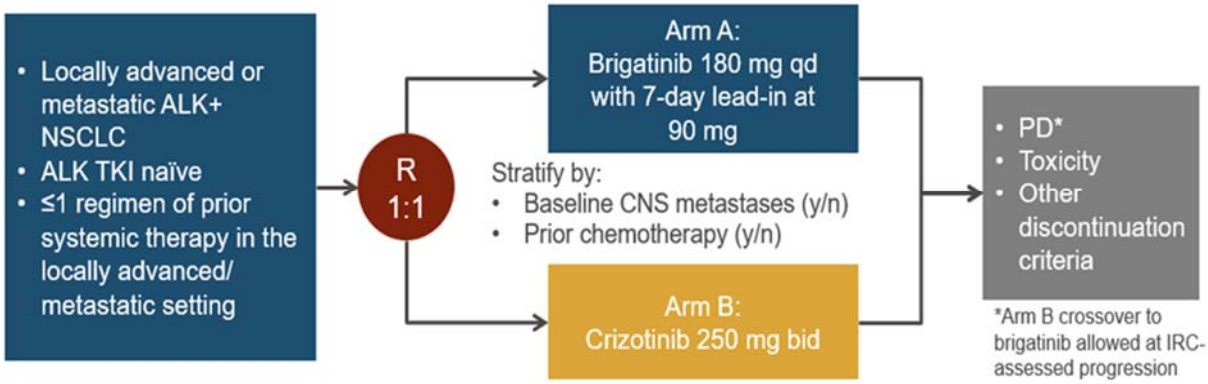


Table 5: Comparative summary of ALTA-1L and ALEX trial methodologies

Trial number (acronym)	**ALTA-1L, (NCT02737501),** Camidge et. al 2018[39]	**ALEX, (NCT02075840)**, Peters et al. 2017 (primary),[59] Camidge et al. 2018 (update),[65] Mok et al. 2019 (final)[40]
Settings and locations where the data were collected	92 study sites located in: Austria, Denmark, France, Germany, Italy, Luxembourg, Netherlands, Norway, Spain, Sweden, Switzerland, **United Kingdom**, Australia, Hong Kong, Taiwan, Singapore, South Korea, United States and Canada.	98 study sites located 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**, Poland, China, Switzerland, France, Spain, Bosnia and Herzegovina, Brazil, Chile, Egypt, Guatemala.
Trial design	Randomised, Phase III multi-centre, international, open-label comparative study to investigate the efficacy and safety of brigatinib compared with crizotinib in adult patients with ALK-positive locally advanced or metastatic NSCLC **who have not been previously treated with an ALK inhibitor.**	Randomised Phase III, open-label, multicentre, open-label randomised study to investigate the efficacy and safety of alectinib compared with crizotinib in patients with **previously untreated** advanced ALK-positive NSCLC.
Eligibility criteria for participants	Inclusion criteria • Male or female aged ≥18 years. • Histologically or cytologically confirmed Stage IIIB (locally advanced or recurrent and was not a candidate for definitive multimodality therapy) or Stage IV NSCLC. • ECOG performance status ≤2. • Patients must have documentation of positive ALK rearrangement by either; o local test assessed using the Vysis ALK Break-Apart FISH Probe Kit (Abbott Molecular) or the Ventana ALK (D5F3) CDx Assay according to manufacturer's instructions or, o different test and adequate tissue available for central laboratory testing by an FDA–approved test. • Sufficient tumour tissue available for central analysis • At least one measurable lesion RECIST v1.1.	Inclusion criteria • Age ≥18 years old. • Histologically or cytologically confirmed diagnosis of advanced or recurrent (Stage IIIB not amenable for multimodality treatment) or metastatic (Stage IV) NSCLC that is ALK-positive as assessed by the Ventana IHC test conducted at a central laboratory. o Sufficient tumour tissue to perform ALK IHC and ALK FISH required (both tests to be conducted at designated central laboratories). • No prior systemic treatment for advanced or recurrent NSCLC or metastatic NSCLC. • Measurable disease as defined by (RECIST v1.1). • ECOG PS 0-2. • Life expectancy ≥12 weeks. • Prior brain or leptomeningeal metastases allowed if asymptomatic (e.g. diagnosed incidentally at study baseline).

	• Recovered from toxicities related to prior anticancer therapy to NCI CTCAE v4.0 Grade ≤1.
	• Adequate organ function defined by the following laboratory results:
	  o aminotransferase (ALT)/aspartate aminotransferase (AST) ≤2.5×ULN; ≤5× ULN is acceptable if liver metastases are present
	  o Total serum bilirubin ≤1.5× ULN
	  o Serum creatinine ≤1.5× ULN
	  o Serum lipase/amylase ≤1.5× ULN
	  o ANC ≥1.5 × 10^9/L
	  o Platelet count ≥75 × 10^9/L
	  o Haemoglobin ≥10 g/dL
	• Normal QT interval on screening ECG evaluation
	• Negative pregnancy test documented before randomisation for females of child bearing age.
	• For female and male patients who were fertile, agreed to use a highly effective form of contraception with their sexual partners during the dosing period and for a period of at least four months after the end of treatment with brigatinib and at least three months after the end of treatment with crizotinib.
	• Signed and dated informed consent.
	• Able and willing to comply with scheduled visit and study procedures.
	
	<u>Key exclusion criteria</u>
	• Previously received an investigational antineoplastic agent for NSCLC.
	• Previously received any prior TKI, including ALK-targeted TKIs.
	• Previously received more than one regimen of systemic anticancer therapy for locally advanced or metastatic disease.
	• Symptomatic CNS metastases (parenchymal or leptomeningeal) at screening or asymptomatic disease requiring an increasing dose of
		• Patients with neurological symptoms must complete whole brain radiation or gamma knife irradiation treatment.
		  o Radiation treatment must be completed ≤14 days before enrolment and patients must be clinically stable
		• Adequate haematologic and end-organ function, defined by the following laboratory results:
		  o Platelet count ≥100×10^9/L
		  o ANC ≥1500 cells/μL
		  o Haemoglobin ≥9.0 g/dL
		  o An estimated GFR calculated using the Modification of Diet in Renal Disease equation of ≥45 mL/min/1.73 m2
		• Patients must have recovered from effects of any major surgery or significant traumatic injury ≤28 days before first dose of study medication.
		• For both female patients and male patients, agreement to remain abstinent or use highly effective form(s) of contraception and to continue its use for three months after the last dose of study medication.
		• For females of childbearing potential, a negative pregnancy test must be obtained within three days before starting study treatment.
		• Able and willing to provide written informed consent and to comply with the study protocol.
		
		<u>Key exclusion criteria</u>
		• Patients with a previous malignancy within the past three years (other than curatively treated basal cell carcinoma of the skin, early GI by endoscopic resection, in situ carcinoma of the cervix, or any cured cancer that is considered to have no impact in PFS and OS for the current NSCLC).
		• Any GI disorder that may affect absorption of oral medicines.
		• Liver disease characterised by either:

	corticosteroids to control symptoms within seven days before randomisation. • Received chemotherapy or radiation within 14 days of the first dose of study drug, except SRS or SBRT. • Received anti-neoplastic monoclonal antibodies within 30 days of the first dose of study drug. • History or presence at baseline of pulmonary. interstitial disease, drug-related pneumonitis, or radiation pneumonitis. • Malabsorption syndrome or other GI illness or condition that could affect oral absorption of the study drug. • Uncontrolled hypertension or active cardiovascular disease. • Prior diagnosis of another primary malignancy other than NSCLC. • Had current spinal cord compression (symptomatic or asymptomatic and detected by radiographic imaging • Hypersensitivity to brigatinib or its excipients. • Hypersensitivity to crizotinib or its excipients.	o ALT or AST >3×ULN (≥5 ULN for patients with confirmed concurrent liver metastasis) o Impaired excretory function, synthetic function or other conditions of decompensated liver disease o Acute hepatitis • Patients with baseline QTc >470 ms or symptomatic bradycardia. • Administration of agents with potential QT interval prolonging effects within 14 days prior to first dose of study medication for all patients and while on treatment through to the end of the study for crizotinib-treated patients only. • Administration of strong/potent cytochrome P450 (CYP)3A inhibitors or inducers within 14 days prior to first dose of study medication and while on treatment.
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) **Intervention(s) (n=[x]) and comparator(s) (n=[x])** **Permitted and disallowed concomitant medication**	*Intervention* (N = 137) Brigatinib 90 mg once daily (QD) orally for 7 days followed by 180 mg QD orally continuously, with or without food until disease progression, unacceptable toxicity, withdrawal of consent or death. Continuation of brigatinib beyond progression was permitted at the investigator's discretion if, there was evidence of continued clinical benefit. *Comparator* (N = 138) Crizotinib 250 mg twice daily orally with or without food until disease progression, unacceptable toxicity, withdrawal of consent or death.	*Intervention* (N = 152) Alectinib, 600mg twice daily (BID) orally with food until disease progression or unacceptable toxicity, withdrawal of consent or death. After progression (as per RECIST v1.1), patients discontinued the study medication after which they were treated at the discretion of the investigator according to local practice. *Comparator* (N = 151) Crizotinib, 250mg twice daily orally with or without food until disease progression, unacceptable toxicity, withdrawal of consent or death.
	1:1 randomisation of patients to the two treatment arms. Patients in the crizotinib arm who had experienced objective progression (assessed by the BIRC) or received radiotherapy to the brain were offered brigatinib as a	1:1 randomisation of patients to the two treatment arms. As per protocol, crossover between the treatment arms was not permitted. However, in countries where alectinib

	cross-over treatment, at the investigator's discretion with the sponsor's medical monitor approval as per protocol. After a washout period of ten days, patients in the 'crossover population' were given brigatinib 90 mg QD for seven days followed by 180 mg QD.	was available, patients who progressed on crizotinib received alectinib.

	Permitted concomitant medications • Palliative therapy and supportive care are permitted during the study for management of symptoms and underlying medical conditions that may develop during the study. • Local radiotherapy for patients with CNS lesions e.g. SRS. Patients are allowed to continue the study drug after appropriate interruption, as determined by the investigator with sponsor agreement; however, for analysis purposes, these patients will be considered to have progressive disease (PD). *Not permitted concomitant medications* • Any other systemic anticancer therapy, including, but not limited to: chemotherapeutic agents,	*Permitted concomitant medications* • Anticoagulants and antithrombotic agents (such as coumarin-derived anticoagulants, unfractionated heparin or low-molecular heparins, aspirin [≤325 mg/day], and clopidogrel). • Paracetamol up to 2 g/day. • Gastric pH elevating medications (such as proton pump inhibitors, H2 blockers, or antacids). • Local therapy (e.g. stereotactic radiotherapy or surgery) may be given to patients with isolated asymptomatic CNS progression (e.g. new CNS oligometastases). • Substrates of P-gp transporter or breast cancer resistance protein transporter o Substrates with a narrow therapeutic index (e.g. methotrexate, digoxin). • Medications which are predominately metabolised by CYP3A o Dose reductions may be required o CYP3A substrates with narrow therapeutic indices. • Medications which are predominately metabolised by CYP2B6 (e.g. bupropion, efavirenz). • Substrates which are predominately metabolised by pregame X receptor and constitutive androstane receptor-regulated enzymes (e.g.CYP3A4, CYP2B6, CYP2C8, CYP2C9, UGT1A1). • Agents known to cause bradycardia (e.g. beta-blockers, non-dihydropyridine calcium channel blockers, clonidine, and digoxin). • Substrates of P-gp (e.g. digoxin, dabigatran, colchicine, pravastatin). *Not permitted concomitant medications* • Potent inducers of CYP3A (e.g., rifampin, rifabutin, phenobarbital, phenytoin, carbamazepine, and St. John's wort) within two weeks or five half-lives (whichever is longer) before the first dose of study

	immunotherapy, biological response modifiers (excluding growth factors), radiotherapy, and/or systemic hormonal therapy (with the exception of local therapies, such as SRS, used for palliative or symptomatic control of existing lesions, with appropriate treatment interruption at the discretion of the investigator). Hormonal contraception is allowed. • Use of any other investigational drug or device. • Medications that are known to be associated with the development of Torsades de Pointes. • Extensive surgery requiring inpatient care (patients may have an interruption in therapy for 14 days should emergency surgery be required). • Medications and dietary (grapefruit-containing products) or herbal products (St John's Wort) that are strong inhibitors or inducers of CYPs, in particular CYP2C8 or CYP3A4, should be avoided. • Avoid CYP3A substrates with narrow therapeutic range, including, but not limited, to alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus in patients taking crizotinib. o If concomitant use of these CYP3A substrates with narrow therapeutic range is required in patients taking crizotinib, dose reductions of the CYP3A substrates may be required due to adverse reactions.	drug treatment and while on treatment with study drugs. • Potent inhibitors of CYP3A (e.g. ketoconazole) within two weeks or five half-lives (whichever is longer) before the first dose of study drug treatment and while on treatment with study drug. • Any concomitant medications known to affect QT interval duration, including but not limited to the following drugs: amiodarone, cisapride, clarithromycin, methadone and quinidine within two weeks before the first dose of study drug treatment for all patients and while on treatment through the end of the study for crizotinib-treated patients only. • Systemic immunosuppressive drugs, cytotoxic or chemotherapeutic agents (other than study drug treatment), ergot derivatives, probenecid, and bile acid-binding resins while on study treatment. • Systemic chemotherapy. • Radiotherapy/radionuclide therapy except for palliative radiotherapy to bone lesions or for pain control. • Additional investigational drug (except for during the follow-up period).

Primary outcomes (including scoring methods and timings of assessments)	**PFS as assessed by blinded independent review committee (BIRC):** defined as the time interval from the date of randomisation until the first date at which PD is objectively documented, or death due to any cause, whichever occurs first. Sensitivity analysis were conducted on the BIRC-assessed PFS based on investigator assessment. **Note: Patients with CNS lesions requiring local radiotherapy such as SRS were considered to have progressive disease.**	**PFS as assessed by the investigator:** defined as the time from randomisation to the first documented PD using RECIST v1.1 or death from any cause, whichever occurs first. **Note: Patients with CNS lesions requiring local radiotherapy such as SRS were not considered to have progressive disease.**
Other outcomes used in the economic model/specified in the scope	• **Confirmed ORR as assessed by BIRC:** defined as percentage of participants who are confirmed to have CR or PR using RECIST v.1.1 criteria in the ITT population. • **Intracranial PFS as assessed by BIRC**: defined as the time interval from the date of randomisation until the first date at which intracranial disease progression is objectively documented, or death due to any cause, whichever occurs first as per modified RECIST. • **Confirmed intracranial ORR as assessed by BIRC**: defined as the proportion of the patients who have achieved CR or PR in the CNS in randomised patients with brain metastases at baseline. • **OS**: defined as time interval from the date of randomisation until death due to any cause in the ITT population. • **HRQoL**: defined as the perceived quality of the participant's life, which includes self-reported multi-dimensional measures of physical and mental health. PROs and HRQoL were collected using the EORTC QLQ-C30 questionnaire (v3.0) and its lung cancer module (LC13). These were mapped to derive EQ-5D-3L scores for use in the model. • **Safety and tolerability** of brigatinib compared to crizotinib.	• **ORR as assessed by investigators**: defined as the percentage of patients who attain CR or PR using RECIST v1.1. • **DOR**: defined as the time from when response (CR or PR) was first documented to, first documented disease progression or death (whichever occurs first). • **Time to CNS progression as assessed by the IRC**: defined as the time from randomisation to the first occurrence of disease progression in the CNS using RECIST v1.1 along with: o C-PR – CNS progression rates at 6, 12, 18 and 24 months on the basis of cumulative incidence o C-ORR – ORR in patients with CNS metastases who have measurable disease in the CNS at baseline o C-DOR – DOR in patients who have a CNS OR • **PFS as assessed by the IRC:** defined time of randomisation to first documented PD using RECIST v1.1 or death from any cause, whichever occurs first. • **OS**: defined as time from randomisation to death from any cause. • **Safety and tolerability**. • **HRQoL**: Time-to-deterioration of lung cancer symptoms, patient functioning, and HRQoL between treatment arms as measured by the EORTC Quality-

		of-Life Questionnaire Core 30 (QLQ-C30) and its Lung Cancer Module (LC13). <u>Exploratory objectives</u> • To evaluate and compare patient's health status as assessed by the EQ-5D-3L questionnaire to generate utility scores for use in economic models for reimbursement.
Pre-planned subgroups	**Randomisation stratification factors:** • Presence of baseline brain metastases (yes or no) • Completion of at least one full cycle of previous chemotherapy for locally advanced or metastatic disease (yes or no) **Other pre-planned subgroups:** • Age (<65 vs ≥65 years) • Gender • ECOG performance status (0 or 1 vs. 2) • Race (Asian vs. non-Asian) • Smoking status (never or former vs. current)	**Randomisation stratification factors:** • Presence or absence of CNS metastases at baseline • ECOG performance status (0 or 1 vs. 2) • Race (Asian vs. non- Asian) **Other pre-planned subgroups:** • Age (<65 vs ≥65 years) • Sex • Patients with pre-treatment radiation therapy for CNS lesions • Smoking status

Secondary outcome list is not exhaustive. ALK, anaplastic lymphoma kinase; ALT, alanine transaminase; ANC, absolute neutrophil count; AST, aspartate transaminase; BIRC, blinded independent review committee; BID, twice daily; C-DOR, CNS duration of response; CNS, central nervous system; C-ORR, CNS objective response rate; C-PR, CNS progression rate; CR, complete response; CYP, cytochrome P450; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ECG, electrocardiogram; EORTC, European Organisation for Research and Treatment of Cancer; EQ-5D-3L, EuroQoL-five dimensions-3 levels; FDA, Food and Drug administration; FISH, fluorescence in situ hybridization; GI, gastrointestinal; GFR, glomerular filtration rate; HRQoL, health-related quality of life; IHC, immunohistochemistry; IRC, Independent Review Committee; NCI CTCAE, National Cancer Institute, common terminology criteria for adverse events; NSCLC, non-small cell lung cancer; OR, objective response; ORR, objective response rate, OS, overall survival; PD, progressive disease; P-gp, Permeability glycoprotein; PFS, progression-free survival; PR, partial response; PRO, patient reported outcomes; QD, once daily; QTc, corrected QT interval; RECIST, response evaluation criteria in solid tumours; SBRT, stereotactic body radiation therapy; SD, stable disease; SRS, stereotactic radiosurgery; TTR, time to treatment response; TKI, tyrosine kinase inhibitor

B.2.3.2 Differences between the ALTA-1L and ALEX study designs

Within this section, the key differences between the ALTA-1L[39] and the ALEX[59] trials in terms of design and patient baseline characteristics are considered. These include whether crossover was permitted, the definition of the progression endpoints and follow-up times reported in the publications as outlined in Table 6.

Table 6: Key trial differences

Design	ALTA-1L	ALEX
Inclusion of patients who had prior chemotherapy for advanced disease	Permitted per protocol	Not permitted per protocol
Treatment crossover after disease progression	Permitted per protocol	Not permitted per protocol
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 or absence of CNS metastases at baseline • ECOG performance status (0 or 1 vs. 2) • Race (Asian vs. non- Asian)
Primary endpoint	BIRC-assessed PFS	Investigator-assessed PFS
Definition of disease progression	• Progressive disease • Death • Local radiotherapy for CNS lesions	• Progressive disease • Death
Median follow-up time (months)	• IA1-11.0 (brigatinib arm.)[39] • IA2 - 24.9 (brigatinib arm.)[72]	• Primary - 18.6 (alectinib arm)[59] • Follow-up- 27.8 (alectinib arm)[65] • Final - 37.8 (alectinib arm)[73]
ALK testing	Local test to enrol patients	Central lab test to enrol patients

ALK, anaplastic lymphoma kinase; BIRC, blinded independent review committee; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; IA, interim analysis; PFS, progression-free survival

B.2.3.2.1 Crossover and subsequent therapies

In the ALTA-1L study, at the discretion of the investigator and with the sponsor's medical monitor approval, patients randomised to crizotinib who experienced progression as assessed by the blinded independent review committee (BIRC) or received radiotherapy to the brain were permitted to cross over to brigatinib in line with the pre-defined trial protocol. This occurred in 44.2% (n=61) of all patients from the crizotinib arm – further subsequent brigatinib use in patients randomised to crizotinib was identified through the concomitant medications (this use may have been at later lines or after the window had closed for being termed an "official switcher"). Therefore, the total amount of crossover summed to 52.9% (n=73). Note: a total of 74 patients in the crizotinib arm had disease progression at this data cut. Therefore, between 82.4-98.6% of patients who progressed whilst on crizotinib switched to brigatinib, depending on the definition of 'switcher'. In contrast, the protocol for ALEX stipulated that crossover was not permitted however, a small proportion (6.6%; n=10) of patients randomised to crizotinib received alectinib as a subsequent therapy after progression.

Subsequent therapy use reported in ALTA-1L and ALEX is outlined in Table 7. Data from the ALEX study is based on published information and hence may not coincide with the latest available data on subsequent therapy used after alectinib. A greater proportion of patients received a second-line ALK inhibitor after progression on crizotinib in the ALTA-1L study than is observed in the crizotinib treated patients from the ALEX trial. The extent of crossover in the ALTA-1L study is reflective of evolving clinical practice – brigatinib, alectinib and ceritinib are now all currently indicated post-crizotinib.

Due to high rates of crossover in ALTA-1L, the OS data is confounded, particularly in the crizotinib arm. Hence, the isolated effect on survival associated with frontline crizotinib treatment alone is not observed in the OS data, but rather the OS data reflects the effects of a pathway of sequential TKIs. To address this confounding issue, treatment switching analyses are conducted to adjust for the impact of subsequent brigatinib use on OS in the crizotinib arm (see Section B.3.3.5.2). However, these analyses are limited in that they introduce uncertainty and only adjust for the effects of crossover from crizotinib to brigatinib but not other ALK inhibitors due to limited data.

Table 7: Differences in subsequent therapies received after frontline treatment

Subsequent Anti-Cancer Treatment	Brigatinib ALTA-1L[39] (N = 137)	Crizotinib ALTA-1L[74] (N = 138)	Alectinib ALEX[55] (N = 152)	Crizotinib ALEX[55] (N = 151)
Surgery, N (%)	0	2 (1.4)	NA	NA
Radiotherapy, N (%)	1 (0.7)	11 (8.0)	NA	NA
Systemic Therapy, N (%)	34 (24.8)	96 (69.6)	40 (26.3)	44 (29.1)
ALK TKI, N (%)	30 (21.9)	93 (67.4)	18 (11.8)	36 (23.8)
Alectinib	10 (7.3)	24 (17.4)	0 (0.0)	10 (6.6)
Alectinib hydrochloride	0	1 (0.7)	NA	NA
Brigatinib	1 (0.7)	73 (52.9)	NA	NA
Ceritinib	4 (2.9)	4 (2.9)	4 (2.6)	14 (9.3)
Crizotinib	11 (8.0)	6 (4.3)	9 (5.9)	2 (1.3)
Lorlatinib	13 (9.5)	11 (8.0)	NA	NA
Other (lorlatinib, brigatinib, gefitinib, entrectinib, erolotinib)	NA	NA	6 (3.9)	10 (6.6)
Chemotherapy N (%)	13 (9.5)	13 (9.4)	39 (25.7)	13 (8.6)
Immunotherapy N (%)	3 (2.2)	4 (2.9)	2 (1.3)	0 (0.0)
VEGF-R N (%)	3 (2.2)	4 (2.9)	2 (1.3)	0 (0.0)
Other, N (%)	2 (1.5)	1 (0.7)	4 (2.6)	1 (0.7)

ALK, anaplastic lymphoma kinase; TKI, tyrosine kinase inhibitor; VEGF-R, vascular endothelial growth factor and receptor; NA, not applicable

Based on the data from Table 7, a greater proportion of patients in the ALTA-1L trial received subsequent ALK inhibitors after brigatinib than after alectinib in the ALEX trial. This is reflective of the rapidly evolving paradigm of treatment for ALK-positive advanced NSCLC and the fact that the ALTA-1L trial was conducted more recently than the ALEX trial, at a time when more ALK TKIs were available. It is anticipated that the final analysis of an even more mature data set from ALTA-1L will provide important information regarding the impact of sequential

therapies on survival. Due to lack of access to the individual patient-level data from the ALEX trial, we cannot address the imbalance of subsequent treatments between the ALTA-1L and ALEX trials, a factor which makes comparative analyses of OS outcomes from these trials highly challenging and uncertain.

B.2.3.2.2 Definition of disease progression

The ALTA-1L study defines disease progression as 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. The variation in the definition of the primary outcome impacts the following endpoints: BIRC-assessed PFS, investigator assessed PFS and BIRC-assessed intracranial PFS outcomes. Feedback obtained during a Takeda organised UK medical advisory board in January 2020 (see Section B.3.10) indicated that clinicians preferred the ALTA-1L definition of progression and considered it more reflective of real-world clinical practice.

Radiotherapy for brain metastases was considered by clinicians as a proxy for progression hence the exclusion of patients receiving radiotherapy to the brain from the primary efficacy measure (PFS) is thought to potentially augment the treatment effect in ALEX. In the ALTA-1L study, the number of BIRC-assessed PFS events occurring due to receipt of radiotherapy to the brain was small; n=2 in the brigatinib arm and n=8 in the crizotinib arm. Therefore, progression due to radiotherapy is considered unlikely to be a key driver of the primary efficacy results. Nevertheless, these are important methodological differences between the ALTA-1L and ALEX trials.

B.2.3.2.3 Follow-up time

The follow-up period in the ALTA-1L and ALEX studies differ by endpoint. Table 8 details the date of data cut-off and length of follow-up for each outcome considered within the economic model.

Table 8: Median follow-up period for key endpoints in the ALTA-1L and ALEX trials

	OS	BIRC-assessed PFS	INV-assessed PFS	Intracranial PFS
Median follow-up period				
Brigatinib arm ALTA-1L	Individual patient level data (DCO: 28 June 2019, IA2) ***24.9 months***			
Crizotinib arm ALTA-1L	Individual patient level data (DCO: 28 June 2019, IA2) ***15.2 months***			
Alectinib arm ALEX	Mok et al. 2019, (DCO: 30 November 2018) - ***37.8 months*** Note: only HRs and associated CIs are reported. KM curves are available for earlier data cuts:	Peters et al. 2017 (DCO: 9 February 2017) - ***18.6 months***	Mok et al. 2019 (DCO: 30 November 2018) - **37.8 months**	NA

	OS	BIRC-assessed PFS	INV-assessed PFS	Intracranial PFS
Median follow-up period				
	Peters et al. 2017 - ***18.6 months*** Camidge et al. 2018 - ***27.8 months***			
Crizotinib arm ALEX	Mok et al. 2019 - ***23 months*** Peters et al. 2017 - ***17.6 months*** Camidge et al. 2018 - ***22.8 months***	Peters et al. 2017 - ***17.6 months***	Mok et al. 2019 - ***23.0 months***	NA

BIRC, blinded independent review committee; CIs, confidence intervals; CNS, central nervous system; DCO, data cut-off; HRs, hazard ratios; IA, interim analysis; INV, investigator assessed; KM, Kaplan Meier; NA, not available; OS, overall survival; PFS, progression-free survival

B.2.3.3 ALTA-1L baseline characteristics and demographics

Baseline characteristics were generally well balanced between the treatment arms in the ALTA-1L study. Overall, the median age of patients in the study was 59 years. While there were no major differences with respect to gender and race, there were numerically slightly fewer female patients, more Asian patients and fewer white patients in the brigatinib arm compared with the crizotinib arm. The clinical characteristics of individuals in the ALTA-1L trial at baseline is reflective of the typical ALK-positive advanced NSCLC population.[75] Most patients entered the trial with a Stage IV diagnosis (94.2% and 91.3% in the brigatinib and crizotinib arms, respectively), a prognostically important factor indicative of advanced disease. Likewise, patients with intracranial brain metastases and who had prior chemotherapy for locally advanced or metastatic disease were included in the trial. The patient distribution of these clinically important characteristics was similar for both treatment arms (Table 9). Overall, no clinically meaningful differences between the brigatinib and crizotinib groups were observed.

Table 9: ALTA-1L patient baseline characteristics, ITT population

	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 (%) [a, b]	40 (29.2)	41 (29.7)	81 (29.5)
Prior chemotherapy for locally advanced/metastatic disease, N (%) [b]	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)
Diagnosis stage at study entry, 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	1.68	1.48	1.61
Histopathological classification at study entry, N (%)			
Adenocarcinoma	126 (92.0)	137 (99.3)	263 (95.6)
Adenosquamous carcinoma	3 (2.2)	1 (0.7)	4 (1.5)
Large cell	2 (1.5)	0	2 (0.7)
Squamous	4 (2.9)	0	4 (1.5)
Other	2 (1.5)	0	2 (0.7)
Organ involvement at study entry, N (%) [c]			
Lung	126 (92.0)	127 (92.0)	253 (92.0)
Other organ(s)	137 (100)	138 (100)	275 (100)
Liver	31 (22.6)	24 (17.4)	55 (20.0)
Bone	36 (26.3)	50 (36.2)	86 (31.3)
Brain - parenchymal	4 (2.9)	3 (2.2)	7 (2.5)
Brain - leptomeningeal	37 (27.0)	39 (28.3)	76 (27.6)

ECOG, Eastern Cooperative Oncology Group; SD, standard deviation
a = As assessed by the investigator
b = Randomisation stratification factor; proportion reflects actual number patients with this baseline characteristic
c = Patients may have more than one organ involved at study entry

B.2.3.4 Differences in patient baseline characteristics for ALTA-1L and ALEX

Key differences in patient baseline characteristics between in the ALTA-1L and ALEX studies are presented in Table 10. These differences are important when considering the results of these trials. Notable parameters include, the proportion of patients with brain metastases at baseline and the proportion who have had prior chemotherapy.

Table 10: Differences in key baseline characteristics between ALTA-1L and ALEX

	ALTA-1L		ALEX	
	Brigatinib (N = 137)	**Crizotinib (N = 138)**	**Alectinib (N = 152)**	**Crizotinib (N = 151)**
Brain metastases at baseline N (%)	40 (29%)	41 (30%)	64 (42%)	58 (38%)
Prior chemotherapy for locally advanced/metastatic disease, N (%)	36 (26%)	37 (27%)	0 (0%)	0 (0%)

B.2.3.4.1 Proportion of patients with brain metastases at baseline

A higher proportion of patients in the ALEX trial had CNS involvement at baseline for both the alectinib and crizotinib arms (42% and 38%, respectively) compared with those seen in the ALTA-1L trial (brigatinib: 29%, crizotinib: 30%).

The proportion of patients with baseline brain metastases in the real-world UK setting is difficult to determine as many centres do not routinely scan for CNS involvement at baseline. Results from a survey by the EORTC (including 66 UK physicians) showed that only 51% of

clinicians conducted brain scans during the diagnosis of NSCLC in patients with positive mutation (ALK or EGFR) across all disease stages.[76] Clinical experts confirm that this is either because of limited capacity in hospitals or patient reluctance due to the potential risk of losing their driving licence in the event that brain metastases are found. The BRIGALK study considered retrospective outcomes from patients treated with brigatinib in a French early access program – this is one of the few publications reporting real-world baseline brain metastases at diagnosis – the proportion of patients with baseline CNS involvement was 28.9% which more closely aligns with the ALTA-1L than the ALEX trial.[77]

There is a lesser impact of brain metastases at baseline on outcomes for patients treated with later generation TKIs (i.e. brigatinib and alectinib) because these are highly CNS active. This is demonstrated in the ALTA-1L study where brigatinib is similarly effective in patients with or without baseline brain metastases (see Section B.3.9). In contrast, studies have shown that patients on crizotinib frequently experience brain metastases due to its poor penetration of the blood-brain barrier.[39, 60-62] As a result, the presence of brain metastases at baseline is, as confirmed by clinicians and supported by data from ALTA-1L, recognised as a critical important prognostic factor for patients treated with crizotinib. The imbalance of patients with baseline brain metastases observed in ALTA-1L and ALEX, is particularly important when the crizotinib data are considered in indirect comparisons. Given the prognostic importance of brain metastases in patients treated with crizotinib, the imbalance between the trials impacts the outcomes observed in the crizotinib arms and therefore affects the relative magnitude of treatment effects for brigatinib vs. crizotinib and alectinib vs. crizotinib.

B.2.3.4.2 Proportion of patients having received prior chemotherapy

In the ALTA-1L study, 26% and 27% in the brigatinib and crizotinib arms, respectively received at least one full cycle of prior chemotherapy whilst the ALEX trial did not permit inclusion of patients who had prior chemotherapy. The relevance and receipt of prior chemotherapy in ALK-positive advanced NSCLC patients is highly dependent on local practice. Discussions with clinical experts indicates that some centres may sometimes initiate chemotherapy prior to receiving molecular test results, for reasons such as clinical need (e.g. to control worrying symptoms), turnaround times and treatment initiation targets. This is supported by real-world evidence from the UK ALK project where 45% of patients enrolled in the database were identified as having had chemotherapy prior to an ALK inhibitor.[78] These indicate that assessing the efficacy of ALK inhibitors following chemotherapy remains a clinically relevant unmet need addressed by the ALTA-1L study.

The inclusion of a cohort of patients who had received prior chemotherapy is seen by UK clinicians as an important strength of the ALTA-1L trial, for two reasons. Firstly, because in real-world clinical practice there is a small minority of patients who still receive chemotherapy first hence having data for the efficacy of brigatinib in this subgroup is important. Secondly, due to lack of evidence from the ALEX trial, alectinib is not NICE recommended nor funded by NHS England for use after chemotherapy, thus leaving these patients at a disadvantage as their only ALK TKI option is the less effective crizotinib. Brigatinib has the potential to address this unmet need in a small but important group of patients.

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

B.2.4.1 Definition of study groups in ALTA-1L

- *Intention-to-Treat (ITT) population* - All patients randomised to either brigatinib or crizotinib regardless of whether they received the allocated study drug or adhered to the assigned dose. The primary analyses of efficacy were based on the ITT population.

- *Treated population* - All patients who received at least one dose of either brigatinib or crizotinib. The safety of the study drugs was analysed using the treated population.

- *Any intracranial CNS disease population* - Patients in the ITT population who were determined by the BIRC assessing intracranial outcomes to have intracranial CNS metastases at baseline, regardless of whether they had at least one lesion that qualified as a target lesion in their baseline assessment.

- *No intracranial CNS disease population* - Patients in the ITT population who were not determined by the BIRC assessing intracranial outcomes to have intracranial CNS metastases at baseline.

- *Measurable intracranial CNS disease population* - Patients in the 'any intracranial CNS disease population' who were determined by the BIRC assessing intracranial outcomes to have had at least one target lesion in their baseline assessment.

- *Non-measurable intracranial CNS disease population* - Patients who were determined to have intracranial CNS disease at baseline but did not have measurable lesions by the BIRC assessing intracranial outcomes. This consists of all patients in the 'any intracranial CNS disease population' who are not included in the 'measurable intracranial CNS disease population'.

- *Crossover population* - Patients randomised to crizotinib who were permitted to crossover to brigatinib (i.e. received at least one dose of brigatinib) following objective progression assessed by the BIRC or receipt of radiotherapy to the brain. Patients who received brigatinib through alternative sources, such as by prescription in areas where it is commercially available, were not included in the crossover population.

- *Patient reported outcomes (PRO)-ITT population* - Patients in the 'ITT population' with a baseline QoL score and at least one post-baseline assessment. The HRQoL analyses were based on patients in the 'PRO-ITT population'.

B.2.4.2 Analysis of endpoints

The primary endpoint of ALTA-1L is PFS by BIRC based on the ITT population. The analysis of the primary endpoint was performed using a two-sided stratified log-rank test (stratification factors: presence of intracranial brain metastases at baseline [Yes vs. No], and prior chemotherapy for locally advanced or metastatic disease [Yes vs. No]) to compare the BIRC-assessed PFS of patients randomised to brigatinib with the BIRC-assessed PFS of patients randomised to crizotinib. The overall (two-sided) Type I error rate was controlled at 0.05. PFS

with a corresponding 95% confidence interval (CI) was estimated for each treatment arm using the Kaplan-Meier method. Treatment effect was estimated as a hazard ratio (HR) with 95% CI using the Cox regression model with the stratification factors as covariates.

Key secondary endpoints were tested using a closed testing procedure to control the overall type I error rate at 0.05. Analysis of a key secondary endpoint was considered significant if the test for that endpoint and comparisons of all other higher-priority secondary endpoints are significant at the two-sided 0.05 significance level. Rank ordering of key secondary endpoints was as follows:

1) Confirmed ORR, as assessed by the BIRC, per RECIST v1.1
2) Confirmed intracranial ORR, as assessed by the BIRC
3) Intracranial PFS, as assessed by the BIRC
4) OS

The primary analysis of the first three secondary endpoints listed above were to be performed at the time of the first interim analysis if the primary endpoint was met. Similarly, an analysis of OS was to proceed at the time of the first interim if the primary endpoint was met. However, the primary assessment of OS was planned to be performed after approximately three years after the last patient is enrolled, which is when 150 OS events are anticipated to be observed.

B.2.4.3 Analysis plan

Two interim analyses (IA) were planned after approximately 50% and 75% of the total expected PFS events (progression, radiotherapy to the brain or death events) have been observed. The final analysis will be conducted when 100% (198) of the total expected events occur. An O'Brien-Fleming Lan-DeMets alpha spending function was used to test for statistical significance at two-sided alpha level of 0.05. The first IA was performed after the first 99 events (data cut-off: 19 February 2018) were observed and the second after 149 events (data cut-off: 28 June 2019).

For the purposes of a sample size calculation, the median PFS for crizotinib was estimated as 10 months. The enrolment of approximately 270 patients in the ITT population was planned; the final enrolment was 275 patients. It was determined that a total of 198 PFS events will provide 90% power to detect a clinically meaningful 6-month improvement in PFS (HR=0.625). To preserve an experiment-wise type 1 error rate of 0.05, this power projection was based on a two-sided log-rank test and controlled at the two-sided 0.043 level, adjusting for the proposed interim analysis plan.

Pre-planned subgroup analyses of the primary endpoint were performed using the following pre-defined baseline factors: age, gender, race, smoking status, ECOG performance, receipt of prior chemotherapy for advanced disease and brain metastases.

B.2.4.4 Data management

In ALTA-1L, for any patient who did not experience the event of interest, their follow-up time was treated as censored in the analysis. A patient was considered not evaluable (NE) for response at a protocol-specified time point if no imaging/measurement was completed, or if

only a subset of lesion measurements were taken. A patient was considered to have a response if the criteria for response had been met at the protocol-specified time points immediately before and after the time point of the missing response. Other specific rules for data handling and censoring applicable to the primary analysis of PFS and sensitivity analyses are documented in the clinical study report (CSR). Imputation rules for missing initial cancer diagnosis dates and for selected prior anticancer therapies are also described.

B.2.4.5 Patient withdrawals

An electronic case report form (eCRF) was to be completed for any patient randomised and an end-of-treatment reason recorded for any patient who was randomised, regardless of whether they received study drug. At the latest data cut, 54.7% of patients randomised to brigatinib and 16.7% to crizotinib were still receiving treatment. The most common reason for discontinuation of study drug is disease progression for both arms. A detailed outline of eligible patients in the ITT population and rationale for attrition is summarised in Appendix D.

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

The methodology and conduct of the pivotal Phase III, randomised and comparative ALTA-1L study is considered to be robust and appropriate for assessing the efficacy and safety of brigatinib and crizotinib. Guidance produced by the Centre for Reviews and Dissemination (CRD) [70] was used to inform the quality assessment of ALTA-1L. In all domains of the Cochrane risk of bias tool, except from performance bias, the level of bias for ALTA-1L was shown to be low.

Selection bias was minimised in ALTA-1L with pre-specified eligibility criteria and all participants recruited in the trials were accounted for with reasons for attrition reported. Efficacy analyses were conducted in the ITT population and safety analyses in the treated population. Owing to the open-label study design, patients and study investigators were unblinded to which treatment is allocated. To limit this performance bias, two independent review committees, whose members were unaware of the trial drug assignments performed disease assessments. One for all disease according to RECIST v1.1 and the other exclusively for the evaluation of intracranial outcomes. In addition, any information collected on individuals following randomisation was concealed from all members of the BIRC. The complete quality assessment for both the ALTA-1L and ALEX studies is presented in Appendix D, and a summary for ALTA-1L is presented below in Table 11.

Table 11: Risk of bias assessment for ALTA-1L

Bias domain	Source of bias	ALTA-1L
Selection bias	Random sequence generation	Low
	Allocation concealment	Low
Performance bias	Blinding of participants and personnel	High
Detection bias	Blinding of outcome assessment	Low
Attrition bias	Incomplete outcome data	Low
Reporting bias	Selective reporting	Low
Other bias	Anything else, ideally prespecified	Low

B.2.6 Clinical effectiveness results of the relevant trials

This section reports the results of the ALTA-1L clinical trial. The results associated with the randomised ALEX clinical trial (alectinib vs. crizotinib) are well documented in the literature[40, 59, 65] and also in the alectinib NICE submission.[55] The key outcomes for efficacy in the ALTA-1L and ALEX studies are summarised in Appendix D.1.1.8, Table 11 and a naïve comparison of the BIRC-assessed PFS Kaplan-Meier curves is presented in Figure 44.

There were two IAs planned for ALTA-1L; the first (IA1) reported after approximately 50% of expected BIRC-assessed PFS events were observed (data cut-off: 19 February 2018)[39] and the second (IA2) after 75% of expected events (data cut-off: 28 June 2019).[72] The final analysis will be conducted after 100% of expected events are observed.

The primary outcome in the randomised ALTA-1L study is efficacy measured using the composite endpoint, PFS as assessed by BIRC. Investigator-assessed PFS was also measured as a protocol-specified sensitivity analysis of the BIRC-assessed PFS. Key secondary endpoints include confirmed ORR, intracranial ORR, intracranial PFS (all assessed by blinded review) and OS.

B.2.6.1 Summary of results from the first interim analysis (IA1)

The primary endpoint was met at the first IA (HR=0.49, (95% CI: 0.33-0.74, p=0.0007). Despite a relatively short median follow-up time (11.0 months for brigatinib and 9.3 months for crizotinib) at the IA1, brigatinib demonstrated significantly superior efficacy compared to crizotinib. The IA2 results for the primary endpoint are consistent with those reported at the first, with both showing highly significant risk reduction in favour of brigatinib (see below).

In line with the pre-defined protocol, analysis of the highest-priority secondary endpoint which is confirmed ORR (assessed by the BIRC) proceeded after the primary endpoint was met (at the first IA). The trend of confirmed responses was in favour of brigatinib over crizotinib. However, this had not yet reached statistical significance. As such, formal statistical testing of secondary endpoints was undertaken at the second IA as per the pre-defined protocol (see Section B.2.4.2).

The latest available data (i.e. IA2) for all endpoints are discussed in more detail below and it is this data that forms the basis of this submission.

B.2.6.2 Primary efficacy endpoint

B.2.6.2.1 Progression-free survival per blinded independent review committee

The primary endpoint in the ALTA-1L trial was progression-free survival (PFS) as assessed by the BIRC, as per RECIST v1.1. PFS was defined as the time interval from the date of randomisation until the first date at which disease progression is objectively documented, or death due to any cause, whichever occurs first in the ITT population. The receipt of local radiotherapy to CNS lesions was also considered a progression event because this was considered to be more reflective of current clinical practice and allows for a cleaner measurement of the efficacy of brigatinib.

At the latest data cut,[72] 150 patients (55%) had experienced a PFS event: 63/137 patients (46%) in the brigatinib arm and 87/138 patients (63%) in the crizotinib arm. The most common reason for patients meeting the PFS criteria in both arms was disease progression. PFS per BIRC was significantly improved in the brigatinib arm compared with the crizotinib arm (HR: 0.49 [95% CI: 0.35-0.68], p<0.0001), equating to a 51% reduction in the risk of a PFS event or death compared with crizotinib. After a median follow-up of 24.9 months for brigatinib and 15.2 months for crizotinib, the median PFS per BIRC in the brigatinib group was longer than that of the crizotinib group (24.0 months [18.5-not evaluable] vs 11 months [9.2-12.9]) as displayed in Table 12

. The 12-month estimated PFS was 69% (95% CI: 60-77) for the brigatinib group compared with 46% (95% CI: 36-54) for the crizotinib group. Furthermore, the 24-month estimated PFS was 48% (95% CI: 39-57) and 26% (95% CI: 18-35) for brigatinib vs. crizotinib, respectively. The magnitude of clinical benefit associated with brigatinib is substantial and clinically meaningful, with clear and sustained separation between treatment groups in the BIRC-assessed PFS time curves appearing as early as three months after randomisation (Figure 4).

Sensitivity analysis was carried out for the primary outcome as per the investigator assessment. As shown in Table 12

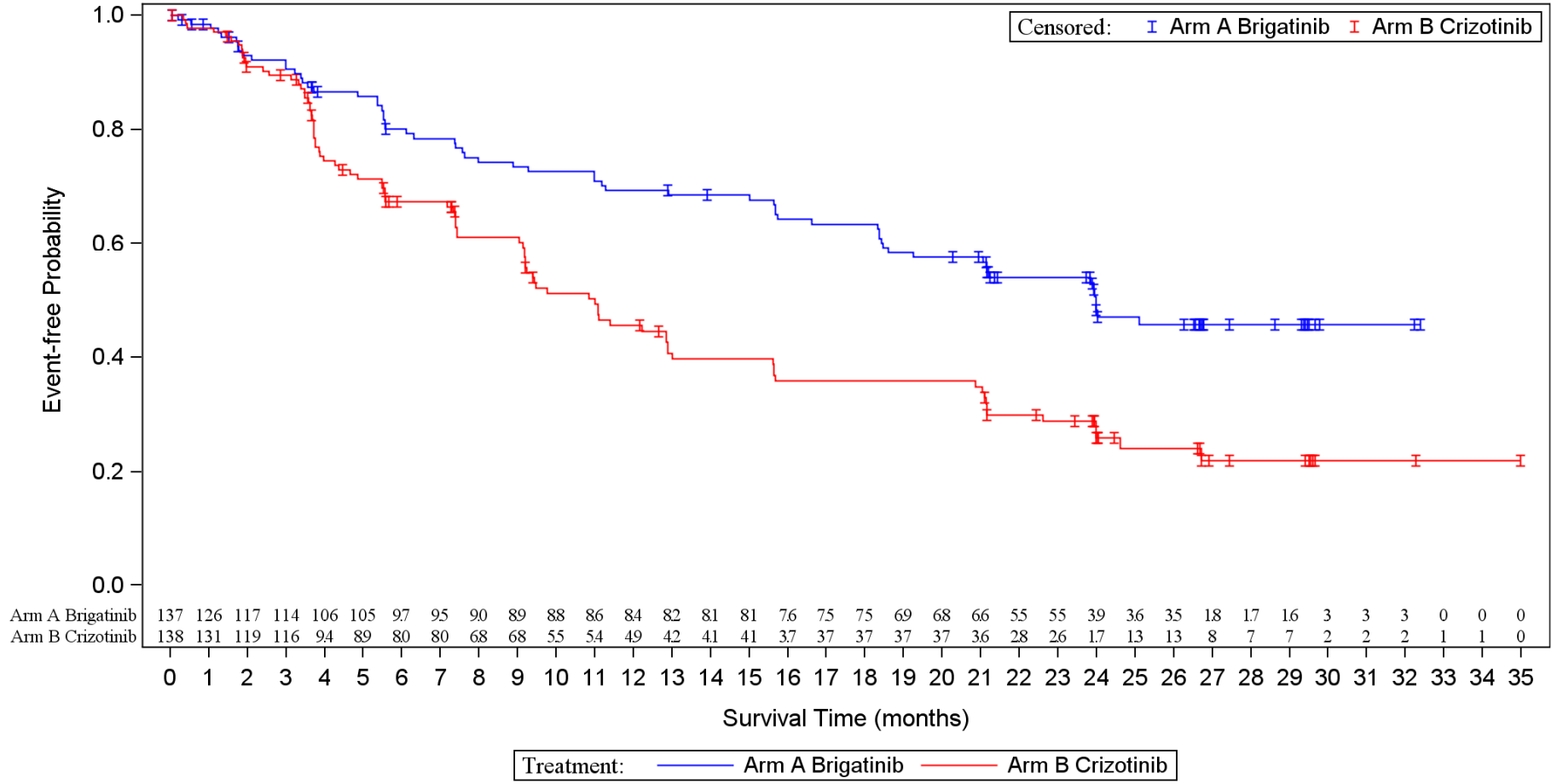
, the investigator (INV)-assessed PFS is supportive and consistent with the BIRC-assessed PFS.

Table 12: BIRC- and INV-assessed PFS in the ITT population

	BIRC-assessed		INV-assessed	
	Arm A Brigatinib (N = 137)	**Arm B Crizotinib (N = 138)**	**Arm A Brigatinib (N = 137)**	**Arm B Crizotinib (N = 138)**
Number with events (%)	63 (46.0)	87 (63.0)	59 (43.1)	92 (66.7)
Death	7 (5.1)	5 (3.6)	8 (5.8)	4 (2.9)
Progressed Disease	54 (39.4)	74 (53.6)	50 (36.5)	84 (60.9)
Palliative radiotherapy to the brain	2 (1.5)	8 (5.8)	1 (0.7)	4 (2.9)
Median PFS (95% CI)	23.984 (18.46, NE)	11.006 (9.17, 12.88)	29.437 (21.22, NE)	9.232 (7.39, 12.88)
HR (95% CI)	0.489 (0.35, 0.68)	--	0.434 (0.31, 0.61)	--
p-value	<0.0001		<0.0001	--
Estimated PFS, % (95% CI), at:				
6 months	80.1 (72, 86)	67.3 (58, 75)	80.4 (72, 86)	65.1 (56, 73)
12 months	69.3 (60, 77)	45.5 (36, 54)	69.4 (61, 77)	43.3 (34, 52)
18 months	63.4 (54, 71)	35.8 (27, 45)	63.0 (54, 71)	33.9 (25, 42)
24 months	48.2 (39, 57)	26.0 (18, 35)	55.6 (46, 64)	23.6 (16, 32)
Log-rank p-value	<0.0001	--	--	--

BIRC: blinded independent review committee; HR: hazard ratio; ITT: intent to treat; KM: Kaplan-Meier; NE: not estimable; PFS: progression-free survival. P-values from a log-rank test stratified by presence of brain metastases and prior chemotherapy for locally advanced or metastatic disease at study entry. The HR and associated p-value were obtained using a Cox proportional hazards model with randomisation stratification factors as covariates.

Figure 4: BIRC-assessed PFS in the ITT population



*Computed from log-rank test

B.2.6.3 Key secondary efficacy endpoints

B.2.6.3.1 Objective response rates

Objective response rate (ORR) as assessed by BIRC, was defined as percentage of participants who are confirmed to have achieved complete response (CR) or partial response (PR) using RECIST v.1.1.[79] At the latest data cut, confirmed ORR was higher in patients treated with brigatinib than in patients treated with crizotinib. As shown in Table 13 confirmed ORR by BIRC assessment was 73.7% (95% CI: 65.52-80.87) in the brigatinib arm compared with 61.6% (95% CI: 52.94-69.74) in the crizotinib arm with an associated odds ratio of 1.73 (95% CI: 1.04-2.88; p=0.0342) in favour of brigatinib. The onset of response was rapid with median time to response by BIRC assessment of 1.8 months with brigatinib and 1.9 months for crizotinib.

Table 13: BIRC-assessed ORR in the ITT population

	Brigatinib (N = 137)	**Crizotinib (N = 138)**
Best confirmed response, N (%)		
CR	20 (14.6)	12 (8.7)
PR	81 (59.1)	73 (52.9)
Stable disease	14 (10.2)	29 (21.0)
PD	7 (5.1)	9 (6.5)
NE [a]	15 (10.9)	15 (10.9)
Confirmed ORR [b]		
N (%)	101 (73.7)	85 (61.6)
(95% CI)	(65.52, 80.87)	(52.94, 69.74)
Odds ratio (95% CI) [c]	1.73 (1.04, 2.88)	--
p-value [c]	0.0342	--
ORR (confirmed + unconfirmed) [d]		
N (%)	108 (78.8)	103 (74.6)
(95% CI)	(71.03, 85.34)	(66.53, 81.65)
Odds ratio (95% CI) [c]	1.25 (0.71, 2.19)	--
P-value [c]	0.4376	--

BIRC, blinded independent review committee; CR, complete response; ITT, intent-to-treat; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours

a = Includes patients who had non-measurable disease at baseline by BIRC with best overall response as PR or non-CR/non-PD, died early, or with unknown response

b = Confirmed ORR was defined as the proportion of patients who achieved confirmed CR or PR per RECIST v1.1.

c = Odds ratios and p-values were from a Cochran-Mantel-Haenszel test

B.2.6.3.2 Duration of response

Duration of response (DOR) as assessed by BIRC among confirmed responders in the ITT population is summarised in Table 14. DOR was defined as the time interval from the date that the criteria for CR/PR is first met (whichever is first recorded) until the first date that progressive disease (PD) is objectively recorded.

85 (61.6%) patients were confirmed responders in the crizotinib arm and the median DOR among them was 13.8 months (95% CI: 9.3-20.8). In the brigatinib arm, 101 (73.7%) patients were confirmed responders by the BIRC however, the median DOR was not reached (median NE, [95% CI: 19.4-NE]). This was due to immature data as 56.4% of confirmed responders were censored indicating longevity of response in those treated with brigatinib. The extended DOR in the brigatinib group was maintained over longer follow-up with the estimated proportion of responders having a sustained response at 24 months being 51.3% (95% CI: 40-61) vs. 29.6% (95% CI: 18-42) in the crizotinib group.

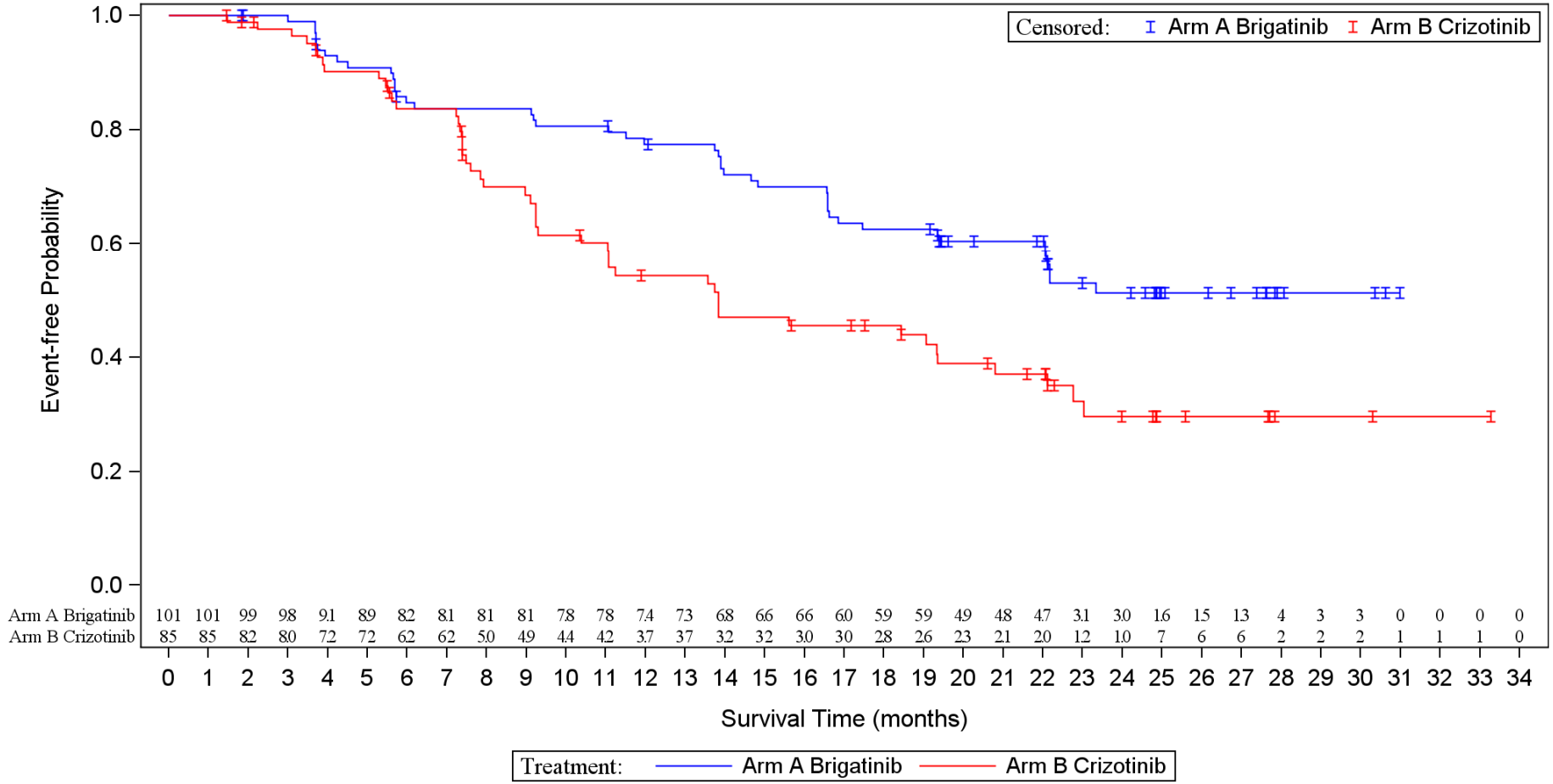
As illustrated in the Kaplan-Meier curve for DOR (Figure 5), separation between brigatinib and crizotinib appeared after approximately seven months, (which reflects about three clinical tumour assessments) and was sustained thereafter.

Table 14: BIRC-assessed DOR in confirmed responders in the ITT population

	Brigatinib (N = 137)	**Crizotinib (N = 138)**
Number with confirmed response (%)	101 (73.7)	85 (61.6)
Number censored (%)	57 (56.4)	37 (43.5)
Median DOR (95% CI)	NE (19.38, NE)	13.83 (9.30, 20.80)
KM estimate PFS % (95% CI) at:		
6 months	84.7 (76, 90)	83.7 (74, 90)
12 months	77.5 (68, 85)	54.4 (42, 65)
18 months	62.6 (52, 71)	45.6 (34, 57)
24 months	51.3 (40, 61)	29.6 (18, 42)

BIRC: blinded independent review committee; DOR: Duration of Response; KM, Kaplan-Meier; PFS, progression-free survival; NE, not evaluable; ITT, intention-to-treat

Figure 5: BIRC-assessed DOR in the ITT population



B.2.6.3.3 Intracranial outcomes

Intracranial progression-free survival

BIRC-assessed intracranial PFS (as per modified RECIST criteria) among patients with any brain metastasis at baseline was significantly longer with brigatinib than with crizotinib. The HR among patients with any brain metastasis at baseline was 0.31 (95% CI: 0.17-0.56), reflecting a very substantial risk reduction of 69% in intracranial progression in patients treated with brigatinib, p<0.0001 (see Table 15).

21/47 (45%) of patients in the brigatinib arm and 32/49 (65%) of patients in the crizotinib arm that had any baseline brain metastases experienced an intracranial event. Median intracranial PFS in the brigatinib arm for this subgroup is 24.0 months (95% CI:12.91-NE), while median intracranial PFS in the crizotinib group is lower at 5.6 months (95% CI: 3.71-7.52). As illustrated in the Kaplan-Meier curve (Figure 6), separation between groups in favour of the brigatinib arm appeared after approximately two months, which corresponds to the first post-baseline tumour assessment, and was sustained thereafter. This pattern indicates that the clinical benefit with brigatinib is obtained very early in the course of treatment.

This clearly demonstrates that patients with baseline brain metastases are a very high-risk group who progress quickly on crizotinib but progress much more slowly on brigatinib.

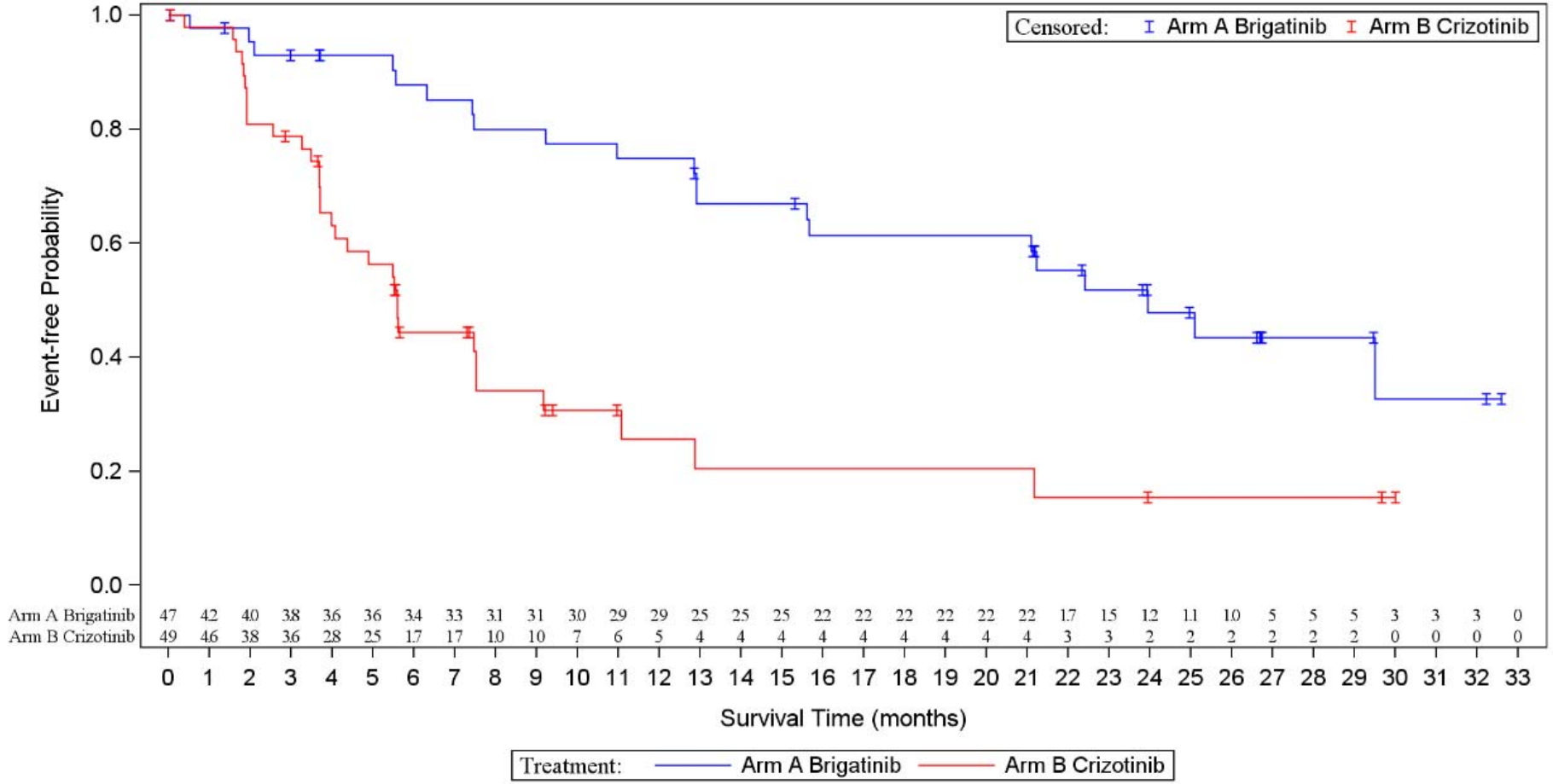
In the ITT population, brigatinib also demonstrated superior intracranial PFS in the combined cohort of patients with and without brain metastases at baseline. Time to intracranial progression was delayed for patients treated with brigatinib compared to crizotinib-treated patients. Median intracranial PFS in the brigatinib arm was 32.30 months (95% CI: 29.51-NE), while in the crizotinib arm this was 24.0 months (95% CI: 12.96-NE)[80] The Kaplan-Meier curve for intracranial PFS in the ITT population is depicted in Section B.3.3.4 (Figure 33).

Table 15: BIRC-assessed intracranial PFS in patients with any baseline brain metastases

	Brigatinib (N = 47) [a]	**Crizotinib (N = 49) [a]**
Number with events (%)	21 (44.7)	32 (65.3)
Median intracranial PFS, months (95% CI)	23.95 (12.91, NE)	5.59 (3.71, 7.52)
HR (95% CI)	0.31(0.17, 0.56)	--
p-value	<0.0001	--
Estimated intracranial PFS, % (95% CI) at:		
6 months	87.7 (73, 95)	44.4 (30, 58)
12 months	74.8 (58, 86)	25.6 (12, 42)
18 months	61.3 (44, 75)	20.5 (8, 37)
24 months	47.9 (30, 63)	15.4 (5, 32)
Log-rank p-value	<0.0001	--

NE: not estimable; HR: hazard ratio; PFS: progression-free survival. p-values from a log-rank test stratified by prior chemotherapy for locally advanced or metastatic disease at study entry. The HR and associated p-value were obtained using a Cox proportional hazards model with randomisation stratification factors as covariates
a = As assessed by the blinded independent review committee

Figure 6: BIRC-assessed intracranial PFS in patients with any brain metastases at baseline



BIRC-assessed intracranial objective response rates

Intracranial objective response rates (ORR) were assessed for patients with measurable, non-measurable and any brain metastases identified at baseline Table 16. Overall, brigatinib was significantly and consistently associated with improved response rates in comparison to crizotinib.

For patients with measurable brain metastases, the confirmed BIRC-assessed intracranial ORR was significantly higher in the brigatinib arm (77.8% [95% CI: 52.36-93.59]) than in the crizotinib arm (26.1% [95% CI:10.23-48.41]) indicating superior efficacy of brigatinib in the brain. This difference was associated with an odds ratio of greater than 11 (p=0.0014 in favour of brigatinib. It is also noteworthy that regardless of tumour size, more patients treated with brigatinib achieved a complete response intracranially compared with crizotinib (44.7% vs 4.4%, respectively for any tumour size in the brain).

Table 16: BIRC-assessed intracranial objective response rates

	Measurable		Non-measurable		Any	
	Brigatinib (N = 18)	**Crizotinib (N = 23)**	**Brigatinib (N = 29)**	**Crizotinib (N = 26)**	**Brigatinib (N = 47)**	**Crizotinib (N = 49)**
Best confirmed response, N (%)						
CR	5 (27.8)	0	16 (55.2)	2 (7.7)	21 (44.7)	2 (4.1)
PR	9 (50.0)	6 (26.1)	1 (3.4)	0	10 (21.3)	6 (12.2)
SD [a]	2 (11.1)	11 (47.8)	5 (17.2)	16 (61.5)	7 (14.9)	27 (55.1)
PD	1 (5.6)	2 (8.7)	3 (10.3)	5 (19.2)	4 (8.5)	7 (14.3)
NE [b]	1 (5.6)	4 (17.4)	4 (13.8)	3 (11.5)	5 (10.6)	7 (14.3)
Confirmed iORR, N (%) (95% CI) [c]	14 (77.8) (52.36, 93.59)	6 (26.1) (10.23, 48.41)	17 (58.6) (38.94, 76.48)	2 (7.7) (0.95, 25.13)	31 (66.0) (50.69, 79.14)	8 (16.3) (7.32, 29.66)
Odds ratio (95% CI) [d]	11.67 (2.15, 63.27)	--	14.76 (3.00, 72.72)	--	11.75 (4.19, 32.91)	--
p-value [d]	0.0014	--	0.0001	--	<0.0001	--
iORR (confirmed + unconfirmed), N (%) (95% CI) [e]	14 (77.8) (52.36, 93.59)	7 (30.4) (13.21, 52.92)	19 (65.5) (45.67, 82.06)	3 (11.5) (2.45, 30.15)	33 (70.2) (55.11, 82.66)	10 (20.4) (10.24, 34.34)
Odds ratio (95% CI) [d]	9.22 (1.76, 48.43)	--	14.20 (3.35, 60.10)	--	11.10 (4.06, 30.39)	--
p-value [d]	0.0036	--	<0.0001	--	<0.0001	--

CI, confidence interval; CR, complete response, ORR, overall response rate; NE, not-estimable; PD, progressed disease; PR, partial response; SD, stable disease

a = Stable disease in patients with only non-measurable brain disease includes those without CR or PD

b = Includes patients who died early, or with unknown response.

c = Confirmed intracranial ORR was defined as the proportion of patients who achieved confirmed intracranial CR or PR

d = Odds ratios and p-values were from a Cochran-Mantel-Haenszel test stratified by prior chemotherapy for locally advanced or metastatic disease at study entry.

e = intracranial ORR is defined as the proportion of patients who achieved confirmed or unconfirmed intracranial CR or PR

BIRC-assessed intracranial duration of response

Intracranial duration of response (DOR) among confirmed responders is summarised in Table 17. For patients with measurable brain metastases at baseline, the median intracranial DOR was not reached for the brigatinib arm and was 9.2 months in the crizotinib arm. This demonstrates a clear trend towards more brigatinib-treated patients exhibiting durable responses of ≥12 months compared with crizotinib-treated patients. Consistent with the median PFS for brigatinib, median intracranial DOR for patients with any brain metastases at baseline was 24.0 months (9.2 months with crizotinib) demonstrating substantial durability of intracranial efficacy with brigatinib.

Table 17: BIRC-assessed intracranial duration of response

	Measurable		Any	
	Brigatinib (N = 18)	**Crizotinib (N = 23)**	**Brigatinib (N = 47)**	**Crizotinib (N = 49)**
Number with confirmed response (%)	14 (77.8)	6 (26.1)	31 (66.0)	8 (16.3)
Number censored (%)	10 (71.4)	3 (50.0)	19 (61.3)	5 (62.5)
iDOR Median (95% CI)	NE (5.65, NE)	9.232 (3.88, 9.23)	24.016 (16.92, NE)	9.232 (3.88, NE)
KM estimate, % (95% CI)				
6 months	83.3 (48, 96)	60.0 (13, 88)	93.1 (75, 98)	71.4 (26, 92)
12 months	75.0 (41, 91)	NE (NE, NE)	79.2 (59, 90)	35.7 (1, 78)
18 months	64.3 (30, 85)	NE (NE, NE)	67.5 (47, 82)	35.7 (1, 78)
24 months	64.3 (30, 85)	NE (NE, NE)	55.0 (32, 73)	NE (NE, NE)

BIRC, blinded independent review committee; CI, confidence interval; KM, Kaplan-Meier; NE, not estimable; iDOR, intracranial duration of response

B.2.6.3.4 Overall Survival

Median OS was not reached for either arm after a median follow-up of 24.9 months in the brigatinib arm and 15.2 months in the crizotinib arm as the OS data is still maturing (Table 18). 70 deaths occurred with 33 (24.1%) among patients treated with brigatinib and 37 (26.8%) with crizotinib (including deaths that occurred during the crossover phase). The most common cause of death was disease progression.

Notably, 44.2% of patients in the crizotinib arm 'officially' crossed over to brigatinib as per the crossover protocol (82.4% of patients who progressed on crizotinib); when considering subsequent therapies as identified through concomitant medications, 52.9% of patients in the crizotinib arm in total crossed over to brigatinib (98.6% of patients who progressed on crizotinib). This high rate of crossover from crizotinib to brigatinib on progression confounds the OS results in the ALTA-1L trial. However, despite this confounding, the HR for OS based on randomised treatment assignments was less than 1 (HR=0.92; 95% CI: 0.57-1.47), indicating a trend towards improved overall survival in the brigatinib arm. As discussed earlier (see Section B.2.3.2), such crossover from crizotinib to alectinib was not allowed per protocol in the ALEX trial, thus making cross-trial comparisons very challenging for OS.

Nevertheless, a naïve comparison of the ALTA-1L and ALEX trials (see Appendix D.1.1.8, Table 11) shows that the 2-year OS of the brigatinib and crizotinib arms in ALTA-1L (76% and 74%, respectively) resembles that of the alectinib arm in ALEX (73%). As expected, the 2-year estimated OS in the crizotinib arm for ALTA-1L appears to be superior to the 2-year OS

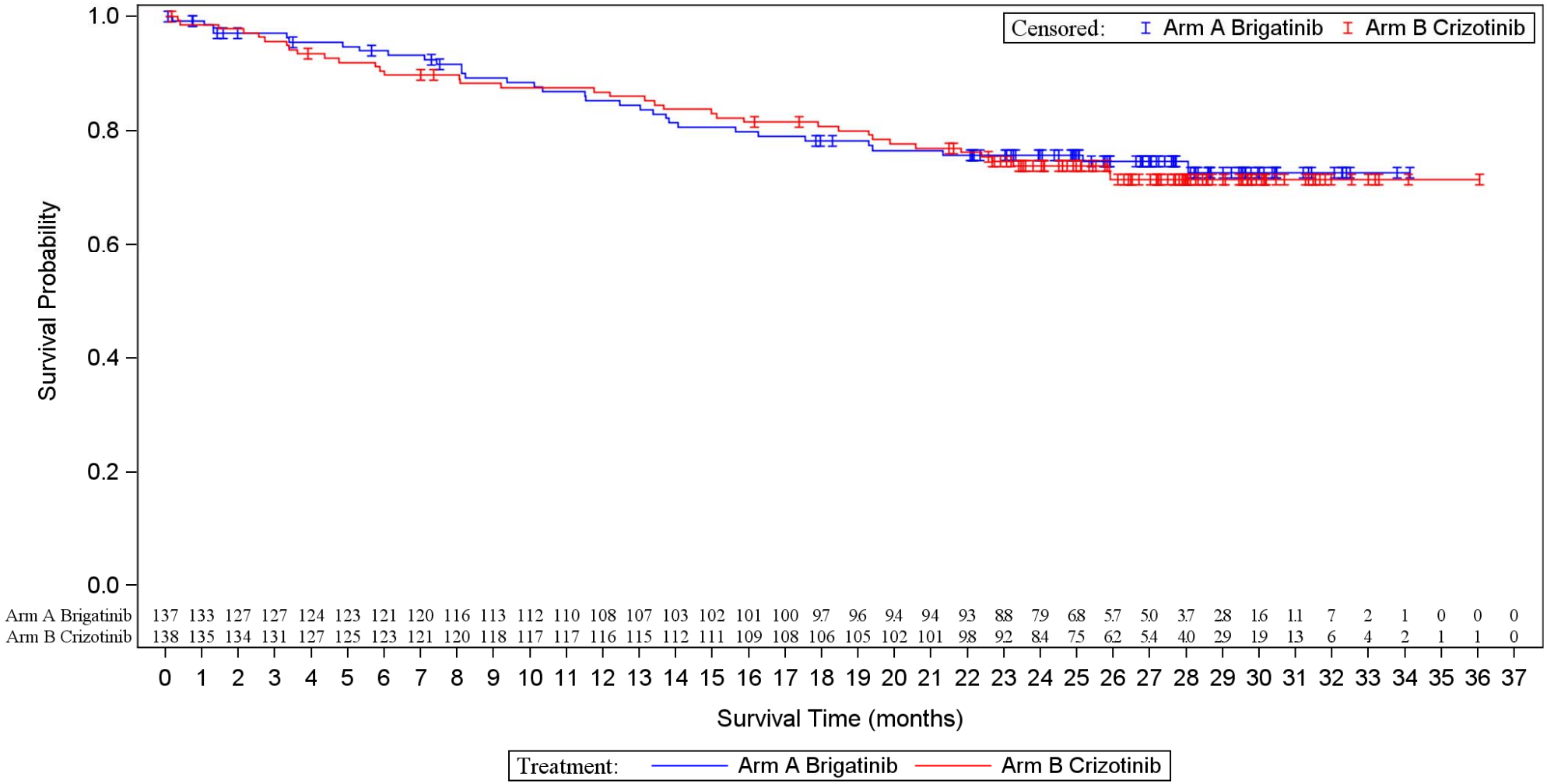
estimated in the crizotinib arm for the ALEX study (65%) reflecting the impact of crossover in ALTA-1L (see Section 3.3.5.2).

Table 18: Overall survival in the ITT population

	Brigatinib (N = 137)	**Crizotinib (N = 138)**
Number of deaths (%)	33 (24.1)	37 (26.8)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
HR (95% CI)	0.916 (0.57, 1.47)	--
p-value	0.7134	--
Estimated OS, % (95% CI) at:		
6 months	94.0 (88, 97)	90.5 (84, 94)
12 months	85.3 (78, 90)	86.8 (80, 91)
18 months	78.2 (70, 84)	80.8 (73, 86)
24 months	75.8 (67, 82)	73.8 (65, 80)
Log-rank p-value	0.7710	--

HR, hazard ratio; ITT, intent to treat; KM: Kaplan-Meier; NE, not estimable; OS, overall survival; PFS, progression-free survival. P-values from a log-rank test stratified by randomisation stratification factors at study entry (presence of brain metastases at baseline and prior chemotherapy for locally advanced or metastatic disease). The HR and associated p value were obtained using a Cox proportional hazards model with randomisation stratification factors as covariates.

Figure 7: Overall Survival in the ITT population



B.2.6.3.5 Health-related quality of life

Global health status (GHS)/QoL and other HRQoL domains were assessed as a change in score on the EORTC QLQ-C30 questionnaire (v.0)[43] in patients in the PRO-ITT population. These are patients in the ITT population with a baseline QoL score and at least one post-baseline QoL assessment (n=131, for brigatinib and crizotinib).

The EORTC QLQ-C30 is a cancer-specific questionnaire with five functional scales (physical, role, cognitive, emotional and social functioning), three symptom scales (fatigue, pain, and nausea/vomiting) and a HRQoL scale. [43] Six single-item scales were also included: dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties. Changes in symptoms of lung cancer were evaluated as time to deterioration in dyspnoea as assessed by the EORTC lung cancer module, QLQ-LC13 (v3.0). The QLQ-LC13 module includes 13 questions tailored to assess symptoms commonly linked with lung cancer, treatment-related side effects and use of pain medication. The use of EORTC QLQ-C30 and QLQ-LC13 questionnaires allows for important factors from the patient's perspective relating to disease burden and treatment tolerability to be adequately captured in the QoL assessment. QoL assessment using the EORTC and LC13 questionnaires were carried out at baseline, per schedule of events throughout the study and at 30-days after last dose visit. Compliance rates for both questionnaires in eligible patients was greater than 90% for both brigatinib and crizotinib arms during treatment cycles (i.e. from baseline prior to end of treatment).

Figure 8 presents the mean change from baseline global QoL and functioning scores. Clear trends in favour of brigatinib compared with crizotinib were observed in GHS/QoL and functioning scores with significant differences in emotional and cognitive functioning. In the symptom domain shown in Figure 9 significant changes in scores reported by brigatinib-treated patients was observed for fatigue, nausea and vomiting, appetite loss and constipation.

Figure 8: Between-group mean differences in overall change from baseline (GHS/QOL and functioning scores in the PRO-ITT population based on EORTC QLQ-C30)

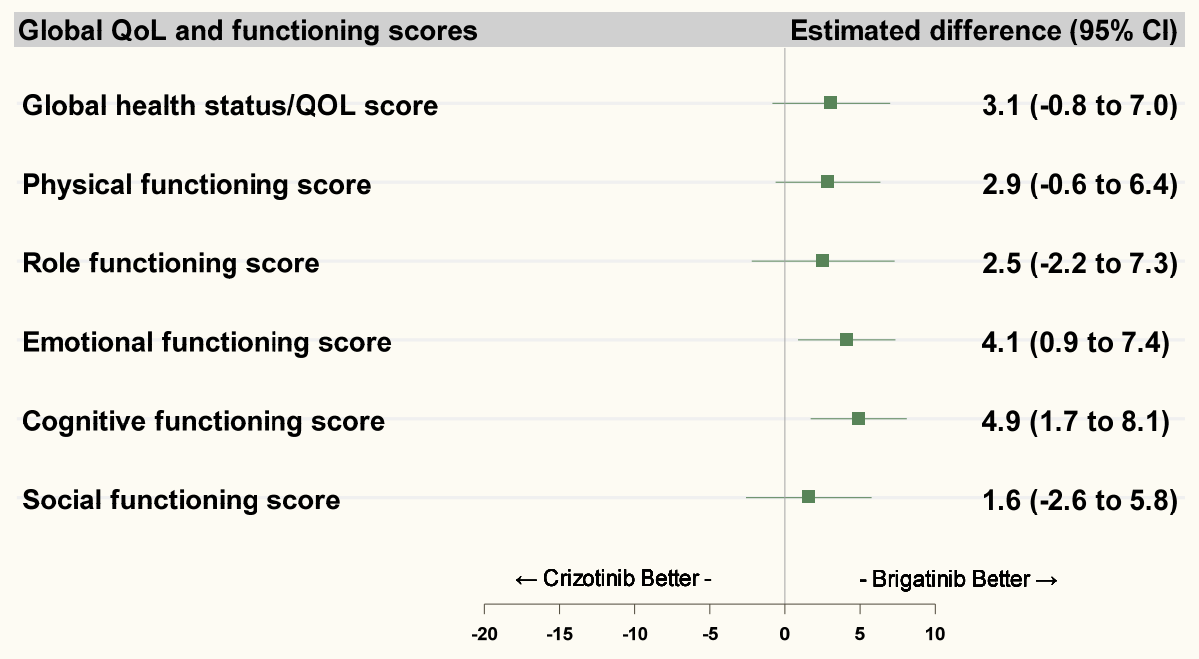
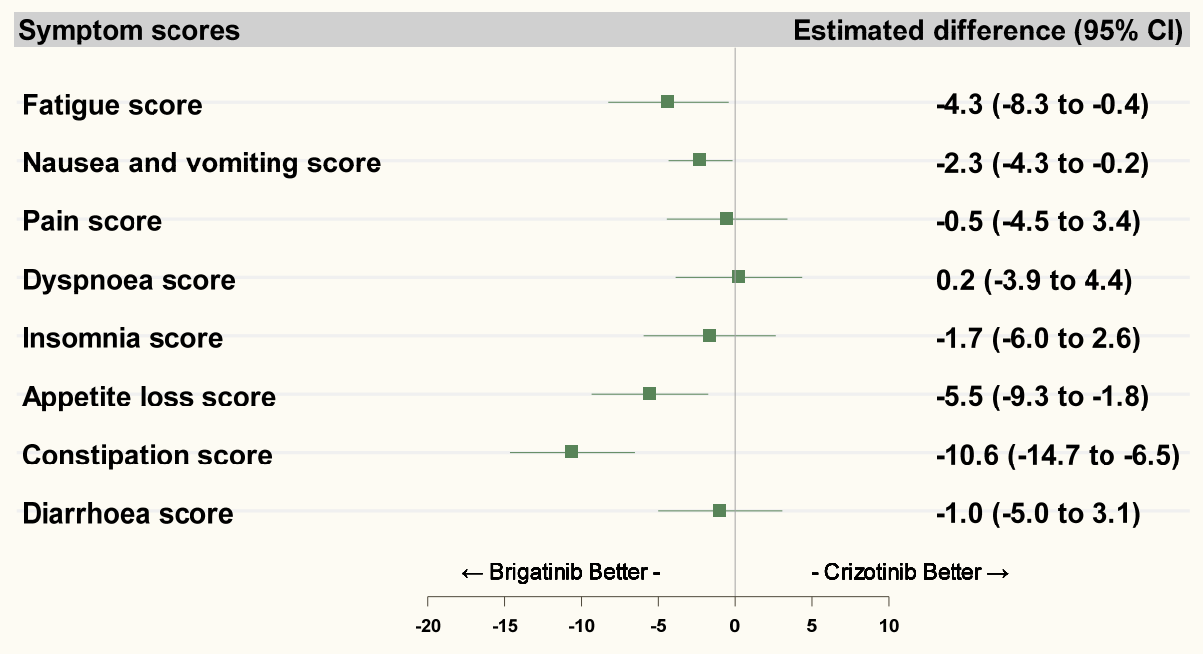


Figure 9: Between-group mean differences in overall change from baseline (Symptom scores in the PRO-ITT population based on EORTC QLQ-C30)



Time to worsening in QoL score

Clinically meaningful time to worsening was defined based on an increase of ≥10 points from baseline score. Brigatinib substantially delayed time to worsening compared with crizotinib based on EORTC QLQ-C30 responses from items 29 to 30. The median time to worsening in QoL score was 26.7 months for brigatinib compared with 8.3 months for crizotinib. The corresponding HR was 0.70 (95% CI: 0.49-1.00; p=0.0485). Brigatinib was shown to have a numeric improvement over crizotinib in time to worsening for all functional domains, with statistically significant improvements observed in emotional and social functioning. In terms of symptom subscales, scores for fatigue, nausea/vomiting, appetite loss and constipation were significantly improved with brigatinib over crizotinib (Table 19). Considering that these are patients with advanced stage disease, the improvements seen with brigatinib over crizotinib are notable.

Table 19: Time to worsening in the PRO-ITT population based on EORTC QLQ-C30

	Brigatinib (N = 131) [a] Median (months)	Crizotinib (N = 131) [a] Median (months)	Hazard Ratio (95% CI)	Log-rank p-value
QoL	26.74 (8.34, NE)	8.31 (5.68, 13.54)	0.70 (0.49, 1.00)	0.0485
Functioning				
Physical functioning	NE (13.86, NE)	10.32 (6.51, 17.54)	0.67 (0.47, 0.97)	0.0505
Role functioning	10.15 (4.30, 21.16)	6.47 (3.88, 9.46)	0.84 (0.61, 1.17)	0.3562
Emotional functioning	NE (22.18, NE)	10.09 (7.62, 14.78)	0.56 (0.38, 0.81)	0.0021
Cognitive functioning	9.30 (4.67, 16.16)	4.47 (3.35, 8.31)	0.75 (0.54, 1.02)	0.0663

Social functioning	27.70 (14.32, NE)	4.76 (2.92, 12.71)	0.59 (0.42, 0.85)	0.0043
Symptoms				
Fatigue	15.64 (7.52, NE)	4.76 (3.25, 8.64)	0.67 (0.48, 0.93)	0.0129
Nausea and vomiting	12.02 (3.98, NE)	2.83 (1.87, 5.59)	0.55 (0.40, 0.76)	0.0002
Pain	12.06 (6.37, 23.20)	8.08 (5.65, 11.63)	0.82 (0.59, 1.15)	0.3008
Dyspnoea	28.58 (10.18, NE)	16.76 (10.15, NE)	0.98 (0.67, 1.43)	0.8391
Insomnia	NE (18.63, NE)	22.11 (12.68, NE)	0.91 (0.61, 1.35)	0.7362
Appetite loss	NE (17.48, NE)	9.23 (6.28, 24.90)	0.62 (0.43, 0.90)	0.0092
Constipation	11.99 (6.47, NE)	2.83 (1.87, 3.88)	0.52 (0.38, 0.73)	<0.0001
Diarrhoea	2.07 (1.87, 3.75)	2.79 (1.91, 3.75)	1.00 (0.75, 1.34)	0.9682
Financial difficulties	NE (24.94, NE)	NE (19.35, NE)	1.04 (0.67, 1.62)	0.8333

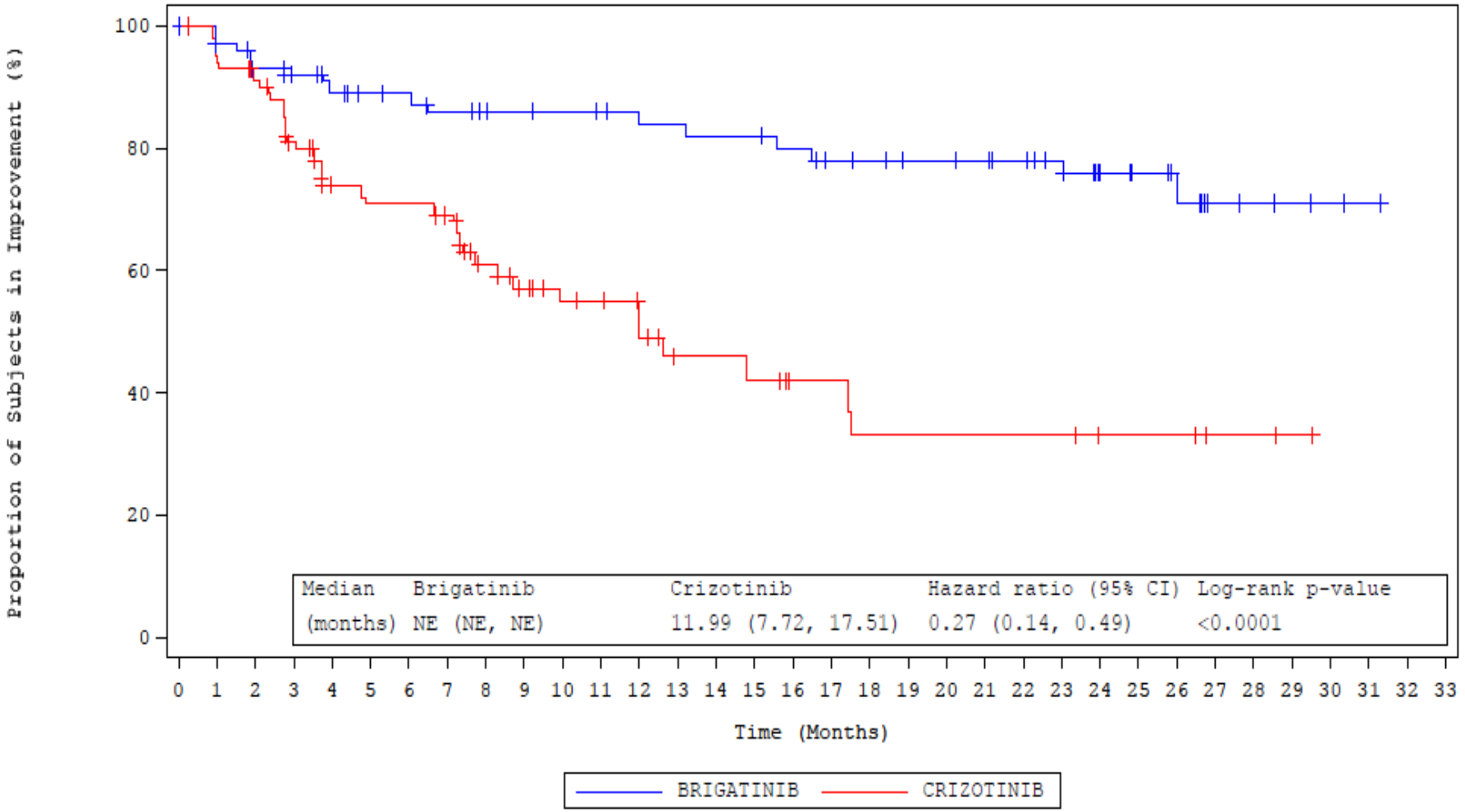
EORTC, European Organisation for Research and Treatment of Cancer; NE, not estimable; QLQ, Quality of Life Questionnaire; QoL, quality of life

[a] = PRO-ITT population is defined as randomised patients with a baseline score and at least one post-baseline assessment

Duration of improvement in QoL

Among patients with any improvement in their QoL score from baseline (defined as an improvement of ≥10 points) during the randomised phase, the duration of observed improvement was assessed to determine if QoL changes were maintained over the course of treatment. The median for brigatinib was not reached, highlighting that patients treated with brigatinib maintained their QoL substantially longer than those treated with crizotinib (median NE vs. 11.99 months HR=0.27 (95% CI: 0.14-0.49); p<0.0001). This is illustrated in Figure 10 below.

Figure 10: Duration of improvement in QoL in the PRO-ITT population

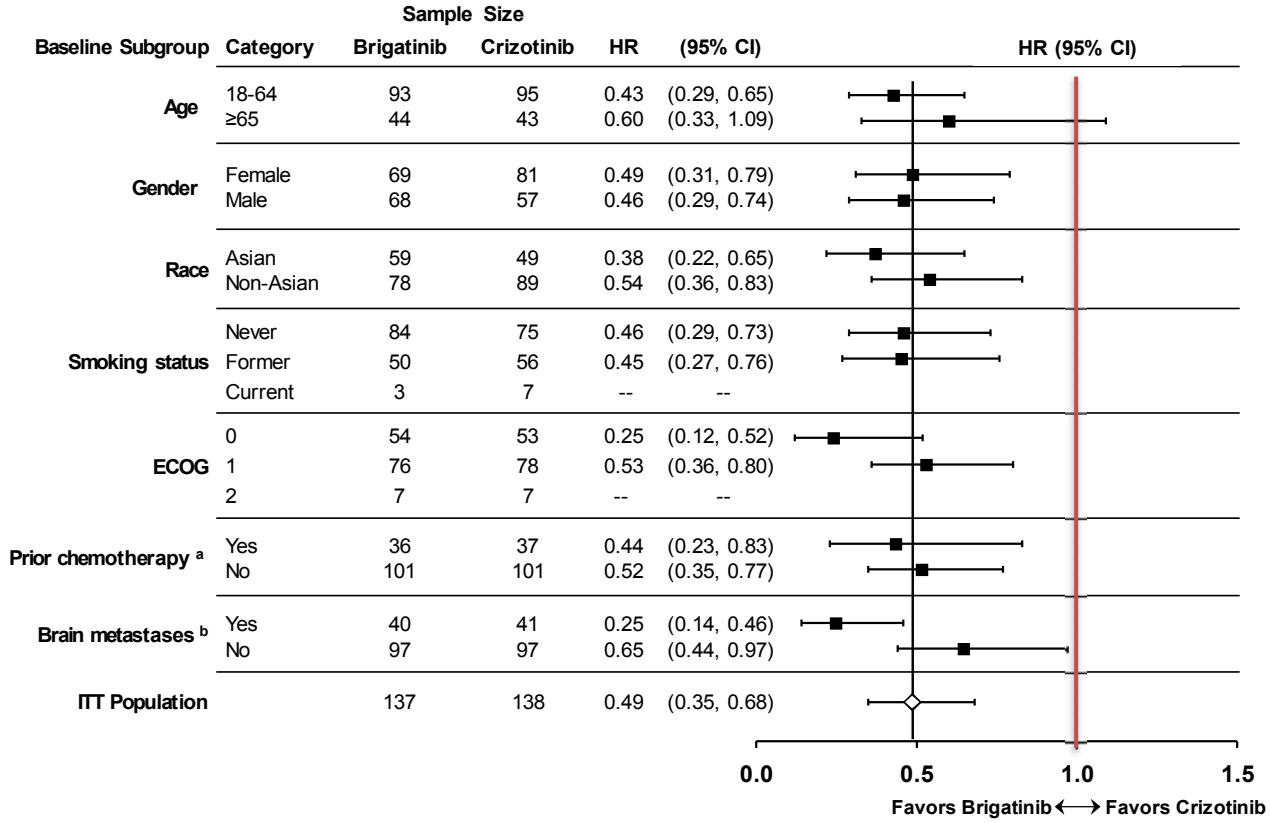


QOL, quality of life; PRO-ITT, patient-reported outcomes; ITT, intention-to-treat

B.2.7 Subgroup analysis

Pre-planned subgroup analyses of PFS by BIRC assessment are presented in Figure 11 by demographics (age, gender, race) and other baseline characteristics (smoking status, ECOG status, NSCLC stage at entry). Analyses of BIRC-assessed PFS were also completed for the two randomisation stratification factors; namely the presence of brain metastases at baseline (yes vs. no) and prior chemotherapy use for locally advanced or metastatic ALK-positive NSCLC (yes vs. no). The proportion of patients who experienced a PFS event was consistently lower in the brigatinib arm compared with the crizotinib arm, reaching statistical significance for all but one subgroup shown. The greatest benefit of brigatinib over crizotinib was observed among patients that are considered more difficult to treat, including those with brain metastases at baseline and with prior chemotherapy use.

Figure 11: Subgroup analyses of BIRC-assessed PFS in the ITT population



ALK, anaplastic lymphoma kinase; BIRC, blinded independent review committee; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; ITT, intent-to-treat; NSCLC, non–small-cell lung cancer; PFS, progression-free survival.
a = Documented ALK-positive status by US FDA–approved test either locally or centrally.
b = Chemotherapy for locally advanced or metastatic disease.
c = Presence of baseline metastases as determined by the investigator

Consistent with the overall population, there was considerably lower risk of experiencing a PFS event in the brigatinib arm than the crizotinib arm among patients with or without baseline brain metastases (HR=0.25 and 0.65, respectively). For patients with brain metastases at baseline, the median PFS per BIRC for brigatinib was 23.95 months vs. only 5.55 months for crizotinib. Although the relative magnitude of the benefit was greater in patients with brain

metastases at baseline (Figure 12), it is clear that brigatinib is also significantly superior to crizotinib in patients without brain metastases at baseline (HR=0.65; p=0.0333) (Figure 13). For patients without brain metastases at baseline, the median PFS per BIRC for brigatinib was 24.0 months vs. 13.0 months for crizotinib.

Irrespective of brain metastases at baseline, most patients in the brigatinib arm remained event-free (i.e. no disease progression, death or radiotherapy to the brain) for at least 18 months. By contrast, fewer than half (47.5%) of crizotinib-treated patients with brain metastases at baseline remained event-free at 6 months. For individuals without brain metastases at baseline, by 24 months only 32.1% remained event-free in the crizotinib arm compared with 50.4% for brigatinib (Table 20).

It is notable that for the brigatinib arm the BIRC-assessed median PFS was the same, at approximately 24 months, for patients either with or without brain metastases at baseline. In light of the known importance of baseline brain metastases as a critical (and negative) prognostic factor in ALK-positive NSCLC, this is a very important finding for brigatinib.

Table 20: BIRC-assessed PFS with or without brain metastases in the ITT population

	Brain Metastases		No Brain Metastases	
	Brigatinib (N = 40) [a]	**Crizotinib (N = 41) [a]**	**Brigatinib (N = 97) [a]**	**Crizotinib (N = 97) [a]**
Number with events (%)	20 (50.0)	30 (73.2)	43 (44.3)	57 (58.8)
Death	0	4 (9.8)	7 (7.2)	1 (1.0)
PD	18 (45.0)	20 (48.8)	36 (37.1)	54 (55.7)
Palliative radiotherapy to the brain	2 (5.0)	6 (14.6)	0	2 (2.1)
Median PFS (95% CI)	23.951 (18.37, NE)	5.552 (3.84, 9.40)	24.016 (15.67, NE)	13.010 (9.46, 21.13)
HR (95% CI)	0.249 (0.14, 0.46)	--	0.649 (0.44, 0.97)	--
P-value	<0.0001	--	0.0333	--
KM estimated PFS, % (95% CI), at:				
6 months	89.0 (73, 96)	47.5 (31, 62)	76.3 (66, 84)	75.7 (65, 83)
12 months	77.9 (61, 88)	21.9 (9, 38)	65.8 (55, 75)	54.6 (43, 65)
18 months	72.1 (54, 84)	14.6 (5, 30)	59.8 (49, 69)	44.0 (33, 54)
24 months	42.9 (25, 59)	9.7 (2, 25)	50.4 (39, 61)	32.1 (22, 43)
Log-rank p-value	<0.0001	--	0.0298	--

HR, hazard ratio; KM, Kaplan-Meier; NE, not estimable; PD, progressive disease; PFS, progression-free survival. Patient status (presence/absence of brain metastases) is based on investigator determination. P-values from a log-rank test stratified by prior chemotherapy for locally advanced or metastatic disease at study entry. The HR and associated p-value were obtained using a Cox proportional hazards model with randomisation stratification factors as covariates.

a = As assessed by the independent investigator

Figure 12: Progression-free survival in patients with any brain metastases at baseline

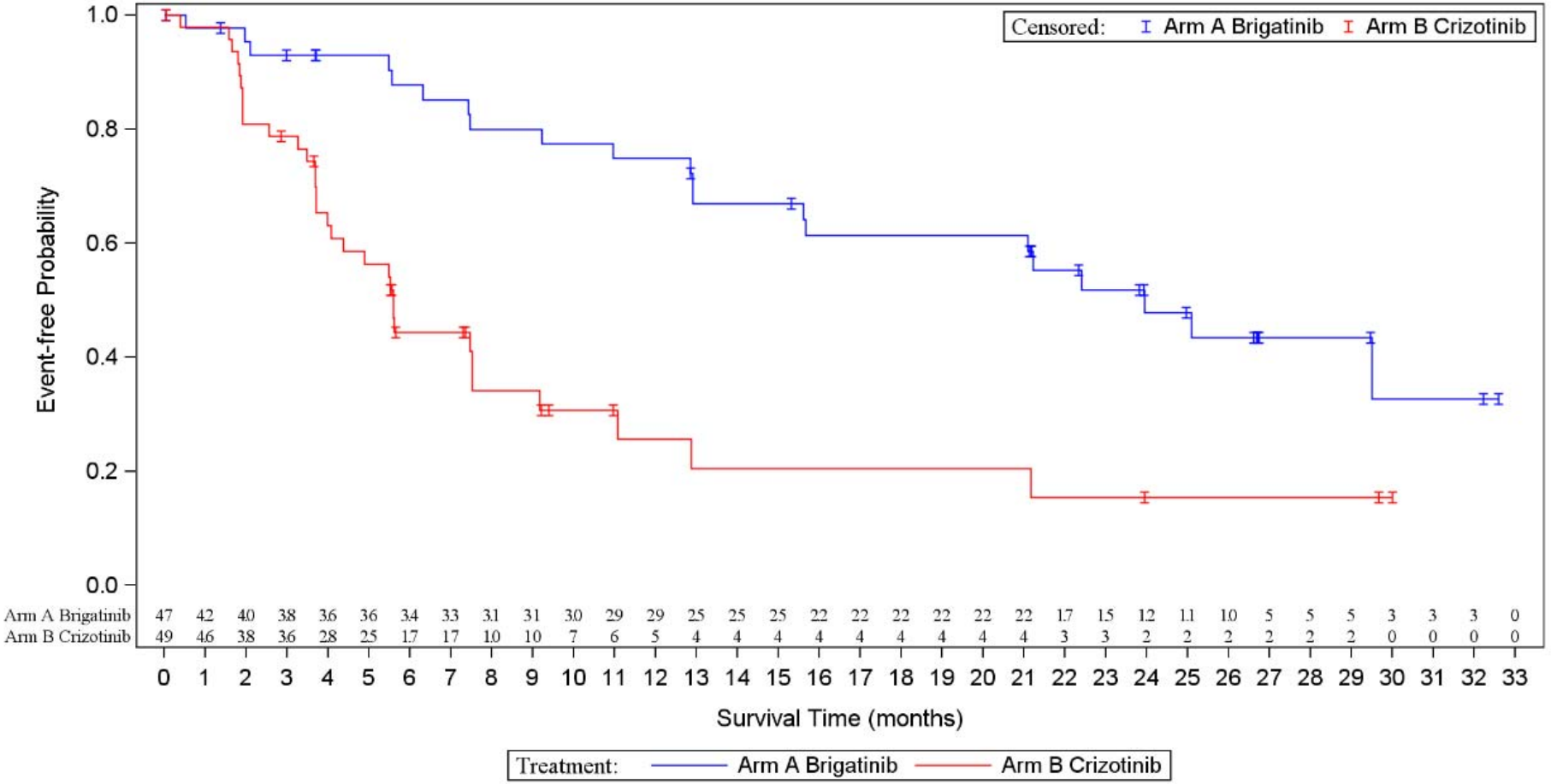
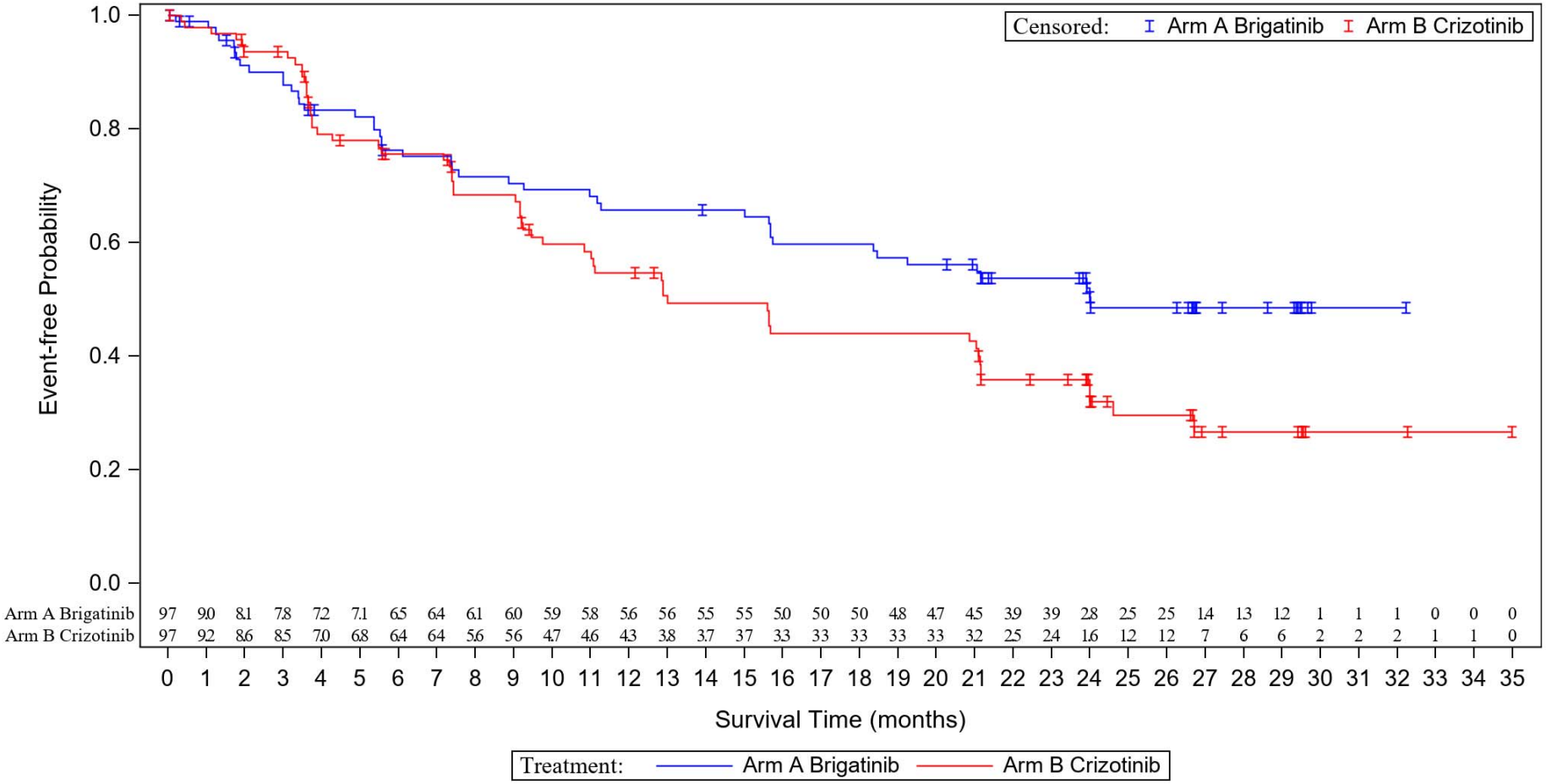


Figure 13: Progression-free survival in patients without brain metastases at baseline



In respect of prior chemotherapy, patients who received brigatinib had a significantly lower risk of experiencing a PFS event whether they had received prior chemotherapy (HR=0.44; p=0.012) or not (HR=0.52; p =0.001) compared to crizotinib. More patients in both subgroups remained event free in the brigatinib arm for at least 18 and 24 months (Table 21). Consistent with the results for the ITT population, median PFS for brigatinib was approximately 24 months compared with 11 months for crizotinib, regardless of prior chemotherapy (see Figure 14 & Figure 15).

Table 21: BIRC-assessed PFS in patients treated/not treated with prior chemotherapy in the ITT population

	Prior Chemotherapy		No Prior Chemotherapy	
	Brigatinib (N = 36)	**Crizotinib (N = 37)**	**Brigatinib (N = 101)**	**Crizotinib (N = 101)**
Number with events (%)	16 (44.4)	26 (70.3)	47 (46.5)	61 (60.4)
Death	0	2 (5.4)	7 (6.9)	3 (3.0)
PD	15 (41.7)	22 (59.5)	39 (38.6)	52 (51.5)
Palliative radiotherapy to the brain	1 (2.8)	2 (5.4)	1 (1.0)	6 (5.9)
Median PFS (95% CI)	24.016 (16.62, NE)	11.006 (7.16, 21.16)	23.951 (18.37, NE)	10.842 (9.13, 15.61)
HR (95% CI)	0.438 (0.23, 0.83)	--	0.519 (0.35, 0.77)	--
P-value	0.0120	--	0.0010	--
KM estimated PFS, % (95% CI), at:				
6 months	88.1 (71, 95)	70.3 (53, 82)	77.1 (67, 84)	66.2 (55, 75)
12 months	78.7 (60, 89)	48.9 (32, 64)	65.9 (55, 75)	44.0 (33, 54)
18 months	66.1 (47, 80)	39.7 (24, 55)	62.5 (52, 72)	34.1 (24, 45)
24 months	53.3 (35, 69)	25.9 (12, 42)	46.0 (35, 57)	26.1 (17, 37)
Log-rank p-value	0.0095	--	0.0005	--

KM: Kaplan-Meier; NE, not estimable; PD, progressive disease; PFS, progression-free survival. P-values from a log-rank test stratified by presence of brain metastases at baseline. The HR and associated p-value were obtained using a Cox proportional hazards model with randomisation stratification factors as covariates

Figure 14: Progression-free survival in patients treated with prior chemotherapy

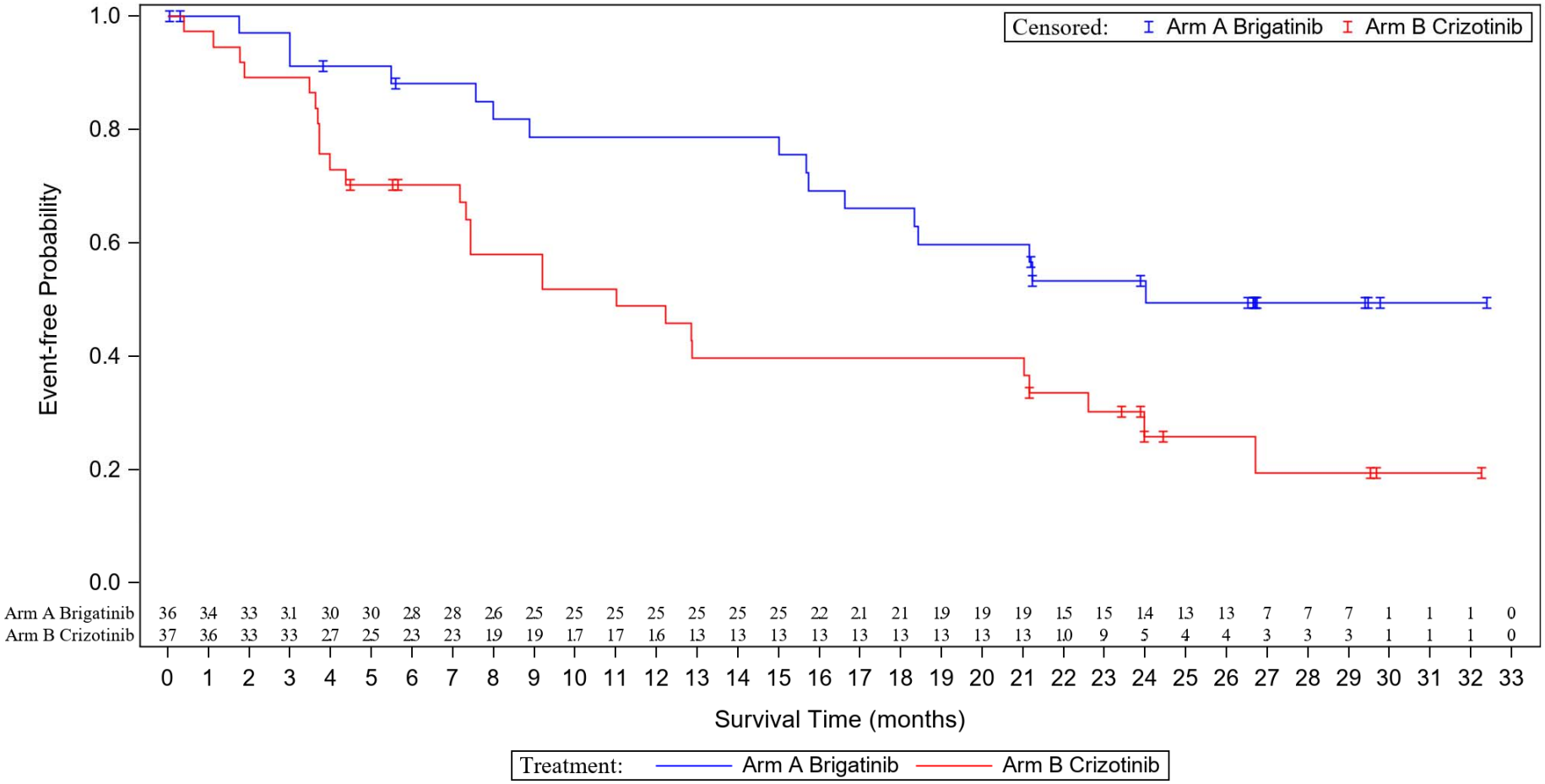
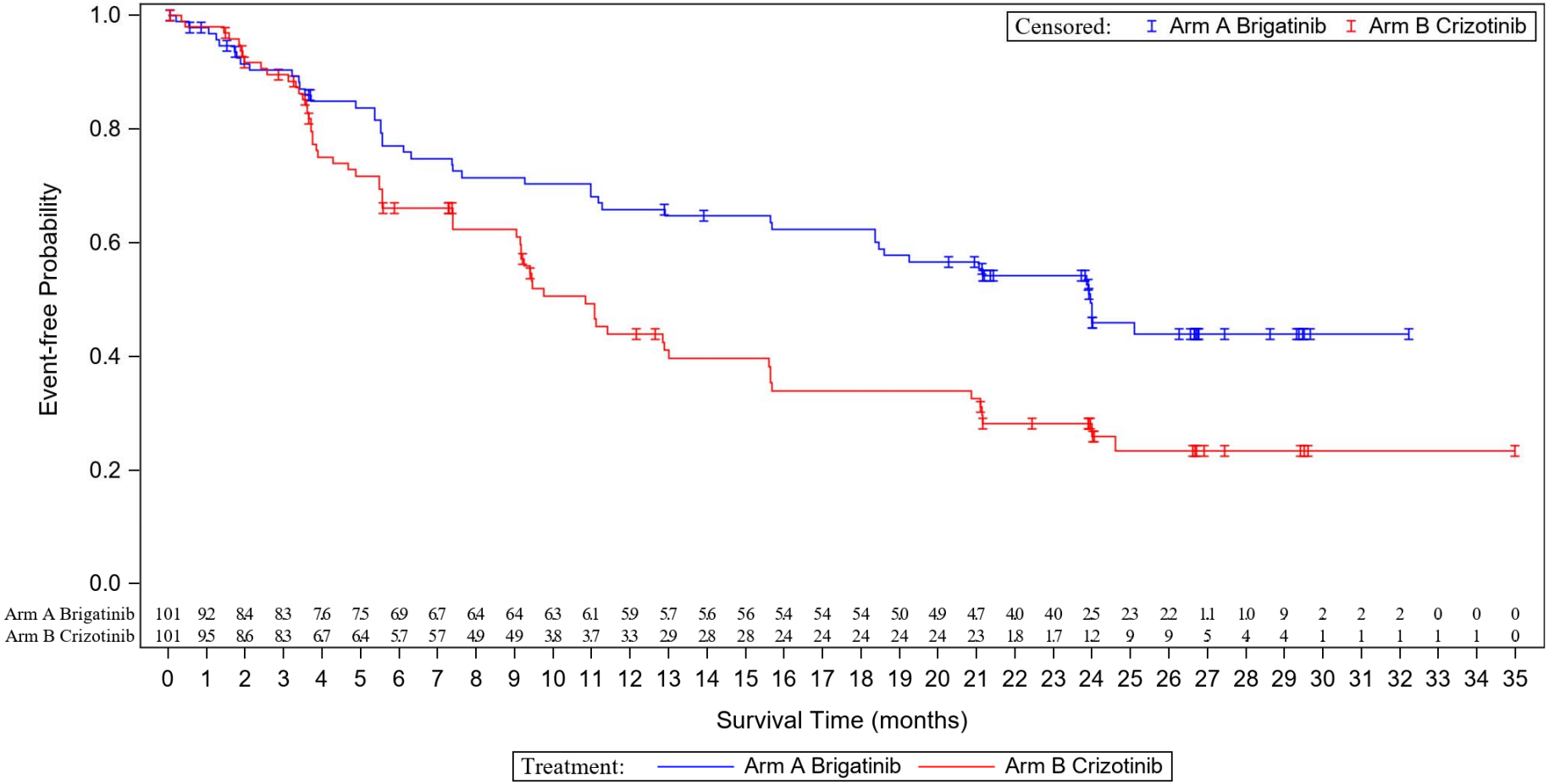


Figure 15: Progression-free survival in patients not treated with prior chemotherapy



B.2.8 Meta-analysis

A meta-analysis was not considered necessary. As identified in the SLR (Appendix D), the only evidence for brigatinib in the frontline treatment of patients with ALK-positive advanced NSCLC includes the pivotal Phase III, ALTA-1L study[39] which directly compared brigatinib to crizotinib, the secondary comparator for this appraisal. The individual patient level data are available from the clinical trial and form the basis of this submission.

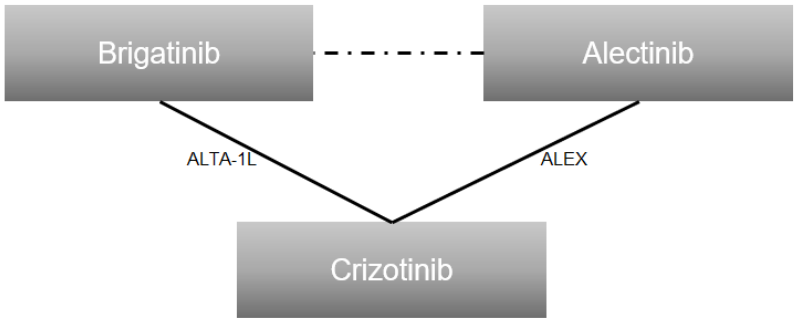
B.2.9 Indirect and mixed treatment comparisons

In the absence of head-to-head data between brigatinib and alectinib, indirect synthesis methods were required.

As discussed in Section B.2.3, there are a number of differences between the ALTA-1L and ALEX clinical trials which need to be recognised prior to conducting any ITC. Key differences include: definition of an event in the PFS outcomes, whether treatment crossover was permitted, the follow-up times from different data cuts, the proportion of patients who had received prior chemotherapy at baseline and the proportion of patients who had brain metastases at baseline. The ITCs attempt to explore and account for these differences as much as is possible given the data. However, no one method can account for all of these differences and so results need to be interpreted carefully.

Figure 16 presents the network diagram; a direct link is available between brigatinib and crizotinib using the data from the ALTA-1L clinical trial and an indirect link is available between brigatinib and alectinib through the common treatment arms (crizotinib) within the ALTA-1L[39] and ALEX[59] clinical trials.

Figure 16: Network plot



Due to the differences in populations between the two clinical trials, population-adjusted methods were pursued. These included an anchored matched adjusted indirect comparison (MAIC) which used the common treatment arms (crizotinib) as an anchor, and an unanchored MAIC which compared the brigatinib and alectinib arms as if they were from single arm trials (i.e. ignores the crizotinib arm). To provide a baseline reference an unweighted Bucher comparison is also conducted – equivalent to an anchored MAIC whereby all the weights assigned to individuals in the ALTA-1L data are set equal to one.

MAIC methodology was pursued rather than regression-based NMA methods as the latter require many trials with the same pairwise comparisons which are unavailable in this setting. Furthermore, MAICs were preferred over simulated treatment comparisons (STCs) due to the small number of events available, particularly for the OS endpoint. Parametric or semi-parametric regression analyses rely on the number of events (not the number of patients) to determine the ESS/degrees of freedom; the lower the number of events, the lower the number of predictors that can be included in the model. It was considered there were insufficient events to be able to pursue an STC.

These methods were applied to PFS BIRC, PFS INV and OS – in line with the economic modelling needs. Note: PFS INV is not used within the economic model due to the high level of congruence observed between this endpoint and PFS BIRC, which was the primary endpoint in the ALTA-1L trial (see Figure 32, Section B.3.3.3.3). However, ITCs explore this endpoint as later data are available from the ALEX trial for PFS INV but not for PFS BIRC (which was only available from the primary analysis).

B.2.9.1 Anchored matching-adjusted indirect comparison (Anchored MAIC)

Feedback from two clinical expert advisory boards (February 2019 & January 2020 – see Section B.3.10) indicated that clinicians considered only baseline brain metastases to be highly prognostic – particularly in patients treated with crizotinib. Clinicians highlighted 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. This is also supported by the data. To investigate this further, statistical analyses were conducted to identify potential prognostic factors or treatment effect modifiers within the ALTA-1L data set (Appendix D). These analyses confirmed that baseline brain metastases was the only significant prognostic factor within the ALTA-1L data.

Therefore, anchored MAICs were conducted using the ALTA-1L and ALEX data with baseline brain metastases as the only variable to be controlled for. Appendix D provides the details of this methodology.

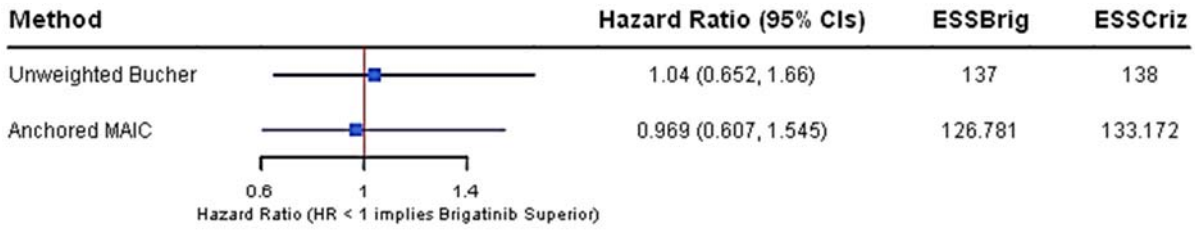
B.2.9.1.1 Progression-free survival per blinded independent review committee

Figure 17 presents the forest plot for the anchored MAIC on PFS BIRC outcomes alongside the reference analysis (unweighted Bucher). The anchored MAIC estimates a HR of 0.969 (95% CI: 0.607-1.545) indicating a very similar efficacy profile between brigatinib and alectinib. The ESS has not reduced substantially between the unweighted Bucher and the anchored MAIC indicating that a large proportion of the ALTA-1L data contributed to these results.

Note: whilst the anchored MAIC attempts to adjust for differences in patient populations. It does not account for differences in study design – the different definitions of a PFS event and the different follow-up times from ALTA-1L and ALEX will bias the anchored MAIC results presented here – see Section B.2.3 for more detail on these differences.

Figure 44 in Section B.3.3.7 presents the Kaplan-Meier data for PFS BIRC from ALTA-1L alongside the digitised Kaplan-Meier data from ALEX for a naïve comparison of the data.

Figure 17: Brigatinib *vs.* Alectinib HR results via different anchored MAIC/Unweighted Bucher methods for BIRC PFS



BIRC, blinded independent review committee; CI, confidence interval; ESS, effective sample size; HR, hazard ratio; MAIC, matched adjusted indirect comparison; PFS, progression-free survival

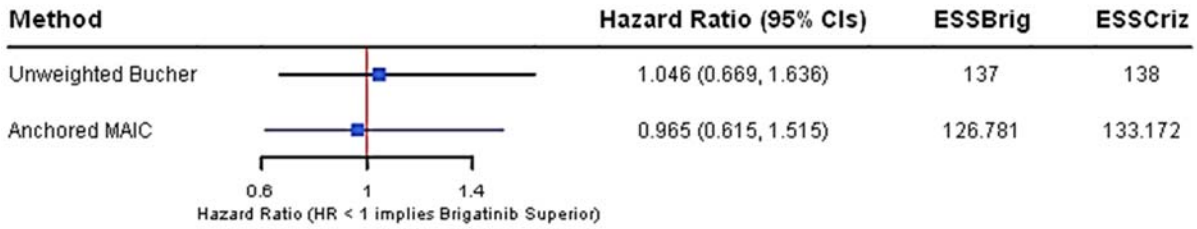
B.2.9.1.2 *Progression-free survival per investigator*

Figure 18 presents the forest plot for the anchored MAIC on PFS INV outcomes alongside the reference analysis (unweighted Bucher). The anchored MAIC estimates a HR of 0.965 (95% CI: 0.615 – 1.515) indicating a very similar efficacy profile between brigatinib and alectinib – these results are consistent with the PFS BIRC outcomes. The ESS has not reduced substantially between the unweighted Bucher and the anchored MAIC indicating that a large proportion of the ALTA-1L data contributed to these results.

Note: whilst the anchored MAIC attempts to adjust for differences in patient populations, it does not account for differences in study design – the different definitions of a PFS event and the different follow-up times from ALTA-1L and ALEX will bias the anchored MAIC results presented here – see Section B.2.3 for more detail on these differences.

Figure 45 in Section B.3.3.7 presents the Kaplan-Meier data for PFS INV from ALTA-1L alongside the digitised Kaplan-Meier data from ALEX for a naïve comparison of the data.

Figure 18: Brigatinib vs. Alectinib HR results via different anchored MAIC/Unweighted Bucher methods for INV PFS



CI, confidence interval; ESS, effective sample size; HR, hazard ratio; INV, investigator assessed; MAIC, matched adjusted indirect comparison; PFS, progression-free survival

B.2.9.1.3 Overall survival

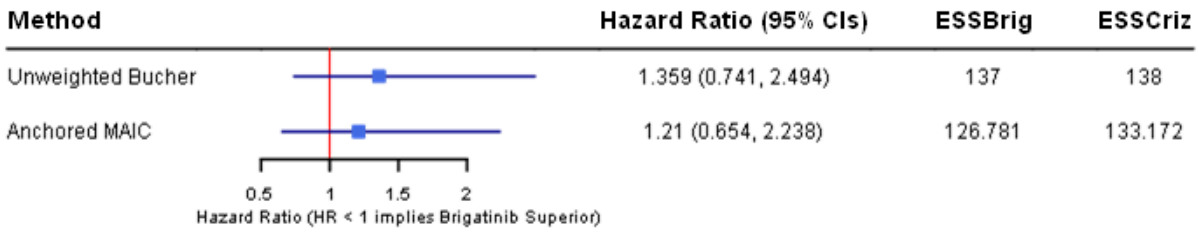
Figure 19 presents the forest plot for the anchored MAIC on OS outcomes alongside the reference analysis (unweighted Bucher). The anchored MAIC estimates a HR of 1.21 (95% CI: 0.654 – 2.238). Figure 46 in Section B.3.3.7 presents the Kaplan-Meier data for OS from ALTA-1L alongside the digitised Kaplan-Meier data from ALEX for a naïve comparison of the data.

Similar to the PFS outcomes, the anchored MAIC only attempts to adjust for differences in patient populations. However, in addition to different follow-up times biasing the results, the high rate of treatment crossover that occurred in the ALTA-1L trial, which was not permitted in the ALEX trial, will have a key influence in terms of relative OS estimates between the two trials. It is likely that this crossover inflates the OS observed in the crizotinib arm in the ALTA-1L study, such that the true treatment effect between brigatinib and crizotinib is minimised. As such crossover (from crizotinib to alectinib) was not allowed in the ALEX trial, the OS observed in the crizotinib arm in the ALEX study will likely be much lower, such that the true treatment effect between alectinib and crizotinib is more clearly seen in the ALEX study. This difference will bias the results estimated through the anchored MAIC. Therefore, the analyses have been conducted using both the unadjusted data from the ALTA-1L trial (Figure 19) and, in scenarios, using the data which have been adjusted using RPSFTM to attempt to account for treatment switching in the ALTA-1L trial (

Figure 20). Section B.3.3.5.2 and Appendix L provide more information on this method.

Figure 20 shows that using the treatment switching adjusted data, HRs for OS range from 1.035 to 1.231 under the anchored MAIC methodology. As discussed in Section B.3.3.5.2, the treatment switching analyses do not appear to be fully accounting for the effects of crossover. For example: counterintuitive results are observed whereby the treatment effect between brigatinib and alectinib deteriorates when treatment switching is accounted for. This is not clinically plausible. The counterintuitive results may be due to immature survival data or may be due to the small number of patients who do not switch providing a reference within the methodology. It is for these reasons that an unanchored MAIC is explored such that the biases introduced through the crizotinib arm relating to treatment switching can be avoided.

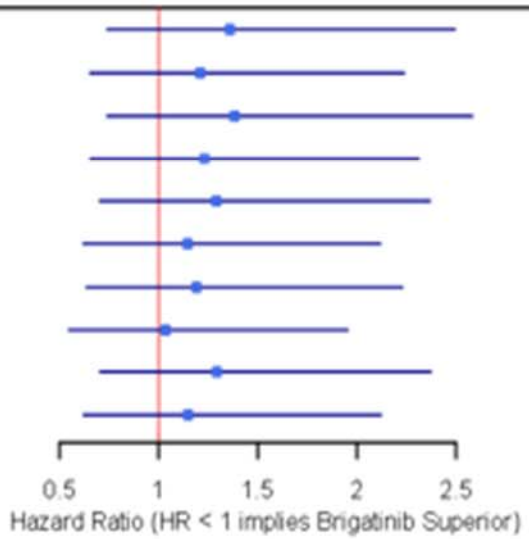
Figure 19: Brigatinib *vs.* Alectinib HR results via different anchored MAIC/unweighted Bucher methods for overall survival



CI, confidence interval; ESS, effective sample size; HR, hazard ratio; MAIC, matched adjusted indirect comparison; OS, overall survival

Figure 20: Brigatinib *vs.* Alectinib overall survival HR results under multiple methods and treatment switch adjusted schemes

Method	Switch Pool	Re-censoring Applied	Hazard Ratio (95% CIs)
Unweighted Bucher	None	Not Applicable	1.359 (0.741, 2.494)
Anchored MAIC	None	Not Applicable	1.21 (0.654, 2.238)
Unweighted Bucher	Official only	Yes	1.383 (0.741, 2.582)
Anchored MAIC	Official only	Yes	1.231 (0.655, 2.312)
Unweighted Bucher	Official only	No	1.291 (0.703, 2.369)
Anchored MAIC	Official only	No	1.146 (0.62, 2.119)
Unweighted Bucher	ConcomitantMeds Added	Yes	1.191 (0.636, 2.229)
Anchored MAIC	ConcomitantMeds Added	Yes	1.035 (0.548, 1.954)
Unweighted Bucher	ConcomitantMeds Added	No	1.293 (0.704, 2.374)
Anchored MAIC	ConcomitantMeds Added	No	1.148 (0.621, 2.122)



CI, confidence interval; HR, hazard ratio; MAIC, matched adjusted indirect comparison; OS, overall survival

B.2.9.2 Unanchored matching-adjusted indirect comparison (Unanchored MAIC)

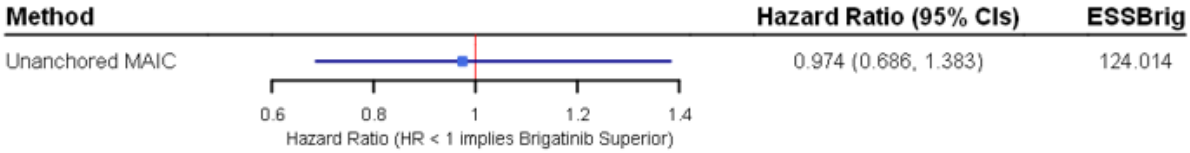
Of the differences between the ALTA-1L[39] and ALEX[59] clinical trials, the proportion of patients with baseline brain metastases and the treatment crossover influence the crizotinib arms only. Therefore, unanchored MAICs were conducted to explore the impact of removing the crizotinib link and estimating the relative efficacy of brigatinib vs. alectinib as if they were from two single arm trials. These analyses were considered particularly important to explore given the failure of the treatment switching methodology to account for the bias introduced by crossover in the ALTA-1L study – rendering the anchored MAIC results for OS difficult to interpret. Appendix D provides the details of this methodology.

B.2.9.2.1 Progression-free survival per BIRC

Figure 21 presents the Forest plot for the unanchored MAIC on PFS BIRC outcomes. The unanchored MAIC estimates a HR of 0.974 (95% CI: 0.686 – 1.383) – this is in line with the anchored MAIC results of 0.969 (95% CI: 0.607 – 1.545). Therefore, indicating that both methods estimate a very similar efficacy profile between brigatinib and alectinib.

The ESS has not reduced substantially in the unanchored MAIC indicating that a large proportion of the brigatinib, ALTA-1L data contributed to these results. Note: whilst the unanchored MAIC attempts to adjust for differences in patient populations. It does not account for differences in study design – the different definitions of a PFS event and the different follow-up times from ALTA-1L and ALEX will bias the unanchored MAIC results presented here – see Section B.2.3 for more detail on these differences. Figure 44 in Section B.3.3.7 presents the Kaplan-Meier data for PFS BIRC from ALTA-1L alongside the digitised Kaplan-Meier data from ALEX for a naïve comparison of the data.

Figure 21: BIRC PFS: Brigatinib *vs.* alectinib HR results via unanchored MAIC



BIRC, blinded independent review committee; CI, confidence interval; ESS, effective sample size; HR, hazard ratio; MAIC, matched adjusted indirect comparison; PFS, progression-free survival

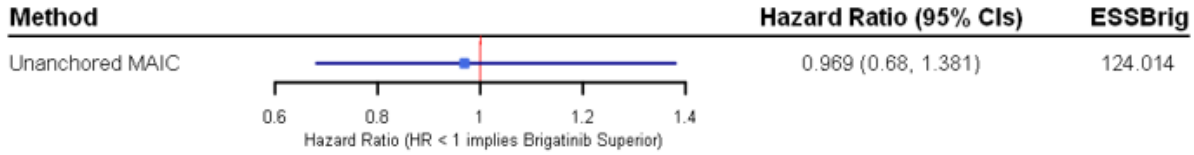
B.2.9.2.2 Progression-free survival per investigator

Figure 22 presents the forest plot for the unanchored MAIC on PFS INV outcomes. The unanchored MAIC estimates a HR of 0.969 (95% CI: 0.680 – 1.381) – this is in line with the anchored MAIC results of 0.965 (95% CI: 0.615 – 1.515). Therefore, indicating that both methods estimate a very similar efficacy profile between brigatinib and alectinib.

The ESS has not reduced substantially in the anchored MAIC, indicating that a large proportion of the brigatinib ALTA-1L data contributed to these results. Note: whilst the unanchored MAIC attempts to adjust for differences in patient populations, it does not account for differences in study design – the different definitions of a PFS event and the different follow-up times from ALTA-1L and ALEX will bias the unanchored MAIC results presented here – see Section B.2.3 for more detail on these differences.

Figure 45 in Section B.3.3.7 presents the Kaplan-Meier data for PFS INV from ALTA-1L alongside the digitised Kaplan-Meier data from ALEX for a naïve comparison of the data.

Figure 22: INV PFS: Brigatinib vs. Alectinib HR results via unanchored MAIC



CI, confidence interval; ESS, effective sample size; HR, hazard ratio; INV, investigator assessed; MAIC, matched adjusted indirect comparison; PFS, progression-free survival

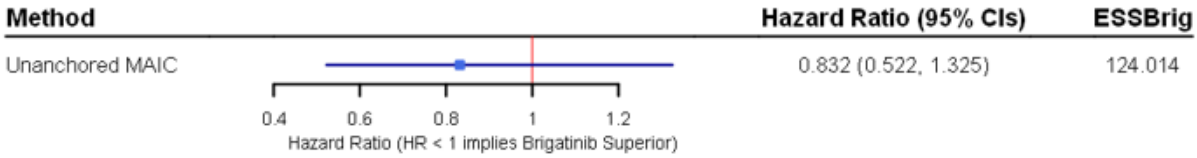
B.2.9.2.3 Overall survival

Figure 23 presents the Forest plot for the unanchored MAIC on OS outcomes. The unanchored MAIC estimates a HR of 0.832 (95% CI: 0.522–1.325) – this is very different from the HR estimated by the anchored MAIC (1.21) or any of the anchored MAIC scenario analyses (1.03 –1.231).

It should be noted that, due to the requirement for a Kaplan-Meier plot from the ALEX trial for the unanchored analysis, the data source varied between the unanchored MAIC and the anchored MAICs. The anchored MAIC used the HR reported using the final data cut from the ALEX study (Mok *et al*.)[40], whereas the unanchored MAIC used the Kaplan-Meier data reported from the second data cut from the ALEX study (Camidge *et al*.)[65] because these data were not included in the final data cut. However, scenario analyses exploring using the earlier data cut within the anchored MAICs indicated that this alone did not explain the differences (HR of 1.105 (95% CI: 0.586–2.082) and ranging from 0.945–1.124 when accounting for treatment switching).

The results of the anchored MAICs and unanchored MAICs were presented at the clinical expert advisory board in January 2020. Clinicians were asked what might be driving this discrepancy and whether any important variables were missing from the candidate list of prognostic factors/treatment effect modifiers which were accounted for in the unanchored MAIC. It was confirmed that no important variables were missing. The only difference was considered to be the bias associated with treatment switching which may still be included in the anchored MAICs, despite attempts to account for this. The advice was to present both the anchored and the unanchored MAIC methods to support the similar efficacy profile between brigatinib and alectinib, while stating the limitations of each method.

Figure 23: Overall Survival: Brigatinib vs. Alectinib HR results via unanchored MAIC



CI, confidence interval; ESS, effective sample size; HR, hazard ratio; MAIC, matched adjusted indirect comparison; OS, overall survival

B.2.9.3 Interpretation of indirect treatment comparisons

The ITCs highlight that brigatinib is at least as good as alectinib in terms of PFS; the point estimates of the HRs fall between 0.965 – 1.046 across all analyses and between different assessments of PFS within the trial (BIRC or INV assessed), where a HR of 1.0 defines equivalence. The results from the analyses all support each other, and the small differences between the unweighted Bucher and anchored/unanchored MAIC can be explained by differences in populations – notably: baseline brain metastases.

The results associated with the OS endpoint are more difficult to interpret, largely because of treatment switching which was permitted in the ALTA-1L trial (but not in the ALEX trial) and also due to the OS data being relatively immature.

For OS, the anchored MAIC produces results which are very different from the unanchored MAIC, and these differences persist even when statistical methods to account for treatment switching are included within the MAIC methodology. It can be concluded that either the treatment switching methodology is flawed or that something is missing from the unanchored MAIC in terms of variables to adjust for. Clinician feedback was sought at the January 2020 advisory board, where the results of all analyses were presented, and clinicians were asked (again) if something was missing from the candidate list of variables. Clinical experts confirmed that all important prognostic/treatment effect modifiers had been accounted for and therefore the focus was on the treatment switching methodology. It appears that the treatment switching methods – described in detail in Section B.3.3.5.2 and Appendix L – do not remove as much OS benefit as would be expected from the crizotinib arm in the ALTA-1L trial. For example: the adjusted crizotinib data still does not align with the crizotinib arm in the ALEX trial. Therefore, our hypothesis (confirmed by clinical experts) is that the treatment switching methodology may not be reflecting the true OS outcomes that would have been seen had patients not received subsequent brigatinib. This is thought to be due to the immature data informing this OS analysis and the high proportion of patients who switched relative to non-switchers. Therefore, the anchored MAICs may be underestimating the relative OS difference, despite incorporating treatment switching methodology.

However, we also acknowledge the known limitations associated with unanchored MAICs, which break the intra-trial randomisation and are usually less preferred than the anchored alternatives. Whilst there are limitations associated with all the OS analyses, we consider that the equivalence clearly demonstrated between brigatinib and alectinib for the PFS outcomes will likely translate into an equivalence in terms of OS outcomes – a statement which was supported by clinicians at the advisory board.

B.2.10 Adverse reactions

All patients in the ITT population who received at least one dose of either brigatinib or crizotinib referred to as the ‘treated population’ were included in the analyses of safety for ALTA-1L. One patient from both study arms did not receive any treatment due to deviation from study protocol or withdrawal of consent. Hence, 136 patients in the brigatinib arm and 137 in the crizotinib arm were evaluated for safety. Adverse events (AEs) were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0 (NCI CTCAE). A treatment-emergent adverse event (referred to as ‘TEAE’) was defined as any AE that started

or worsened in severity, on or after the first dose of study drug and no later than 30 days after the last dose. A TEAE was considered to be treatment-related (referred to as 'TRAE') if causality to either brigatinib or crizotinib was established by the investigator. The latest available data on safety are discussed in this section.

B.2.10.1 Overview of adverse events

The safety of brigatinib has been previously evaluated in crizotinib-treated ALK-positive patients.[81] Overall, the ALTA-1L safety data in patients who have not been treated with an ALK inhibitor is consistent with the known safety profile of brigatinib and no new safety concerns or risks were identified. The median duration of study drug exposure in patients was longer with brigatinib (24.3 months) compared to crizotinib (8.4 months), hence there was increased likelihood of reporting on AEs associated with brigatinib. A total of 67.6% of patients in the brigatinib arm had ≥12 months of study drug exposure, whereas, only 38.0% of patients in the crizotinib arm had ≥12 months of study drug exposure.

As shown in Table 22 below, treatment discontinuations due to TEAEs occurred in similar proportions of patients treated with brigatinib (12.5%) and crizotinib (8.8%).The rate of dose reduction due to AEs of any causality was 38.2% for brigatinib and 24.8% for crizotinib. A greater proportion of patients (≥5% absolute increase) in the brigatinib arm had a dose reduction mostly because of asymptomatic laboratory abnormalities such as, increased blood CPK and lipase levels. Partly, this reflects stricter protocol-mandated dose modifications for laboratory abnormalities reported for brigatinib compared with crizotinib dose modifications, which followed standard labelling. By contrast, the most common AEs leading to dose reductions in crizotinib-treated patients were symptomatic clinical events of nausea and vomiting. However, the median relative dose intensities were similar between both groups; 96.9% in the brigatinib arm and 99.1% in the crizotinib arm indicating good treatment compliance. In terms of severity, there was a greater proportion of patients with at least one serious TEAE in the crizotinib arm compared with brigatinib (37.2% and 33.1%, respectively).

Table 22: Summary of ALTA-1L safety profile

	Brigatinib (N = 136)	**Crizotinib (N = 137)**
Duration of exposure, months (range) [a]	24.3 (0.1-34.6)	8.4 (0.1-36.0)
Dose intensity (mg/day) [b]	163.83 (36.9, 180.0)	495.64(215.5-500.0)
Median relative dose intensity (range) [c]	96.89% (23.7-136.8)	99.12% (43.1-100.0)
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%

B.2.10.2 Most common adverse events

Table 23 provides a summary of common AEs of any grade reported in ≥10% of patients in either treatment arm or with ≥5% absolute difference ordered by decreasing frequency in the brigatinib group. Consistent with previous studies,[81, 82] TEAEs of any causality that occurred at a higher incidence (≥5% absolute increase and ≥10% of patients) with brigatinib compared to crizotinib included an increased creatine phosphokinase (CPK) (brigatinib [46%] vs. crizotinib [17%]), cough (35% vs. 20%), hypertension (32% vs. 8%), increased lipase (23% vs. 15%), pruritus (18% vs. 5%), increased amylase (18% vs. 9%) and rash (15% vs. 3%). The differences between the brigatinib and crizotinib arms in cough, pruritus, and rash were mainly observed as Grade 1 or 2 events. The most common Grade 3 to Grade 5 events among these TEAEs for brigatinib (reported in ≥10% of patients) included hypertension (12%), lipase (14%) and increased CPK (24%). Hypertension is manageable with appropriate treatment and more importantly, there were no differences between patients treated with brigatinib and crizotinib with respect to occurrences of cardiovascular events. There were also no clinical diagnoses associated with elevated lipase levels such as, pancreatitis or rhabdomyolysis. Likewise, clinically relevant symptoms associated with increased CPK namely, myalgia and muscle pain did not differ substantially between brigatinib and crizotinib-treated patients (Table 23). Furthermore, no Grade 3 to 5 myalgia or musculoskeletal pain was reported for either treatment during the randomised phase.

AEs that were more common with crizotinib than brigatinib included nausea (crizotinib [58%] vs. brigatinib [30%]), increased ALT (35% vs. 21%), vomiting (44% vs. 21%), constipation (42% vs. 18%), dizziness (20% vs. 15%), decreased appetite (19% vs. 9%), dyspepsia (16% vs. 8%), bradycardia (15% vs. 8%), peripheral oedema (45% vs. 7%), upper abdominal pain (18% vs. 6%), pain in the extremity (15% vs. 5%), increased blood creatinine (15% vs. 4%), dysgeusia (14% vs. 3%), decreased neutrophil count (10% vs. 2%), photopsia (20% vs. 1%), gastroesophageal reflux disease (11% vs. 1%) and visual impairment (17% vs. 0%). It was noted that more GI related AEs were observed and deemed as treatment-related with crizotinib. Overall, the safety report of crizotinib in ALTA-1L is consistent with the known safety profile in previous trials .[59, 60]

B.2.10.3 Adverse events of special interest

Interstitial lung disease (ILD) or pneumonitis of any Grade occurring within 14 days after the initiation of treatment was considered to be an early-onset pulmonary event (EOPEs). EOPEs occurred in four (3%) patients in the brigatinib arm and no patients in the crizotinib arm. In line with the protocol, all four patients with reported EOPEs discontinued brigatinib. Notably, the frequency of EOPEs among patients treated with brigatinib in the ALTA-1L study (2.9%) is only half of that seen in the ALTA trial of brigatinib in the post-crizotinib setting (6.4%), despite similar exposure levels.[81] Similarly, lower rates of EOPEs were reported among patients who crossed over to brigatinib from crizotinib after disease progression in ALTA-1L (1.6%) This demonstrates that starting brigatinib at a low dose (90 mg/day) before titrating to the higher dose (180 mg/day), not having had prior treatment with an ALK TKI and the application of a 10-day washout period before switching from crizotinib to brigatinib can substantially reduce the risk of this rare AE. Notably, no fatal cases were reported and all EOPEs had either resolved or improved in severity at the latest safety report.

In the population evaluated for safety, there were a similar number of deaths for patients on brigatinib and crizotinib due to AEs of any causality occurring within 30 days after the last dose of study drug (nine vs. ten patients, respectively). Five patient deaths in the brigatinib arm were attributed to neoplasm progression or other lung cancer-related causes. Three patient deaths in the crizotinib arm were attributed to a lung cancer-related cause. Overall, none of the AEs that led to death were deemed related to treatment with either brigatinib or crizotinib.

Table 23: Most common TEAEs in ≥10% of patients in either treatment arm or with ≥5% absolute difference

Number of patients (%)	Brigatinib (N = 136)			Crizotinib (N = 137)		
	Any Grade TEAEs	Treatment-related TEAEs	Grade ≥3 TEAEs	Any Grade TEAEs	Treatment-related TEAEs	Grade ≥3 TEAEs
Diarrhoea	71 (52.2)	55 (40.4)	3 (2.2)	77 (56.2)	72 (52.6)	4 (2.9)
Increased blood creatine phosphokinase [a]	63 (46.3)	60 (44.1)	33 (24.3)	23 (16.8)	21 (15.3)	2 (1.5)
Cough	47 (34.6)	13 (9.6)	0	27 (19.7)	3 (2.2)	0
Hypertension	43 (31.6)	23 (16.9)	16 (11.8)	11 (8.0)	2 (1.5)	4 (2.9)
Nausea	41 (30.1)	31 (22.8)	3 (2.2)	80 (58.4)	69 (50.4)	4 (2.9)
Increased aspartate aminotransferase	35 (25.7)	29 (21.3)	5 (3.7)	36 (26.3)	32 (23.4)	9 (6.6)
Increased lipase [b]	31 (22.8)	30 (22.1)	19 (14.0)	21 (15.3)	16 (11.7)	9 (6.6)
Increased alanine aminotransferase	29 (21.3)	24 (17.6)	5 (3.7)	48 (35.0)	45 (32.8)	14 (10.2)
Back pain	29 (21.3)	3 (2.2)	1 (0.7)	23 (16.8)	0	2 (1.5)
Headache	29 (21.3)	5 (3.7)	3 (2.2)	23 (16.8)	4 (2.9)	0
Vomiting	28 (20.6)	12 (8.8)	1 (0.7)	60 (43.8)	41 (29.9)	3 (2.2)
Dyspnoea	28 (20.6)	6 (4.4)	3 (2.2)	28 (20.4)	4 (2.9)	6 (4.4)
Fatigue	26 (19.1)	13 (9.6)	0	31 (22.6)	18 (13.1)	1 (0.7)
Constipation	25 (18.4)	8 (5.9)	0	57 (41.6)	32 (23.4)	0
Pruritus	25 (18.4)	18 (13.2)	1 (0.7)	7 (5.1)	3 (2.2)	1 (0.7)
Increased amylase [b]	24 (17.6)	24 (17.6)	8 (5.9)	12 (8.8)	9 (6.6)	2 (1.5)
Asthenia	21 (15.4)	9 (6.6)	2 (1.5)	26 (19.0)	16 (11.7)	2 (1.5)
Dizziness	20 (14.7)	6 (4.4)	1 (0.7)	28 (20.4)	16 (11.7)	1 (0.7)
Pyrexia	20 (14.7)	1 (0.7)	1 (0.7)	21 (15.3)	1 (0.7)	0
Rash	20 (14.7)	12 (8.8)	0	4 (2.9)	4 (2.9)	0
Arthralgia	19 (14.0)	8 (5.9)	0	17 (12.4)	4 (2.9)	0
Muscle spasms	19 (14.0)	10 (7.4)	0	14 (10.2)	10 (7.3)	0
Abdominal pain	18 (13.2)	9 (6.6)	0	20 (14.6)	10 (7.3)	2 (1.5)
Increased blood alkaline phosphatase	16 (11.8)	13 (9.6)	4 (2.9)	17 (12.4)	14 (10.2)	1 (0.7)
Upper respiratory tract infection	16 (11.8)	0	0	13 (9.5)	≤1 (0.7%)	0
Decreased appetite	12 (8.8)	7 (5.1)	1 (0.7)	26 (19.0)	18 (13.1)	4 (2.9)
Dermatitis acneiform	12 (8.8)	10 (7.4)	0	3 (2.2)	2 (1.5)	0
Dyspepsia	11 (8.1)	5 (3.7)	0	22 (16.1)	9 (6.6)	1 (0.7)
Bradycardia	11 (8.1)	5 (3.7)	1 (0.7)	21 (15.3)	16 (11.7)	0
Oedema peripheral	9 (6.6)	3 (2.2)	1 (0.7)	61 (44.5)	47 (34.3)	1 (0.7)

Increased blood cholesterol	9 (6.6)	5 (3.7)	0	1 (0.7)	1 (0.7)	0
Epistaxis	9 (6.6)	2 (1.5)	0	0	0	0
Upper abdominal pain	8 (5.9)	3 (2.2)	1 (0.7)	24 (17.5)	14 (10.2)	2 (1.5)
Hypokalaemia	8 (5.9)	1 (0.7)	0	1 (0.7)	0	0
Rash erythematous	8 (5.9)	4 (2.9)	0	1 (0.7)	1 (0.7)	0
Hypercholesterolaemia	8 (5.9)	3 (2.2)	0	0	0	0
Pain in extremity	7 (5.1)	1 (0.7)	0	20 (14.6)	5 (3.6)	1 (0.7)
Increased blood creatinine	5 (3.7)	3 (2.2)	0	20 (14.6)	13 (9.5)	1 (0.7)
Dysgeusia	4 (2.9)	4 (2.9)	0	19 (13.9)	17 (12.4)	0
Dysphagia	3 (2.2)	0	1 (0.7)	12 (8.8)	2 (1.5)	2 (1.5)
Pleural Effusion	3 (2.2)	0	2 (1.5)	11 (8.0)	2 (1.5)	3 (2.2)
Decreased neutrophil count	2 (1.5)	2 (1.5)	0	14 (10.2)	14 (10.2)	7 (5.1)
Hypocalcaemia	2 (1.5)	1 (0.7)	0	10 (7.3)	3 (2.2)	0
Photopsia	1 (0.7)	0	0	28 (20.4)	27 (19.7)	1 (0.7)
Gastroesophageal reflux disease	1 (0.7)	0	0	15 (10.9)	7 (5.1%)	0
Hypoalbuminemia	1 (0.7)	0	0	10 (7.3)	3 (2.2)	1 (0.7)
Hypotension	1 (0.7)	0	0	10 (7.3)	4 (2.9)	0
Visual impairment	0	0	0	23 (16.8)	23 (16.8)	0
Deep vein thrombosis	0	0	0	9 (6.6)	1 (0.7)	0

Source: Data on file [83]. TEAE, treatment-emergent adverse events; TRAE, treatment-related adverse events. TEAEs of any Grade are ordered by decreasing frequency (brigatinib arm) and occurred in 10% or greater of patients in either treatment arm or had a 5% or greater absolute difference between arms. Patients with one or more TEAEs within a level of MedDRA term are counted only once in that level.

a = Myalgia was reported in **9.6%** of patients in the brigatinib group and **7.3%** patients in the crizotinib group; musculoskeletal pain was reported in **9.6%** and **8.0%** of the patients, respectively. No patients reported Grade 3 or greater myalgia; **0.7%** of patients in both treatment groups reported Grade 3 or greater musculoskeletal pain.

b = No clinical cases of pancreatitis were reported in either group

B.2.11 Ongoing studies

The ALTA-1L trial is still ongoing; at the latest data cut, 54.7% of patients randomised to brigatinib and 16.7% to crizotinib were still receiving treatment.[72] As discussed in section B.2.6, the information for brigatinib in this submission is based on the second IA (IA2) data cut, taken after 75% of expected events have occurred. There will be a final data extraction when 100% of expected PFS events are observed with an estimated study completion date of 31 July 2020.[84] The data from the final analysis is expected to be submitted to EMA by June 30th 2021. There are no other ongoing studies of brigatinib for patients with ALK-positive advanced NSCLC who have not been previously treated with an ALK inhibitor.

B.2.12 Innovation

The ALK TKIs crizotinib, ceritinib, and alectinib are currently approved for the first-line treatment of advanced ALK-positive NSCLC. Despite the marked improvements in outcomes for patients, disease progression still occurs. Each of these therapies is subject to limitations, particularly relating to safety, emergence of resistance mutations, or effectiveness against brain metastases.[36, 37] For example, the current standard of care alectinib is associated with clinically relevant AEs such as constipation, myalgia (including musculoskeletal pain), and oedema.[66, 67] Given the variability in the AE profiles of the different ALK TKIs, there remains a continuing unmet need for an additional treatment option for patients with ALK-positive advanced NSCLC.

There are subtle differences between the available ALK inhibitors in terms of chemical and molecular structure, binding specificities to the ALK kinase, and kinase inhibition potency. These characteristics are reflected in variable safety profiles, variable efficacy in the presence of certain mutations, and variable ability to penetrate the blood brain barrier and target brain metastases. [36, 37] Hence, brigatinib fulfils an important unmet clinical need for new and subtly different ALK-targeted therapy. Brigatinib is a novel next-generation ALK inhibitor that binds to and inhibits ALK kinase and fusion proteins, as well as EGFR and mutant forms. Brigatinib has demonstrated superior efficacy and safety compared to crizotinib among ALK-positive patients who are: ALK inhibitor-naïve, pre-treated with chemotherapy for advanced disease and have brain metastases at baseline.

In addition, brigatinib is administered as a once-daily, single tablet treatment that can be taken with or without food,[3] thereby offering significant patient convenience advantages over the other ALK-inhibitors which require;

- either twice-daily dosing (alectinib and crizotinib) or,
- multiple capsules to be taken daily (alectinib and ceritinib, eight and three capsules, respectively) or,
- must be taken with food (alectinib and ceritinib).[66, 85]

In the ALTA-1L trial, patients treated with brigatinib reported statistically significantly improved QoL scores compared to crizotinib-treated patients, this was linked to clinically relevant and commonly reported symptoms associated with NSCLC such as fatigue, cognitive and emotional functioning, appetite loss, nausea and vomiting, and constipation. Given that the population in ALTA-1L were in advanced disease stages, the QoL of improvements observed

with brigatinib are particularly notable. We believe brigatinib is the first ALK inhibitor to show such an improvement in QoL over crizotinib in the 1L setting.

PROs were collected in the ALTA-1L trial, using the EORTC valuation method. In line with the NICE Methods Guide, these were mapped to derive EQ-5D values for use in the health economic model. However, mapping resulted in some of the differences in QoL scores that were statistically significant becoming non-significant, suggesting that the EQ-5D may not be sensitive enough to pick up important changes in HRQoL. As a result, the QoL benefits associated with brigatinib may not be adequately captured in the QALY calculation and therefore may not be reflected fully in the ICERs.

B.2.13 Interpretation of clinical effectiveness and safety evidence

The primary outcome in the randomised ALTA-1L study is efficacy measured using the composite endpoint of PFS as assessed by BIRC. Key secondary endpoints include confirmed ORR, intracranial ORR, intracranial PFS (all assessed by the BIRC) and OS. Intracranial outcomes were evaluated in the ALTA-1L trial because of their important clinical relevance owing to the high risk of developing brain metastases in those with ALK-positive NSCLC.

In ALTA-1L, brigatinib has demonstrated clinically and statistically significant benefits over crizotinib among patients with ALK-positive advanced NSCLC who are ALK inhibitor-naïve, regardless of active brain metastases or pre-treatment with chemotherapy.[39] Notably, the magnitude of PFS benefit seen with brigatinib appears to be similar - as determined through indirect comparison methods - to that demonstrated by alectinib in its head-to-head Phase III trial vs. crizotinib in the frontline setting (the ALEX trial[59]).

B.2.13.1 Clinical efficacy

Data from ALTA-1L demonstrates that brigatinib substantially slows disease progression compared to crizotinib, with a 51% risk reduction in PFS (HR=0.489) in the ITT population. After a median follow-up of 24.9 months for brigatinib and 15.2 months for crizotinib, the median PFS in the brigatinib group was longer than that in the crizotinib group (24.0 months vs. 11 months). The superior efficacy of brigatinib is further supported by the key secondary endpoint of BIRC-assessed confirmed ORR which showed that more patients had an overall response to brigatinib, 73.7% for brigatinib compared to 61.6% for crizotinib. It is also noted that more patients achieved a confirmed complete response (CR) by the BIRC with brigatinib compared to crizotinib (14.6% vs 8.7%). The median DOR among patients who responded to brigatinib was also longer (median: not evaluable vs. 13.8 months), with a sustained response at 24 months of 51.3% vs 29.6% for crizotinib. For ALK-positive patients, this translates into durable disease control and relief of symptom burden. Median OS was not reached for either arm after a median follow-up of 24.9 months in the brigatinib arm vs. 15.2 months in the crizotinib arm. The OS data from ALTA-1L is immature and confounded as a high proportion of patients who progressed on crizotinib then crossed over to receive brigatinib.

The treatment landscape for ALK-positive advanced NSCLC has changed since the ALTA-1L study was initiated. The active comparator in the ALTA-1L trial, crizotinib is now regarded as a less preferred treatment in UK practice, with most clinicians now using alectinib as the first line treatment of choice for treatment-naive patients. There is no head-to-head trial comparing

brigatinib to the current standard of care, alectinib. However, clinical experts familiar with both the ALEX trial (alectinib vs. crizotinib) and the ALTA-1L data, consider brigatinib to have similar efficacy and tolerability to alectinib. Furthermore, a range of results from ITCs suggest that brigatinib is at least as efficacious as alectinib (see Section B.2.9). It is therefore expected that brigatinib will, at a minimum, provide the same benefits as those seen with alectinib in clinical practice.

As mentioned, the presence of brain metastases is an important (and negative) prognostic factor for patients with ALK-positive NSCLC, especially for those treated with crizotinib. In the ALTA-1L trial, brigatinib demonstrated significantly better efficacy than crizotinib, irrespective of the presence or absence of brain metastases at baseline; in patients either with or without baseline brain metastases, the median PFS was approximately 24 months in the brigatinib arm. This is a very important finding as it suggests that brigatinib is as effective in patients with brain metastases as it is in those without. By contrast, for crizotinib, the median PFS was 13 months in the absence of brain metastases at baseline but only 5.6 months in patients with brain metastases at baseline. In relation to intracranial efficacy, specifically among patients with any brain metastasis at baseline, the HR for intracranial PFS was 0.31 (95% CI: 0.17-0.56), reflecting a substantial risk reduction of 69% in favour of brigatinib. This is further supported by the confirmed intracranial ORR for patients with measurable brain metastases at baseline which is markedly improved with brigatinib (77.8% vs. 26.1% for crizotinib; p=0.0014). Effective systemic and intracranial disease control is crucial in patients with ALK-positive NSCLC due to high rates of metastatic disease in the brain. Given that the aim of treatment for ALK-positive patients is to delay progression whilst maintaining QoL, the CNS data indicates that brigatinib is well-positioned to address the significant QoL burden associated with treatment failure, particularly in the brain. ALTA-1L demonstrates that brigatinib has durable efficacy, regardless of the presence or absence of brain metastases at baseline.

The superior efficacy shown by brigatinib in the ALTA-1L trial is particularly important in light of the general characteristics of patients with ALK-positive NSCLC. As described earlier, these patients tend to be younger and are therefore more likely to be working and/or raising a family than the average person with lung cancer. The improved systemic and intracranial efficacy seen with brigatinib offers these patients greater disease control, giving them an opportunity to continue working and participating more fully in family life. In addition, as a once-daily, single tablet treatment that can be taken with or without food, brigatinib offers significant patient convenience advantages over alectinib which requires four capsules to be taken twice-daily with food.[3] Brigatinib is also well tolerated and has a known and manageable side-effect profile which makes it suitable for long-term treatment (see below).

Quality of life for patients diagnosed with ALK-positive NSCLC is severely impacted, particularly in those with brain metastases. Patients in the ALTA-1L trial treated with brigatinib reported improved QoL scores compared to crizotinib-treated patients, linked to commonly reported symptoms associated with NSCLC such as fatigue, appetite loss, constipation, breathlessness, cognitive functioning and nausea and vomiting. A clinically meaningful lag in the time to worsening of QoL was also observed with brigatinib compared to crizotinib. The median time to worsening in QoL score was 26.7 months for brigatinib compared with only 8.3 months for crizotinib, a clear difference in favour of brigatinib (HR=0.70; p=0.0485). Brigatinib

was shown to have a numeric improvement over crizotinib in time to worsening for all functional domains, with statistically significant improvements observed in emotional and social functioning. Furthermore, the duration of QoL improvement was significantly longer for patients treated with brigatinib than crizotinib (median: NE vs 11.99 months; HR=0.27 (95% CI: 0.14-0.49) p<0.0001).

B.2.13.2 Safety and tolerability

With over two years of patient exposure to brigatinib in the ALTA-1L trial in ALK inhibitor naïve patients, and previously in the post-crizotinib setting, the safety profile of brigatinib is well-known. No new safety concerns or risks for brigatinib were identified in ALTA-1L. Many of the dose modifications for brigatinib were predominantly protocol-mandated for asymptomatic laboratory abnormalities, namely increased levels of blood CPK and lipase. However, there were no clinical cases of pancreatitis associated with the elevated lipase levels and the incidence of myalgia or muscle pain was low despite the raised CPK levels. Hence, these laboratory abnormalities were not associated with adverse clinical sequelae and they are considered to be to manageable in real-world clinical practice.

Notably, the frequency of early onset pulmonary events (EOPEs) among ALK inhibitor naïve patients treated with brigatinib in the ALTA-1L study (2.9%) is much lower than that seen in the ALTA trial of brigatinib in the post-crizotinib setting (6.4%).[81] This is attributable both to the dose step-up of brigatinib (90 mg/day for 7 days and thereafter 180 mg/day), and the lack of prior treatment with another ALK inhibitor. Importantly, no fatalities occurred in the small number of patients with EOPEs, and all cases either resolved or improved in severity, thus indicating that EOPEs are rare and can also be managed successfully.

A greater number of GI AEs such as nausea and vomiting were reported in patients treated with crizotinib. This is consistent with the ALTA-1L quality of life data, which showed that more patients treated with brigatinib reported improved QoL scores for clinically relevant symptoms including nausea and vomiting (as compared with crizotinib). Given the absence of head-to-head data, it is difficult to directly compare the safety profile of brigatinib against the current standard of care (i.e. alectinib). However, evidence from the ALTA-1L and ALEX studies and discussions with clinical experts familiar with both brigatinib and alectinib indicate that brigatinib is considered to be well-tolerated with a different but, non-inferior safety profile compared to alectinib.

B.2.13.3 Additional strengths or limitations

There are a number of key strengths of the ALTA-1L trial which we would like to highlight. These have been validated with clinical experts who attended a Takeda organised UK medical advisory board in January 2020.

Firstly, ALTA-1L is a high quality RCT (see Section B.2.5) which provides direct head-to-head evidence for the comparison of brigatinib with crizotinib. While it is true that crizotinib has largely been superseded by alectinib in the frontline setting, it nevertheless remains a relevant comparator and is particularly relevant for patients who have had prior treatment with chemotherapy as it is the only first-line ALK inhibitor that is recommended by NICE and

reimbursed by NHS England in this setting. Having direct, high quality evidence compared to crizotinib is a key strength of brigatinib and the ALTA-1L trial.

Secondly, the ALTA-1L trial is recognised by clinical experts in the UK as providing an evidence base that they regard as easily generalisable to the real-world UK patient population. There are a number of aspects to this, including:

- The baseline characteristics and demographics of patients enrolled in the ALTA-1L trial are representative of the typical advanced ALK positive NSCLC patients seen in routine clinical practice. Retrospective studies of real-world patient characteristics support that patient demographics in the real-world are consistent with those of patients enrolled in the ALTA-1L trial[13, 86]

- The inclusion of a cohort of patients that have received chemotherapy prior to commencing on either brigatinib or crizotinib as their first ALK inhibitor. As explained in Section B.1.3.2, this remains a small but important group of patients in current UK clinical practice. These patients have a large unmet need as their only currently reimbursed ALK TKI is crizotinib which is known to have significant limitations, particularly in respect of its limited CNS efficacy. Having high quality RCT evidence in this setting makes brigatinib unique among the later generation ALK inhibitors.

- The proportion of patients with brain metastases at baseline in the ALTA-1L trial (~30%) is seen as broadly representative of the proportion of UK patients that are likely to have brain metastases in the frontline setting (although it is recognised by UK clinical experts that this proportion is not currently known with precision, because many centres do not routinely scan for CNS involvement at baseline).

- The definition of PFS used in the ALTA-1L trial is seen as being highly reflective of real-world practice as local radiotherapy to the brain is included in the definition of progressive disease (by comparison such use of radiotherapy is not included as a progression event in the ALEX trial of alectinib vs. crizotinib).

- In ALTA-1L, patients who progressed on crizotinib (i.e. following BIRC-assessed PD or radiotherapy to the brain) were permitted to crossover to brigatinib. This protocol-defined crossover occurred in 44.2% (n=61) of patients from the crizotinib arm. Although this confounds the OS analysis in ALTA-1L, the use of brigatinib after progression on crizotinib is reflective of the current UK treatment pathway and real-world clinical practice.

- The use of a local test, rather than central laboratory testing, to confirm ALK status increases the generalisability of the ALTA-1L trial outcomes.

A potential limitation of the ALTA-1L study is that a small number of patients received subsequent therapies that are not funded by NHS England. However, as outlined in Table 7, the absolute number of patients receiving these therapies in the trial was small and therefore the impact on the trial outcomes was minimal. Furthermore, because a greater proportion of patients in the crizotinib arm received these subsequent treatments, any potential bias in outcomes would likely be in favour of crizotinib and against brigatinib. A further potential

limitation of the ALTA-1L trial is its open label design, although we would note that this is not unusual in this setting and that the ALEX trial of alectinib vs. crizotinib also had an open label design. Furthermore, the primary and intracranial outcomes in ALTA-1L were assessed by a blinded independent review committee thereby, minimising the potential for bias.

B.2.13.4 End-of-life criteria

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

Table 24: End-of-life criteria

Criterion	Data available	Reference in submission (section and page number)
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Recent study showed that the OS benefit in patients receiving multiple TKIs in sequence is NR (> 4 years) in patients who received crizotinib as the first treatment.[41] For alectinib, whilst the OS data is still immature, the 4-years OS rate was reported at 64.5%.[40]	Section B.1.3.1, page 14.
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	OS data for brigatinib in ALTA-1L is not mature and confounded by subsequent treatment. Due to these factors, a clear OS benefit over crizotinib has not been observed in ALTA-1L. Given the lack of head-to-head evidence, naïve comparisons to the standard of care alectinib were undertaken. The model indicates no clear difference in the OS benefit between brigatinib and alectinib.	Section B.2.6.3.4, page 50. Section B.3.3.5, page 106.

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

An economic SLR was conducted to identify modelling approaches that have been used previously for ALK inhibitors in untreated advanced or metastatic ALK-positive NSCLC. The original SLR was conducted in May 2018 – this was subsequently updated in May 2019.

Thirty publications were identified in total; 16 PartSA models, 10 state transition models, three budget impact models and one unknown. These include the NICE submissions for alectinib [TA536][54], ceritinib [TA500][53] and crizotinib [TA406][52]. Appendix G summarises the key outcomes from the PartSA and state transition models (n=26) and the details associated with the SLR and the search strategy.

The key comparator to brigatinib is alectinib (see Section B.1.1). Therefore, the model structure and inputs are largely derived from the alectinib NICE submission (TA536)[55].

B.3.2 Economic analysis

B.3.2.1 Patient population

Brigatinib is indicated as monotherapy for the treatment of adult patients with ALK-positive advanced NSCLC previously not treated with an ALK inhibitor. The economic evaluation considers the role of brigatinib for this population, represented by patients enrolled in the ALTA-1L clinical trial. This population is consistent with the NICE final scope for this technology appraisal, the marketing authorisation and the study population of ALTA-1L.[39]

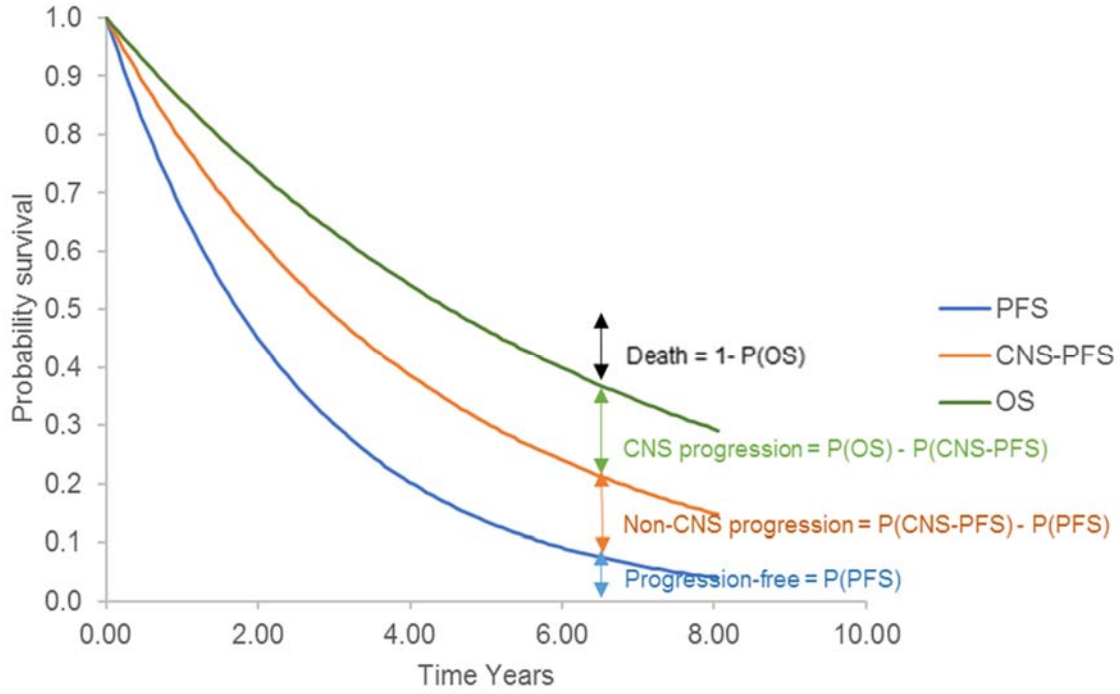
B.3.2.2 Model structure

An economic model has been developed in Microsoft Excel 2010® as an area-under-the-curve (AUC) partitioned survival analysis (PartSA) with four health states: pre-progression, CNS progression, non-CNS progression and death (Figure 24).

This model structure reflects the structure used in the alectinib frontline ALK-positive advanced NSCLC NICE submission (TA536).[55] In line with this published appraisal, it was considered important to separate out CNS and non-CNS progression due to the considerable cost and health-related quality of life (HRQoL) burden associated with CNS progression. Furthermore, efficacy in the CNS is one of the key differentiating factors influencing treatment choice in this disease area. Therefore, it was considered an important outcome to reflect within the model structure.

The AUC model extrapolates three endpoints from the ALTA-1L trial (PFS, intracranial PFS and OS) to inform the efficacy associated with brigatinib and crizotinib – the state membership is determined by a series of independently modelled, non-mutually exclusive survival curves. Due to lack of head-to-head data, ITCs inform the relative efficacy estimates for brigatinib vs. alectinib for each of these outcomes.

Figure 24: Model structure



CNS-PFS= intracranial PFS; CNS, central nervous system; OS, overall survival; PFS, progression-free survival

As shown in Section B.2.9, the ITCs support equivalence between brigatinib and alectinib. Furthermore, expert judgement from two advisory boards (detailed in Section B.3.10) indicate that the real-world experience of brigatinib and alectinib are similar. Therefore, the model also explores a scenario where the efficacy of alectinib is equal to that of brigatinib. Under this scenario the cost-effectiveness model is reduced to a simple cost-comparison framework. This is in line with the NICE Methods Guide which states*: "A cost comparison case can be made if a health 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 same indication."* [87]

The base case analysis considers a 30-year time horizon – at this stage more than 98% of patients have died across all treatment arms. Scenario analyses considered the impact of a 5-year and 10-year time horizon. The model used a 28-day cycle length with a half-cycle correction applied. Costs and health outcomes (QALYs) were discounted at the annual rate of 3.5%. Table 25 summaries the key features of this analysis compared with three previous NICE appraisals in the ALK-positive advanced NSCLC frontline setting.

Table 25: Features of the economic analysis

	Previous appraisals			Current appraisal	
	Crizotinib for untreated ALK+ advanced NSCLC (TA406)[53]	**Ceritinib for untreated ALK+ NSCLC (TA500)[54]**	**Alectinib for untreated ALK+ advanced NSCLC (TA536)[55]**	**Chosen values**	**Justification**
Time horizon	15-years	20-years	30-years	30-years	A lifetime horizon was selected as brigatinib is considered to accrue benefits over a patient's lifetime. At 30-years, more than 98% of patients have died across all treatment arms.
Treatment waning effect?	None applied	Scenario analyses explored the same progressive disease survival for ceritinib as crizotinib	Scenario analyses capped OS and PFS treatment effect duration at 3-, 5-, 7- and 10-years	Scenario analyses assume same mortality rate after 7-, 10- and 20-years.	These scenarios are explored in line with the alectinib NICE submission (TA536). Capping the mortality rate at 3- and 5-years (as conducted in the alectinib submission) was considered inappropriate given 37% and 19% of patients remain on treatment with brigatinib at these time points. By 7-years <10% of patients remain on treatment and by 10-years <4% of patients remain on treatment. Note approximately all patients have discontinued treatment by 20-years.
Source of utilities	The company estimated health state utilities from PROFILE 1014 for progression free disease with crizotinib or with chemotherapy. The company estimated utility values for the	Utility values for the progression-free health state was estimated using data from ASCEND-4[64] for ceritinib and for crizotinib, PROFILE 1014 (Felip et al. 2015).[60] Values for the progressed	The company estimated health state utilities from ALEX for progression free disease and non-CNS progression. The company estimated utility values for CNS	Health state utilities for the pre-progression health state and progressed disease on-treatment with an ALK-inhibitor are derived from the ALTA-1L mapped utility values (mapped from EORTC QLQ-C30 to EQ-5D-3L). Multipliers from the	The utilities for pre-progression and progressed disease receiving treatment with an ALK inhibitor are informed using estimates directly from the patients and measured using a choice-based method – as per the NICE Methods Guide.[89]

	Previous appraisals			Current appraisal	
	Crizotinib for untreated ALK+ advanced NSCLC (TA406)[53]	**Ceritinib for untreated ALK+ NSCLC (TA500)[54]**	**Alectinib for untreated ALK+ advanced NSCLC (TA536)[55]**	**Chosen values**	**Justification**
	progressed disease state in the second-line (treatment with docetaxel) and for third-line treatment (with best supportive care) from PROFILE 1007 and Nafees et al. 2008, respectively.[88]	disease health states were derived from Chouaid et al. (2013).[44]	progression from Peters et al. (2016) and Roughley et al. (2014)[46]	literature are applied to these utility values to estimate HRQoL for CNS progression, progressed disease receiving chemotherapy and progressed disease receiving BSC. The literature includes: Peters et al. (2016) and Roughley et al. (2014) (for CNS progression), PROFILE 1007 (for chemotherapy in progressed disease) and Nafees et al. (2008) (for BSC in progressed disease).	Due to the limited follow-up after progression within the ALTA-1L trial, multipliers from the literature were applied to the estimates derived from the clinical data – combining values from the literature via multiplicative methods align with NICE TSD 12.[90]
Source of costs	Drugs costs from MIMs and eMIT. Resource use and adverse events were based on TA296, TA162,[91] TA188,[92] TA181[93] and TA258[92] and costed using NHS Reference costs and PSSRU. Cost year: 2014/2015[94]	Drugs costs from MIMs and eMIT. Resource use and adverse events were based on TA406,[53] TA296,[95] TA162,[91] TA181[93] and TA258[92] and costed using NHS Reference costs, PSSRU. Cost year: 2015/2016.[94]	Drugs costs from BNF. Resource use derived from TA406 and updated and/or validated by clinical experts. Resource use and AEs costed using NHS Reference costs and PSSRU. Cost year: 2014/2015/2016.[94]	Drug costs from BNF. Resource use derived from TA536 and updated and/or validated by clinical experts. Resource use and AEs costed using the NHS Reference costs and PSSRU. Cost year: 2018/2019.[94]	Costs sources align with the NICE reference case – as specified in the NICE Methods Guide. Resource use aligns with the most recent and relevant NICE appraisal in untreated ALK+ advanced NSCLC. Clinical expert feedback was sought to validate these inputs and provide clarity where clinical practice has evolved from 2015/2016.

B.3.2.3 Intervention technology and comparators

The intervention under review is brigatinib. Brigatinib is evaluated in line with its recently approved marketing authorisation i.e. as monotherapy for the treatment of adult patients with ALK-positive advanced NSCLC previously not treated with an ALK inhibitor.

The final NICE scope specifies the following as being available treatment options and therefore comparators: crizotinib, alectinib and ceritinib. As discussed in Section B.1, alectinib is the main comparator to brigatinib in this setting. However, crizotinib remains a relevant option, particularly for patients who receive chemotherapy as a frontline treatment. Ceritinib is not considered a relevant treatment in the UK as it has a negligible market share and is not used in the frontline setting. Therefore, the economic model considers alectinib and crizotinib only. Please refer to Section B.1 for more information.

B.3.3 Clinical parameters and variables

B.3.3.1 Clinical data

The patient level data from the IA2 analysis of the ALTA-1L clinical trial (median follow-up of 24.9 months for brigatinib) provides evidence for brigatinib vs. crizotinib. Due to lack of head-to-head data, ITCs were required to obtain relative efficacy estimates for brigatinib vs. alectinib. The ALEX clinical trial of alectinib vs. crizotinib informs these ITCs in addition to the ALTA-1L data. The ALEX trial has had different data cuts reported across three different publications: Peters et al. (2017; primary data analysis),[59] Camidge et al. (2018; updated analysis)[65] and Mok et al. (2019; final data cut for PFS).[40] The key outcomes for efficacy in the ALTA-1L and ALEX studies are summarised in Appendix D.1.1.8, Table 11 and a naïve comparison of the BIRC-assessed PFS Kaplan-Meier curves is presented in Figure 44.

B.3.3.2 Extrapolated outcomes

To inform the inputs for brigatinib and crizotinib in the economic model, the data from the ALTA-1L trial were extrapolated for the following outcomes: OS, PFS BIRC and intracranial PFS. The definition of each endpoint is presented in Table 26. Note: the model base case applies the PFS BIRC data in line with the primary endpoint from the ALTA-1L trial. A visual comparison of PFS BIRC and PFS INV Kaplan-Meier data indicate a high level of congruency (Figure 32).

Assessment of proportional hazards determined whether to use stratified or independent parametric models for the treatment arms. Following this, seven parametric distributions (exponential, Weibull, Gompertz, gamma, log-normal, log-logistic and generalised gamma) were fit to the patient level data for each outcome. The fit of each parametric model to the survival data was assessed through AIC/BIC statistics, comparison with the Kaplan-Meier curves and experts' judgements on long-term clinical plausibility. All curves were fitted using the *'flexsurv'* package in the statistical software R.

Table 26: Definition of endpoints from ALTA-1L informing the economic model

	Review	Event	Censor
PFS BIRC	Central independent review committee	• Death • BIRC determined RECIST progression • Radiotherapy for brain metastases	• Patients who did not experience an event • Missing or incomplete baseline scans or no evaluable on-treatment scans • Commencement of any other anti-cancer therapy prior to a PFS event • Two consecutive missed disease assessments
Intracranial PFS	Intracranial disease burden was assessed using a different central independent review committee	• Death • Radiological progression of brain lesions as assessed by modified RECIST criteria • Radiotherapy for brain metastases	• Patients who did not experience an event • Missing or incomplete baseline scans or no evaluable on-treatment scans • Commencement of any other anti-cancer therapy prior to a PFS event • Two consecutive missed disease assessments
OS	NA	• Death of any cause	• Censored for patients still alive at end of follow-up

BIRC, blinded independent review committee; CNS, central nervous system; INV, investigator; NA, not applicable; OS, overall survival; PFS, progression-free survival

It is important to note that the intracranial PFS outcome is assessed by a different central independent review committee to PFS BIRC and considered a modified RECIST.

The modified RECIST considers three groups of patients categorised on baseline brain metastases status: (1) no intracranial disease – these patients are followed up for new lesions in the brain, (2) intracranial disease present but not measurable – readers were instructed to enter as many non-target lesions as possible and (3) measurable intracranial disease – patients in this category must have at least one target lesion (i.e. ≥10 mm in the longest diameter). The standard RECIST criteria allows up to five target lesions but specifies that no more than two target lesions can be in the same organ system. Whereas, the modified RECIST assessment allows up to five target lesions in the brain. It is important to note: if a patient progresses due to lesions outside the brain, this patient is continued to be evaluated as stable disease (SD), partial response (PR) or complete response (CR) in this analysis until progression in the brain or discontinuation from the study treatment. Therefore, events in the intracranial PFS variable may reflect progressions during frontline treatment or later line treatment.

Due to these differences, there are a small number of inconsistencies between the endpoints i.e. where a progression event has been recorded under intracranial PFS but not under PFS BIRC (n=12). This inconsistency is to be expected as the modified RECIST measurement tool is more sensitive and will highlight progressions that would not be identified under the standard RECIST criteria. This is the same issue that was faced in the alectinib NICE submission (TA536).[55] In line with the alectinib NICE submission, three approaches have been explored:

- Unadjusted data for PFS BIRC and intracranial PFS. Note: this will include the inconsistencies between endpoints
- Where there is an inconsistency define progression as per the modified RECIST i.e. add the event to the PFS BIRC data 'PFS adjusted to intracranial PFS'
- Where there is an inconsistency define intracranial progression as per the standard RECIST i.e. remove the event from the intracranial PFS data to 'intracranial PFS adjusted to PFS'

Each of these analyses are included within the model and can be selected on the *'Model Controls'* sheet. In the base case the third option is considered, this most closely aligns with current clinical practice where the standard RECIST criteria are applied. Note: feedback from UK clinicians indicated that the modified RECIST criteria applied for the intracranial PFS outcome is not followed in clinical practice. This method also maintains the original data for the primary endpoint of PFS BIRC and only adjusts the intracranial PFS data. Furthermore, this method is in line with the method used for final decision making in the alectinib NICE submission (TA536). Both the unadjusted and adjusted analyses are presented in the sections below for PFS BIRC and intracranial PFS.

Despite the challenges in capturing intracranial efficacy, we consider these are outweighed by the importance of including intracranial outcomes within the model. Progression in the brain has extensive cost implications for the NHS and important HRQoL consequences for patients. It is one of the key differentiating factors for brigatinib when compared to crizotinib.

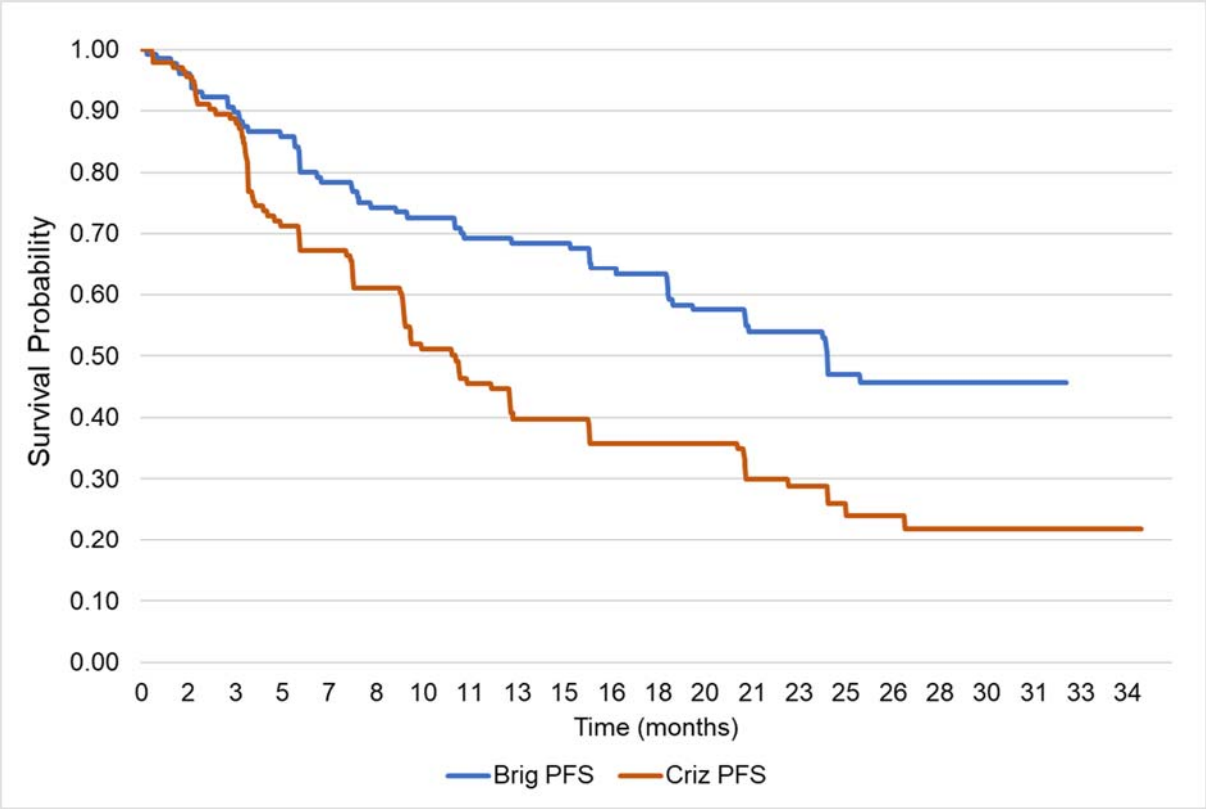
B.3.3.3 Progression-free survival per BIRC

This section presents the unadjusted analyses for PFS BIRC (based on the standard RECIST criteria) and the adjusted analyses for PFS BIRC (based on the modified RECIST criteria). Note: the unadjusted analyses are applied in the base case.

B.3.3.3.1 Unadjusted (base case)

The Kaplan-Meier plot for PFS BIRC outcomes for brigatinib vs. crizotinib from the ALTA-1L trial is presented in Figure 25.

Figure 25: Kaplan-Meier data for BIRC-assessed PFS



BIRC, blinded independent review committee; Brig, brigatinib; Criz, crizotinib; PFS, progression-free survival

Figure 26 presents an assessment of proportional hazards; the log cumulative hazard plot indicates early crossing between the curves, followed by some separation, indicating a potential violation of proportional hazards. This conclusion is supported by the Schoenfeld residuals plot, where the drawn curves should be horizontal if the proportional hazards assumption holds.

These statistical tests align with clinical expert judgement indicating that, due to their different pharmacological profiles, they would not expect proportional hazards to hold between brigatinib and crizotinib, for either PFS or OS outcomes. Therefore, independent parametric models were fit to the brigatinib and crizotinib data. This is also in line with the approach taken in the alectinib NICE submission (TA536).[55]

Figure 26: Log-cumulative hazard plot and Schoenfeld residuals for BIRC-assessed PFS

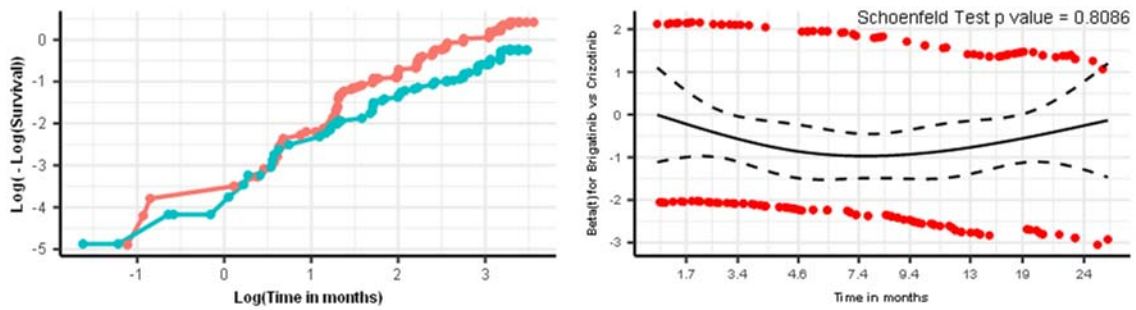


Table 27 presents the AIC and BIC values for each parametric survival distribution. There are limited differences in terms of how well each of the parametric curves fit the observed data; only three points between the AIC and only eight points between the BIC for brigatinib and only six points between the AIC and only seven points between the BIC for crizotinib. The exponential appears the best fit to the observed data for brigatinib. The log-logistic, log-normal, generalised gamma and the exponential provide reasonable fits to the crizotinib data.

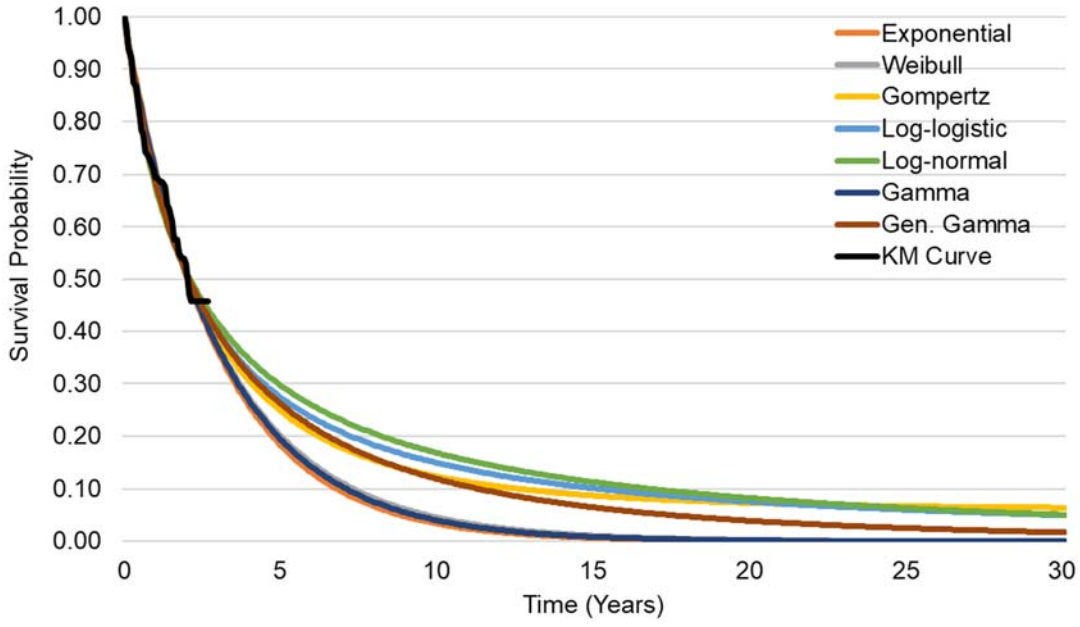
Table 27: Goodness-of-fit statistics BIRC-assessed PFS (unadjusted)

	Brigatinib		Crizotinib	
Models	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	577	580	677	679
Weibull	579	585	678	684
Gompertz	578	584	677	683
Log-logistic	578	584	672	678
Log-normal	578	584	672	677
Gamma	579	585	678	684
Gen. Gamma	580	588	674	682

AIC, Akaike information criterion; BIC, Bayes information criterion; BIRC, blinded independent review committee; PFS, progression-free survival

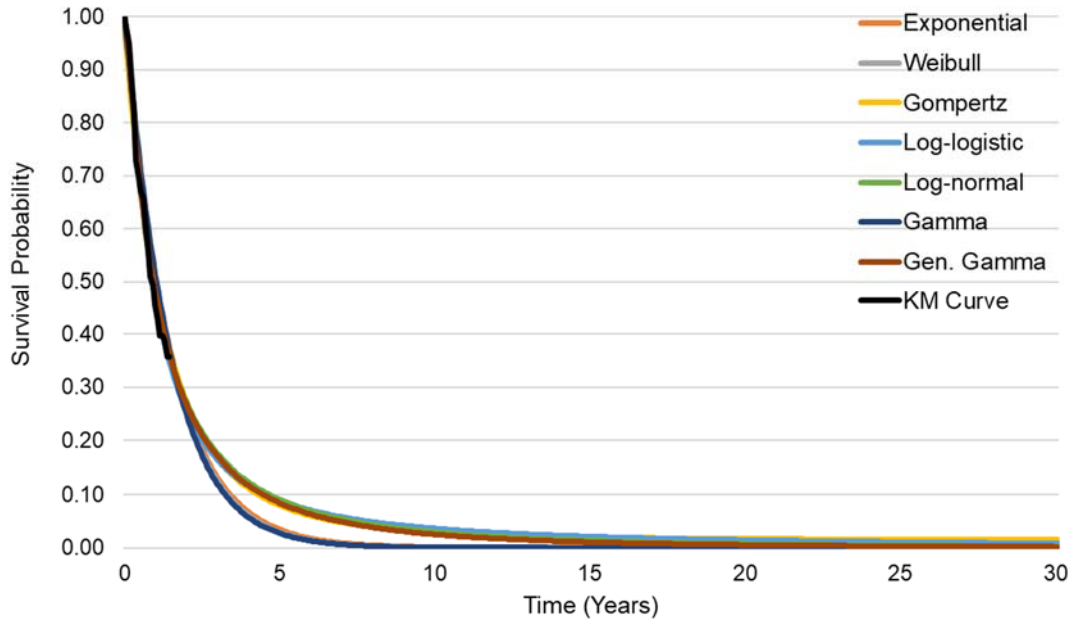
A comparison of the Kaplan-Meier plots with the extrapolated curves is presented in Figure 27 and Figure 28 for brigatinib and crizotinib, respectively. As would be expected given the maturity of the data, the choice of parametric curve has a larger impact for brigatinib outcomes compared to crizotinib outcomes.

Figure 27: Extrapolated BIRC-assessed PFS (unadjusted) compared with KM data - brigatinib



BIRC, blinded independent review committee; PFS, progression-free survival

Figure 28: Extrapolated BIRC-assessed PFS (unadjusted) compared with the KM data - crizotinib



BIRC, blinded independent review committee; PFS, progression-free survival

The exponential curve is selected in the base case for both brigatinib and crizotinib. This is supported by the AIC/BIC statistics, aligns with the parametric curves from which a final decision was made in the alectinib NICE submission (TA536) and aligned with clinical expert judgement from an advisory board (see Section B.3.10). It is notable that the exponential curves here are the least optimistic for brigatinib and one of the least optimistic for crizotinib. Alternative parametric curves are explored in a scenario analysis.

B.3.3.3.2 Adjusted

The adjusted PFS BIRC outcomes are considered in a scenario analysis only. In this scenario, where there is an inconsistency between PFS BIRC and intracranial PFS the event observed in the intracranial PFS is added to the PFS BIRC i.e. PFS BIRC includes both standard RECIST and the modified RECIST.

Figure 29 presents a comparison of the unadjusted PFS BIRC Kaplan-Meier curves with the adjusted PFS BIRC Kaplan-Meier curves – it should be noted that the change is minimal.

Figure 29: Comparison of unadjusted PFS BIRC and adjusted PFS BIRC (including progressions as per modified RECIST)

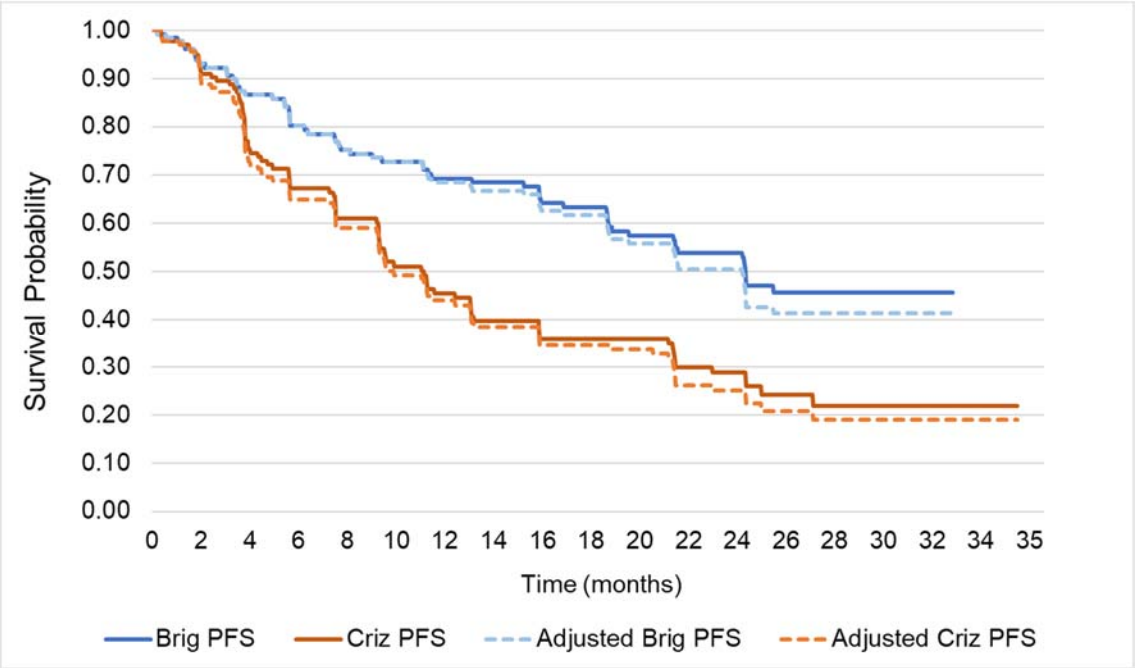


Table 28 presents the AIC and BIC values for each parametric survival distribution. The rank of the goodness of fit statistics are in line with those for the unadjusted PFS BIRC.

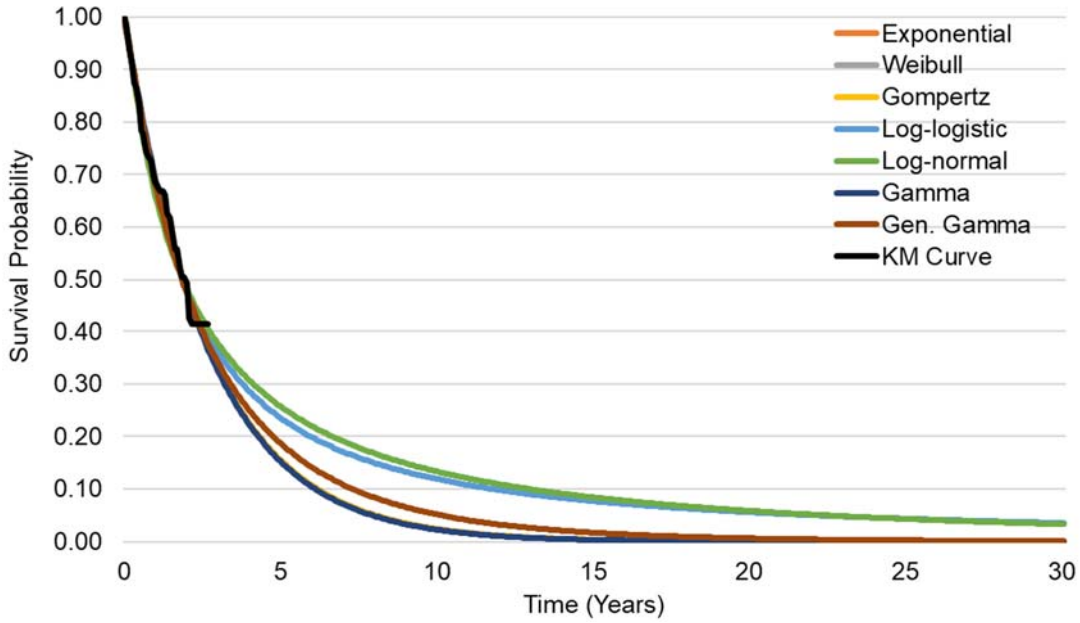
Table 28: Goodness-of-fit statistics BIRC-assessed PFS (adjusted)

	Brigatinib		Crizotinib	
Models	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	610	613	715	718
Weibull	612	618	717	723
Gompertz	612	618	716	722
Log-logistic	612	618	711	717
Log-normal	613	619	710	716
Gamma	612	618	716	722
Gen. Gamma	614	622	712	721

AIC, Akaike information criterion; BIC, Bayes information criterion; BIRC, blinded independent review committee; PFS, progression-free survival

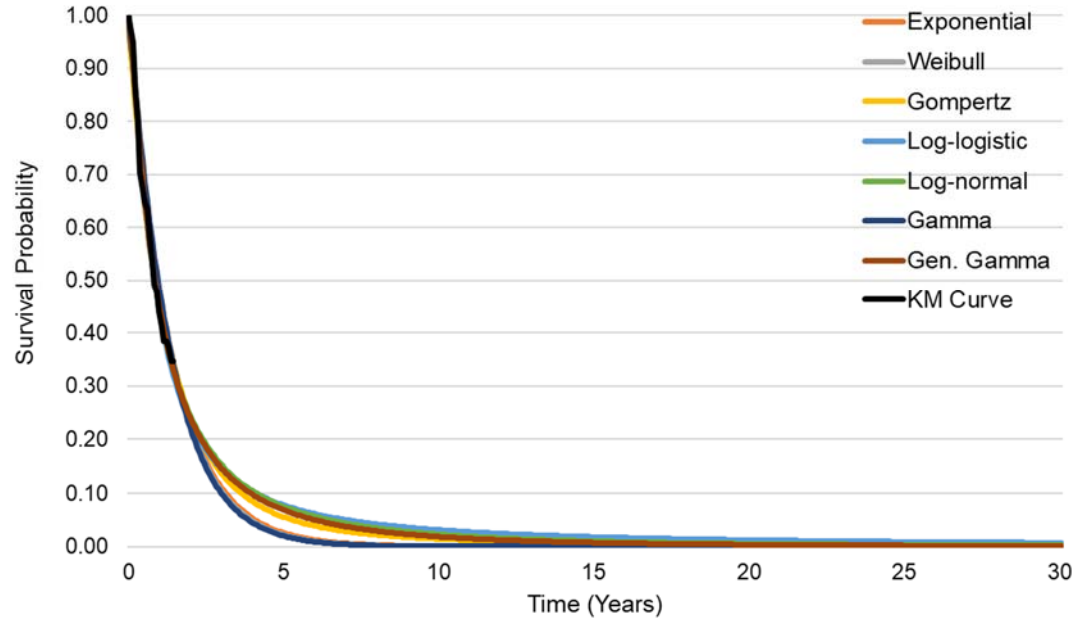
A comparison of the Kaplan-Meier plots with the extrapolated curves is presented in Figure 30 and Figure 31 for brigatinib and crizotinib, respectively.

Figure 30: Extrapolated BIRC-assessed PFS (adjusted) compared with the KM data - brigatinib



BIRC, blinded independent review committee; PFS, progression-free survival

Figure 31: Extrapolated BIRC-assessed PFS (adjusted) compared with the KM data - crizotinib



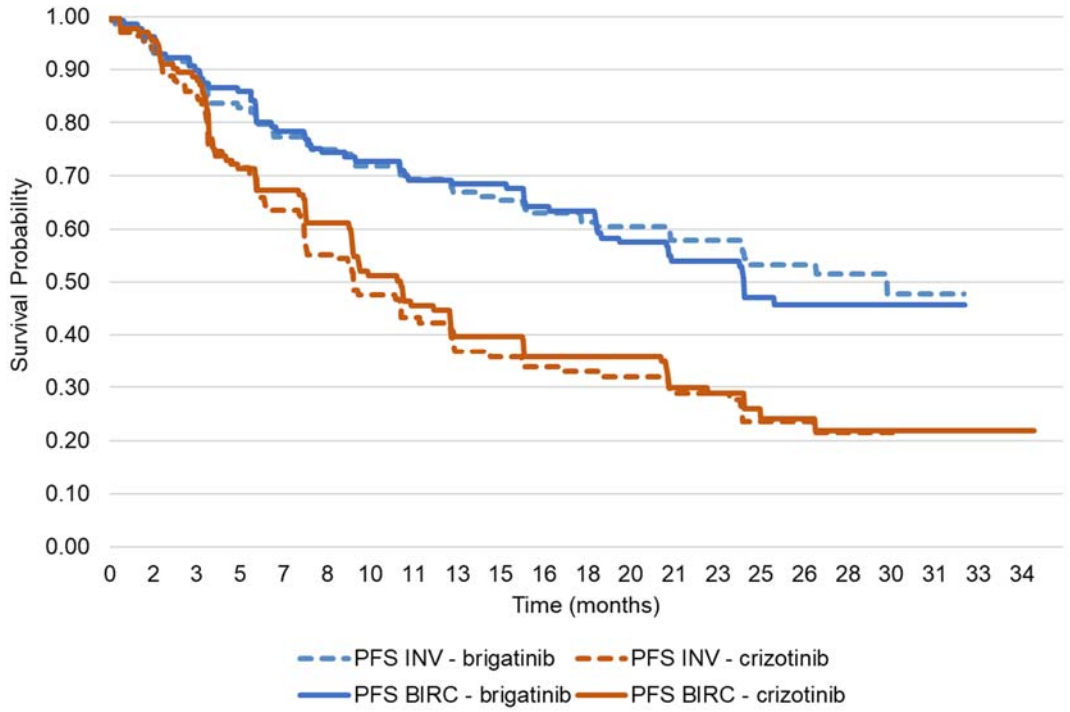
BIRC, blinded independent review committee; PFS, progression-free survival

B.3.3.3.3 Progression-free survival per investigator

The model includes PFS data as per BIRC assessment only. This reflects the primary endpoint from the ALTA-1L clinical trial and aligns with the preferred method of assessment in the

alectinib NICE submission (TA536).[55] Figure 32 presents a comparison between the Kaplan-Meier data for PFS BIRC and PFS INV. This comparison indicates the high level of congruency between the per BIRC and per INV results.

Figure 32: KM BIRC-assessed PFS compared with INV-assessed PFS



BIRC, blinded independent review committee; INV, investigator; PFS progression-free survival

B.3.3.4 Intracranial progression-free survival

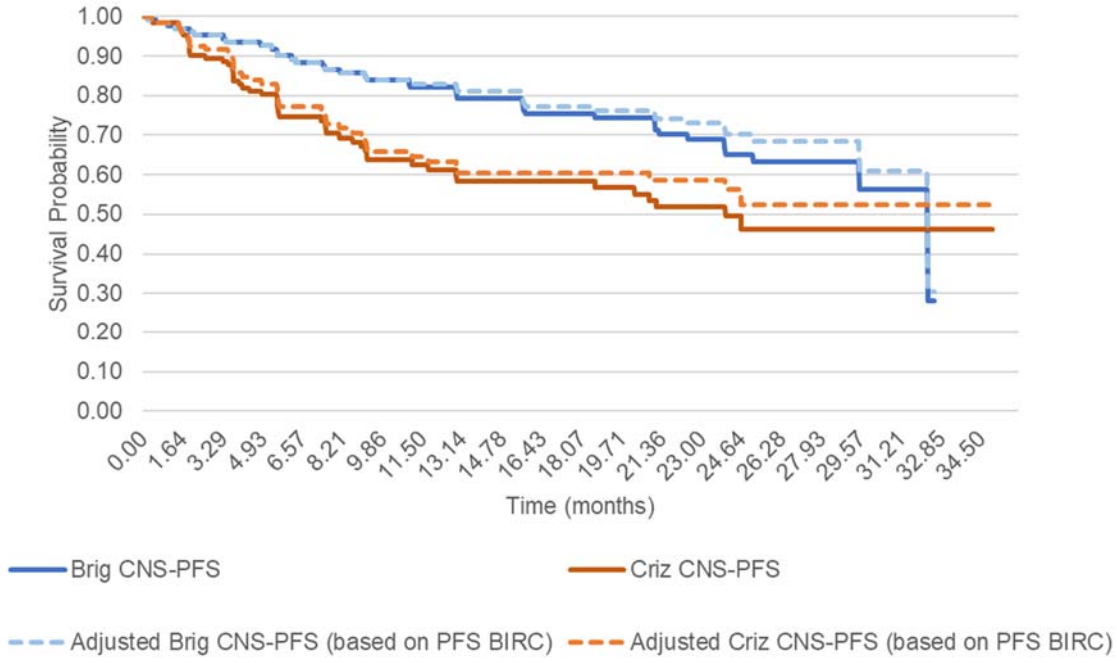
This section presents the unadjusted analyses for intracranial PFS (based on the modified RECIST criteria) and the adjusted analyses for intracranial PFS (based on the standard RECIST criteria). Note: the adjusted analyses are applied in the base case.

B.3.3.4.1 Adjusted

The adjusted intracranial PFS based on PFS BIRC makes an adjustment to align the intracranial PFS outcomes with the PFS BIRC outcomes i.e. to remove any events defined by the modified RECIST which were not identified by the standard RECIST. Therefore, this method considers the standard RECIST and is more reflective of real-word practice, making it an appropriate base case.

Figure 33 indicates that there is little difference between the unadjusted and adjusted intracranial PFS data.

Figure 33: Comparison of unadjusted intracranial PFS and adjusted intracranial PFS



CNS-PFS = intracranial PFS. BIRC, blinded independent review committee; CNS, central nervous system; PFS, progression free survival

In line with PFS BIRC outcomes, independent parametric curves were fit to the data. Table 29 presents the AIC and BIC values for each parametric survival distribution. The exponential appears the best fit to the observed data for brigatinib. The log-normal, Gompertz and generalised gamma provide the best fits to the crizotinib data.

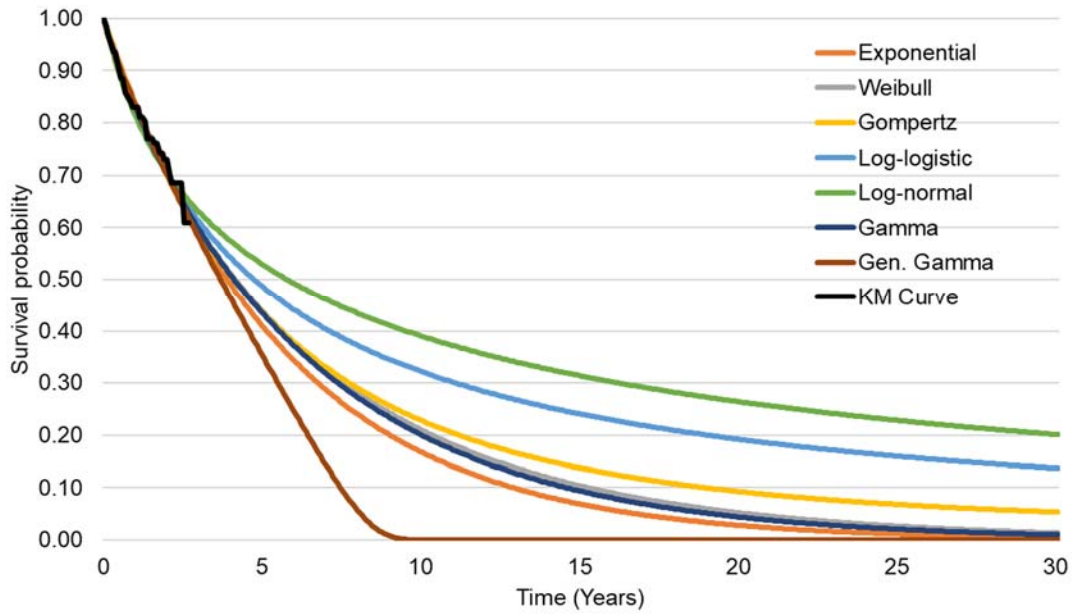
Table 29: Goodness-of-fit statistics intracranial PFS (adjusted for BIRC-assessed PFS)

	Brigatinib		Crizotinib	
Models	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	366	369	402	405
Weibull	368	374	403	409
Gompertz	368	374	397	403
Log-logistic	369	374	399	405
Log-normal	370	375	397	402
Gamma	368	374	404	409
Gen. Gamma	370	379	397	406

AIC, Akaike information criterion; BIC, Bayes information criterion; BIRC, blinded independent review committee; CNS, central nervous system; PFS, progression-free survival

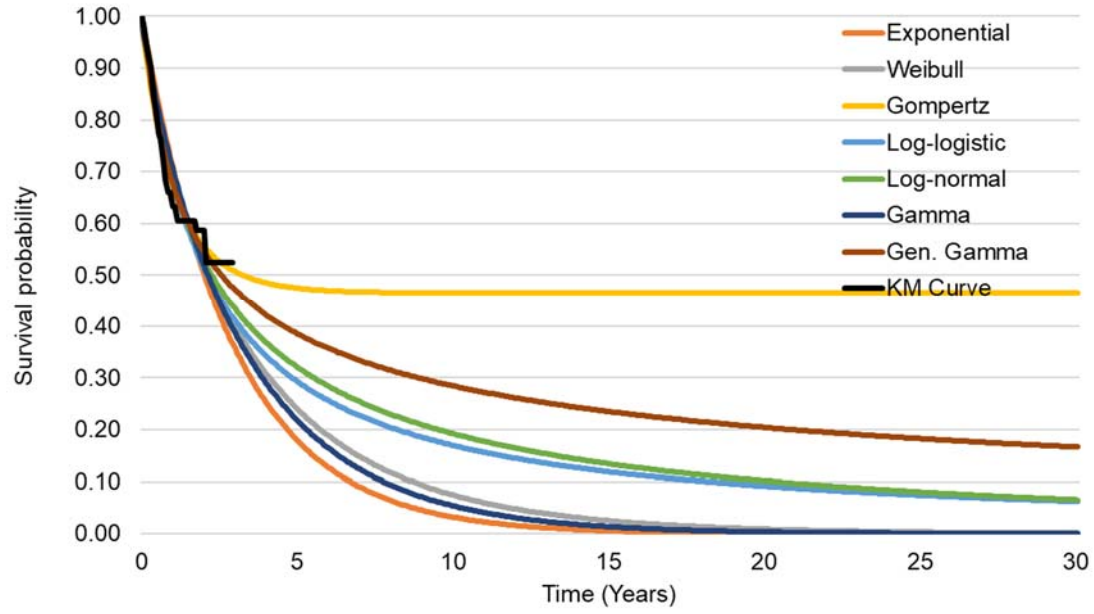
A comparison of the Kaplan-Meier plots with the extrapolated curves is presented in Figure 34 and Figure 35 for brigatinib and crizotinib, respectively.

Figure 34: Extrapolated intracranial PFS (adjusted for BIRC-assessed PFS) compared with the KM data - brigatinib



BIRC, blinded independent review committee; CNS, central nervous system; PFS, progression-free survival

Figure 35: Extrapolated intracranial PFS (adjusted for BIRC-assessed PFS) compared with the KM data - crizotinib



BIRC, blinded independent review committee; PFS, progression-free survival

The exponential curve is selected in the base case for both brigatinib and crizotinib. This is supported by the AIC/BIC statistics and aligns with the base case parametric curves selected for PFS BIRC. It is notable that the exponential curve is the least optimistic one for crizotinib

and the second least optimistic for brigatinib. Alternative parametric curves are explored in a scenario analysis.

B.3.3.4.2 Unadjusted

The unadjusted intracranial PFS are based on the modified RECIST criteria. Table 30 presents the AIC and BIC values for each parametric survival distribution. The rank of the goodness of fit statistics are in line with those for the adjusted intracranial PFS.

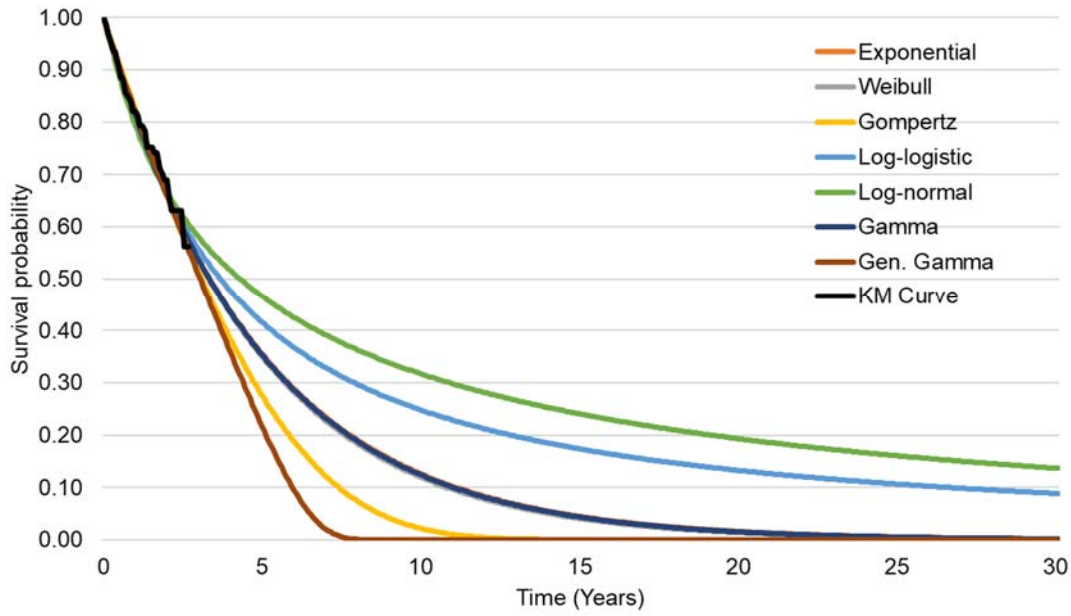
Table 30: Goodness-of-fit statistics intracranial PFS (unadjusted)

	Brigatinib		Crizotinib	
Models	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	407	409	450	453
Weibull	409	414	451	457
Gompertz	408	414	447	453
Log-logistic	409	415	447	453
Log-normal	412	418	444	450
Gamma	409	414	452	458
Gen. Gamma	410	419	445	454

AIC, Akaike information criterion; BIC, Bayes information criterion; BIRC, blinded independent review committee; PFS, progression-free survival

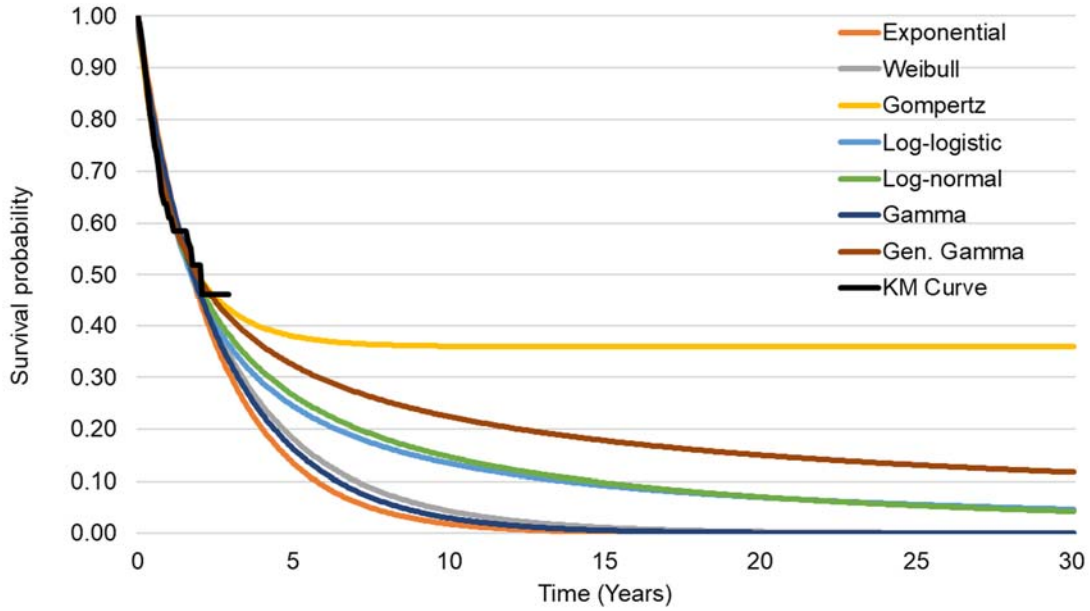
A comparison of the Kaplan-Meier plots with the extrapolated curves is presented in Figure 36 and Figure 37 for brigatinib and crizotinib, respectively.

Figure 36: Extrapolated intracranial PFS (unadjusted) compared with the KM data - brigatinib



CNS, central nervous system; KM, Kaplan-Meier; PFS, progression-free survival

Figure 37: Extrapolated intracranial PFS (unadjusted) compared with the KM data - crizotinib



CNS, central nervous system; KM, Kaplan-Meier; PFS, progression-free survival

B.3.3.5 Overall survival

In addition to being immature, the OS data observed in the ALTA-1L trial is also confounded by crossover; n=61 patients officially switched per protocol from crizotinib to brigatinib on progression, an additional n=12 patients were identified as having received brigatinib after crizotinib at some stage. In the IA2 data, n=74 of patients had progressed in the crizotinib arm. Therefore, the majority of patients progressing in the crizotinib arm went onto receive brigatinib.

Brigatinib is already available and reimbursed as a post-crizotinib treatment in the UK. Therefore, the treatment switching permitted within the ALTA-1L clinical trial is reflective of the UK treatment pathway. However, the bias introduced through treatment switching is particularly important when making comparisons between brigatinib and alectinib, because the ALEX clinical trial (which compared alectinib to crizotinib) did not allow for treatment switching. Therefore, any unadjusted anchored ITCs considering the OS endpoint will underestimate the relative impact of brigatinib compared to alectinib.

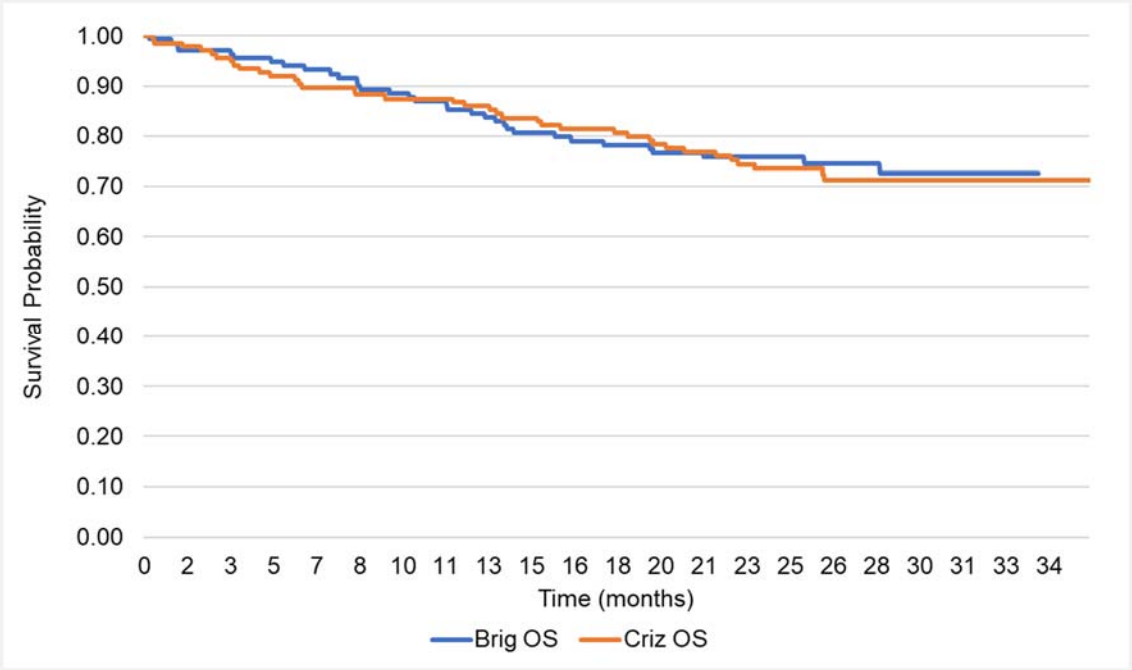
For this reason, treatment switching analyses have been conducted to attempt to remove the effect of subsequent brigatinib from the crizotinib arm. This analysis is primarily relevant to the brigatinib vs. alectinib comparison – discussed in further detail in Section B.3.3.7. However, it is also included as a scenario analysis for the comparison of brigatinib vs. crizotinib. Importantly, these scenarios allow for a more even comparison with the outcomes predicted in the alectinib NICE submission (TA536),[55] for example, in terms of validating the OS outcomes in the crizotinib arm.

The drop-down list on the 'Model Controls' sheet allows the user to select unadjusted or treatment switching adjusted survival data for crizotinib. In the base case, unadjusted data are applied in line with UK clinical practice which is to use brigatinib after progression on 1L crizotinib (as was allowed and done in the ALTA-1L trial).

B.3.3.5.1 Unadjusted

The Kaplan-Meier plot for OS outcomes for brigatinib vs. crizotinib from the ALTA-1L trial is presented in Figure 38.

Figure 38: KM data for OS



Brig, brigatinib; Criz, crizotinib; OS, overall survival

Figure 39 presents an assessment of proportional hazards; the log cumulative hazard plot indicates substantial crossing – reflecting the crossing observed in the Kaplan-Meier OS data, likely due to immature data. These plots suggest that the data are too immature to truly assess the proportional hazards assumption.

Therefore, in line with clinical feedback, the PFS BIRC/intracranial PFS outcomes and the alectinib NICE submission,[55] independent parametric curves were fit to the OS data.

Figure 39: Log-cumulative hazard plot and Schoenfeld residuals for OS

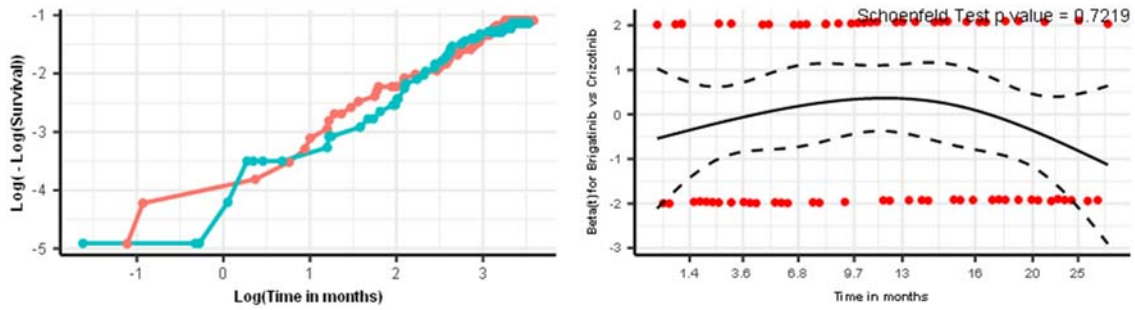


Table 31 presents the AIC and BIC values for each parametric survival distribution. There are limited differences in terms of how well each of the parametric curves fit the observed data; less than three points between the AIC and less than nine points between the BIC for brigatinib and crizotinib. The most reasonable fits to the observed data include: exponential, Gompertz, log-logistic and log-normal.

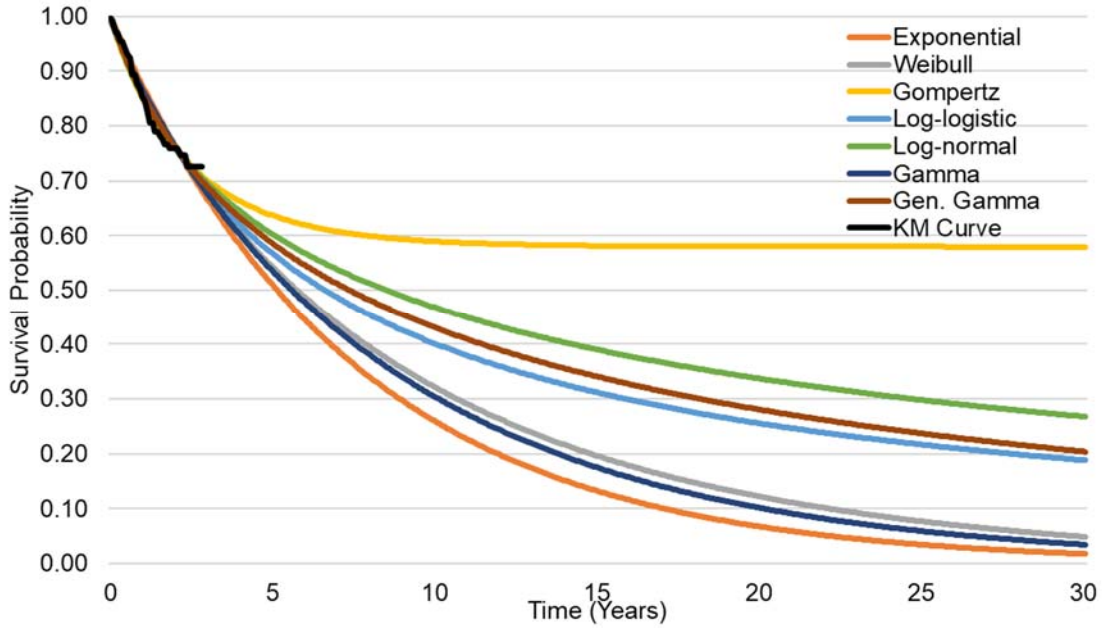
Table 31: Goodness-of-fit statistics OS (unadjusted)

	Brigatinib		Crizotinib	
Models	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	364	367	403	406
Weibull	366	371	404	410
Gompertz	364	370	404	410
Log-logistic	365	371	404	410
Log-normal	365	371	404	410
Gamma	366	371	404	410
Gen. Gamma	367	376	406	415

AIC, Akaike information criterion; BIC, Bayes information criterion; OS, overall survival

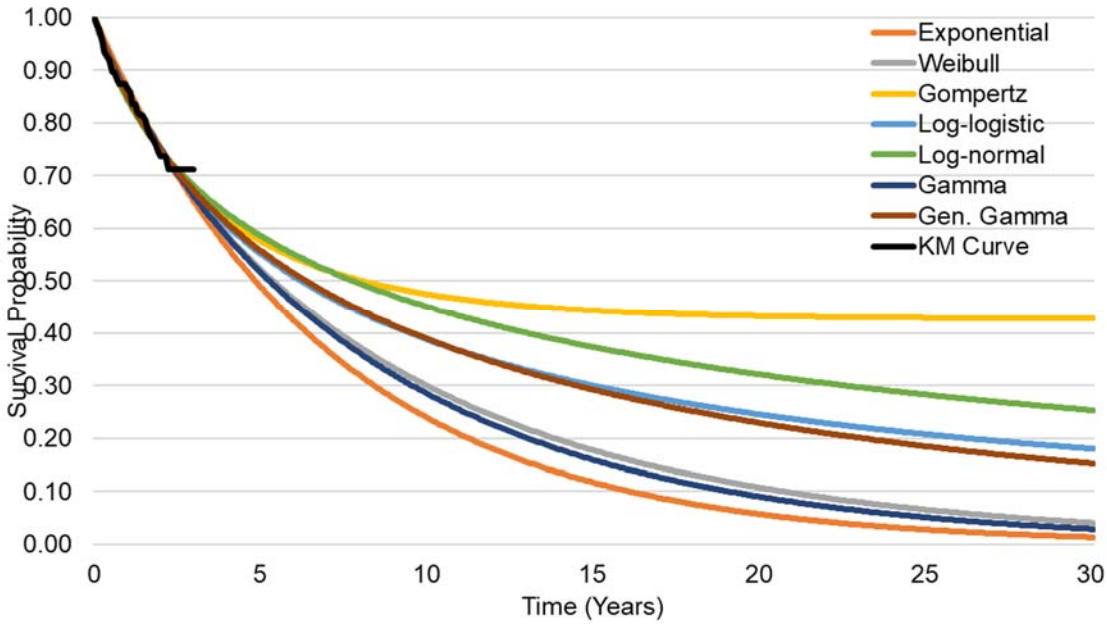
A comparison of the Kaplan-Meier plots with the extrapolated curves is presented in Figure 40 and Figure 41 for brigatinib and crizotinib, respectively.

Figure 40: Extrapolated OS (unadjusted) compared with the KM data - brigatinib



KM, Kaplan-Meier; OS, overall survival

Figure 41: Extrapolated OS (unadjusted) compared with the KM data - crizotinib



KM, Kaplan-Meier; OS, overall survival

The exponential curve is selected in the base case for both brigatinib and crizotinib. This is supported by the AIC/BIC statistics, aligns with the parametric curves from which a final decision was made in the alectinib NICE submission (TA536[55]) and aligned with clinical expert judgement from an advisory board (see Section B.3.10). It is notable that this is the least optimistic curve for brigatinib. Alternative parametric curves are explored in a scenario analysis.

B.3.3.5.2 Treatment switching adjustment

Scenario analyses attempt to remove the bias associated with subsequent brigatinib use in the crizotinib arm. As per NICE TSD 16,[96] the following methods were considered for the treatment switching analysis: Inverse Probability of Censoring weighting (IPCW), 2-stage method and Rank-preserving structural failure time model (RPSFTM).

The IPCW was not pursued for several reasons. Firstly, the IPCW method cannot work if there are levels of any covariates which ensure treatment switching will occur i.e. the probability equals one – progression is one such covariate associated with a probability of switching close to one. Secondly, the assumption of no unmeasured confounders i.e. the method necessitates that data must be available on baseline and time-dependent variables that predict both treatment-switching and prognosis. Whilst important prognostic factors were collected at baseline within the ALTA-1L clinical trial, these were not routinely collected at progression. Finally, due to the high proportion of switchers, the weights applied to the 'non-switching' population would be considered large.

The 2-stage method was considered inappropriate here due to the wide disparity in the length of time between progression diagnosis and the initiation of the switch (range: 5-days and 6.8 months). Therefore, the assumption of no time-dependent confounding between the time of disease progression and time of treatment is difficult to justify.

The RPSFTM was considered as a method to explore the treatment switching in the ALTA-1L trial. This method does not rely upon the no unmeasured confounders assumption and identified the treatment effect using only the randomisation of the trial, observed survival and observed treatment history. The limitation of the RPSFTM structure is the assumption of a common treatment effect which states that the relative treatment effect is the same for all participants regardless of when the treatment is received i.e. the relative efficacy of brigatinib vs. crizotinib is the same at frontline as it is at later lines. Note: the iterative parameter estimation (IPE) approach was also considered; however, this method is similar to the RPSFTM model but also requires establishing a suitable parametric form. Any treatment switching analysis applied to the IA2 data will be uncertain due to the immature OS data. Therefore, at this stage, analyses requiring additional assumptions beyond the RPSFTM were not considered.

Appendix L describes the RPSFTM method in full – here only a summary is provided. Four different analyses were considered:

1. Official switchers only (n=61, 44.2%), no re-censoring
2. Official switchers only (n=61, 44.2%), re-censoring included
3. All switchers (n=73, 52.90%), no re-censoring
4. All switchers (n=73, 52.90%), re-censoring included

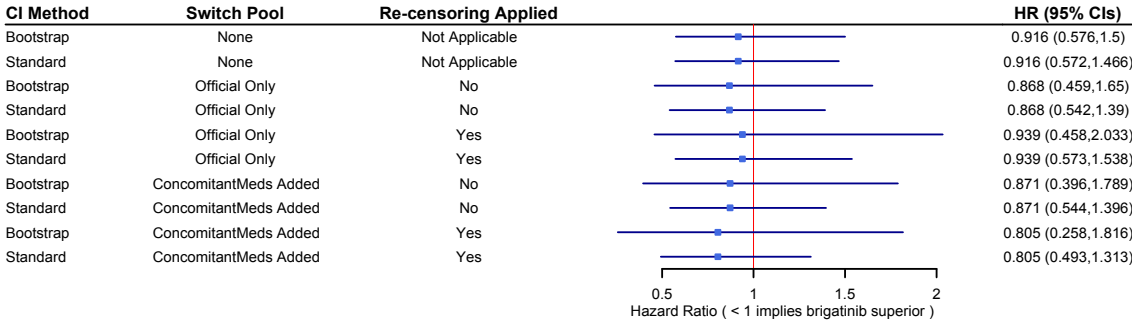
Additional scenarios explored how to account for the uncertainty within the RPSFTM method – non-parametric bootstrapping vs. non-bootstrapped values. Note: the analyses presented also adjusted for treatment switching from the brigatinib arm to the crizotinib arm (n=11). However, due to the small number of patients who made this switch and the fact that the

impact on survival is negligible, the adjusted brigatinib data were not considered within the economic model.

Figure 42 presents the HRs in a forest plot for brigatinib vs. crizotinib, showing the alternative treatment switching adjustment scenarios. In some scenarios the adjusted HRs improve in brigatinib's favour – as would be expected when removing the effect of subsequent brigatinib in the crizotinib arm. However, in some scenarios the point estimate is shown to worsen in favour of crizotinib – this is not considered clinically plausible.

Additionally, the change in HR observed across other scenarios is not as large as anticipated; given the similar PFS BIRC HR seen in the ALTA-1L for brigatinib vs. crizotinib (HR: 0.49) and in the ALEX trial for alectinib vs. crizotinib (HR: 0.50), it was expected that the OS outcomes from the ALTA-1L trial without treatment switching bias would align with the ALEX trial – the final data cut from the ALEX trial showed a HR of 0.69 (median follow up of 37.8 months for alectinib). These reasonings coupled with the counterintuitive results in one scenario lead us to conclude that the OS data from ALTA-1L are simply too immature (see Section B.2.6.3.4) to allow for robust treatment switching analyses, or that the common treatment effect underlying the RPSFTM method is flawed.

Figure 42: Brigatinib vs. Crizotinib OS HR Forest Plot: Alternative Treatment Switch Adjustment Schemes Bootstrapped (Normal CIs) & Standard (non-bootstrapped)

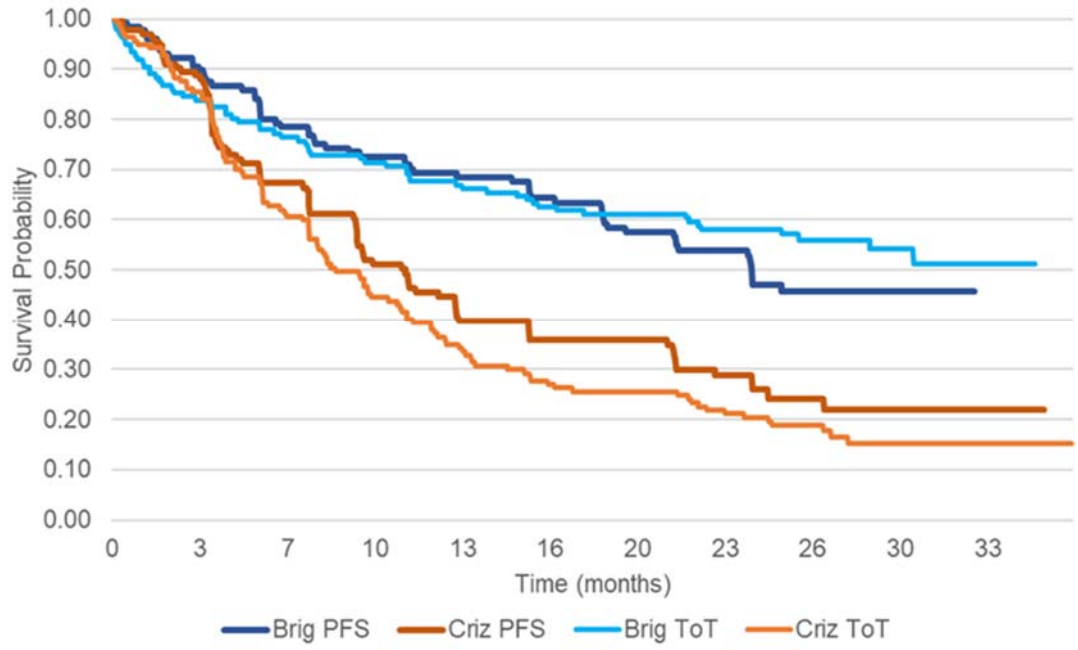


CI, confidence intervals; HR, hazard ratio; OS, overall survival

B.3.3.6 Time on treatment

Patients in the ALTA-1L clinical trial continued treatment with brigatinib or crizotinib until they experienced BIRC assessed progressive disease, intolerable toxicity, or were discontinued for other reasons. It was permitted that patients in the brigatinib arm who experienced BIRC-assessed progressive disease could continue to be treated with brigatinib if, in the opinion of the treating investigator, they continued to experience clinical benefit. Patients in the crizotinib arm were not permitted to continue treatment with crizotinib on study after BIRC-assessed progressive disease. However, these patients were permitted to crossover to the brigatinib arm. Figure 43 presents the Kaplan-Meier data for time on treatment (ToT) compared with PFS BIRC for brigatinib and crizotinib. The median exposure time in the ALTA-1L trial for brigatinib was 24.3 vs. 8.4 months for crizotinib; compared with the median PFS BIRC of 24 vs.11 months, respectively. The mean exposure time was 18.99 vs. 12 months, respectively.

Figure 43: ToT compared with BIRC-assessed PFS from ALTA-1L



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

Based on the ALTA-1L clinical trial and clinical expert feedback from an advisory board (see Section B.3.10), the base case assumes that all patients receive treatment until progression. This is also aligned with the alectinib NICE submission (TA536[55]). As well as being supported by the data, this also avoids having to make an additional assumption for ToT relating to alectinib as little data are publicly available on this endpoint in the literature.

To explore real-world use of ALK inhibitors beyond progression, three scenarios are considered: treatment for one, two or three cycles beyond progression. Clinical expert feedback indicates that their decision to keep a patient on treatment depends not only on disease progression but also the potential for continued clinical benefit, whether the patient is symptomatic and the availability of subsequent efficacious therapies. Therefore, some patients may remain on treatment for a short time beyond progression. This is reflected in the clinical trials to date in the ALK-positive advanced NSCLC setting; a recent review of clinical trials explored the relationship between time to treatment discontinuation and PFS and found that a proportion of patients with ALK-positive advanced NSCLC continued treatment beyond progression – 22.9% received ≥3 months of treatment beyond progression.[97] This review included trials for brigatinib post-crizotinib, frontline alectinib and frontline crizotinib. A similar trend was also observed in the ceritinib trial (ASCEND-4): 84% of patients received at least one dose of ceritinib after disease progression and 49% continued for at least two cycles – the additional median exposure was 9.6-weeks.[54] Therefore, scenario analyses explore the impact of up to three cycles (12-weeks) beyond disease progression.

B.3.3.7 Indirect and mixed treatment comparisons

In the absence of head-to-head data between brigatinib and alectinib, ITCs were required to inform the relative efficacy inputs in the model for PFS BIRC and OS. HRs were also estimated using PFS INV outcomes to make use of the final data cut from the ALEX trial; BIRC assessed PFS was not collected beyond the primary analysis in the ALEX trial. Section B.2.9 and Appendix D describe these analyses in more detail and present the results.

Three methods were considered;

1) unweighted Bucher,
2) anchored MAIC and,
3) unanchored MAIC.

The unweighted Bucher analysis was conducted as a reference comparison – this method utilises a Cox regression between brigatinib and alectinib that matches the MAIC setup, except that there are no predictors other than treatment and all weights are set to one. It then applies the standard Bucher formula. The common crizotinib arms from ALTA-1L and ALEX provide the necessary inter-trial link required for this analysis.

Exploratory analyses were conducted using the ALTA-1L data to identify any treatment effect modifiers; Cox proportional hazard models were run for each potential candidate, including: gender, age, smoking status, race (Asian vs. non-Asian), baseline brain metastases and ECOG score (0/1 vs. 2). The candidate list was informed by clinical expert feedback received during the brigatinib post-crizotinib NICE submission (TA571)[2] and was validated by clinical experts at an advisory board for the frontline setting (Section B.3.10). Not surprisingly, the proportion of patients with baseline brain metastases was shown to be a significant driver of outcomes for PFS BIRC and OS endpoints (p=0.030 and p=0.020, respectively).

Given the disparity in the proportion of patients with baseline brain metastases between the ALTA-1L and ALEX clinical trials (29% vs. 30% for brigatinib vs. crizotinib in the ALTA-1L trial and 42% vs. 38% for alectinib vs. crizotinib in the ALEX trial), the unweighted Bucher comparisons will be biased. Therefore, anchored MAIC methodology is applied to attempt to remove the bias associated with differences in the proportion of baseline brain metastases. The anchored MAIC involved two separate matchings on baseline brain metastases proportions: (1) brigatinib ALTA-1L patient level data were matched to the alectinib arm in ALEX and (2) crizotinib ALTA-1L patient level data were matched to the crizotinib arm in ALEX.

As the unweighted Bucher method and the anchored MAIC method use the crizotinib link to estimate a relative efficacy estimate, the OS estimates are also biased by the treatment switching which occurred in the ALTA-1L crizotinib arm and not in the ALEX crizotinib arm. Therefore, these methods are applied using the unadjusted OS data and the treatment switching adjusted data derived from each of the four scenarios presented in Section B.3.3.5.2. Note: these scenarios are relevant to OS outcomes only.

As discussed in Section B.3.3.5.2, the treatment switching analyses do not appear to have fully adjusted for subsequent brigatinib use in the crizotinib arm. Therefore, the anchored MAICs utilising the adjusted data for crizotinib may still have some bias incorporated in the

estimates related to treatment switching. To explore this further, unanchored MAICs were considered. The unanchored MAIC considers the brigatinib arm from the ALTA-1L trial and the alectinib arm from the ALEX trial as if they were from single arm studies and ignores the data from the crizotinib arms. Therefore, this analysis avoids the bias that would be introduced relating to the crizotinib arms. The unanchored MAIC balances the data based on: age, smoking status, race, baseline brain metastases, ECOG score and receipt of prior chemotherapy – this list was informed by clinical expert feedback received during the brigatinib post-crizotinib NICE submission (TA571[2]) and was validated by clinical experts at an advisory board for the frontline setting (Section B.3.10).

As discussed with NICE in the decision problem meeting, Takeda consider there to be limitations associated with all of the ITC analyses. These limitations are driven by the differences between the ALTA-1L clinical trial and the ALEX trial, differences which cannot be totally adjusted for (see Section B.2.3). We have conducted numerous analyses attempting to adjust for the different biases and we consider that overall the evidence shows that clinical outcomes with brigatinib and alectinib are extremely similar.

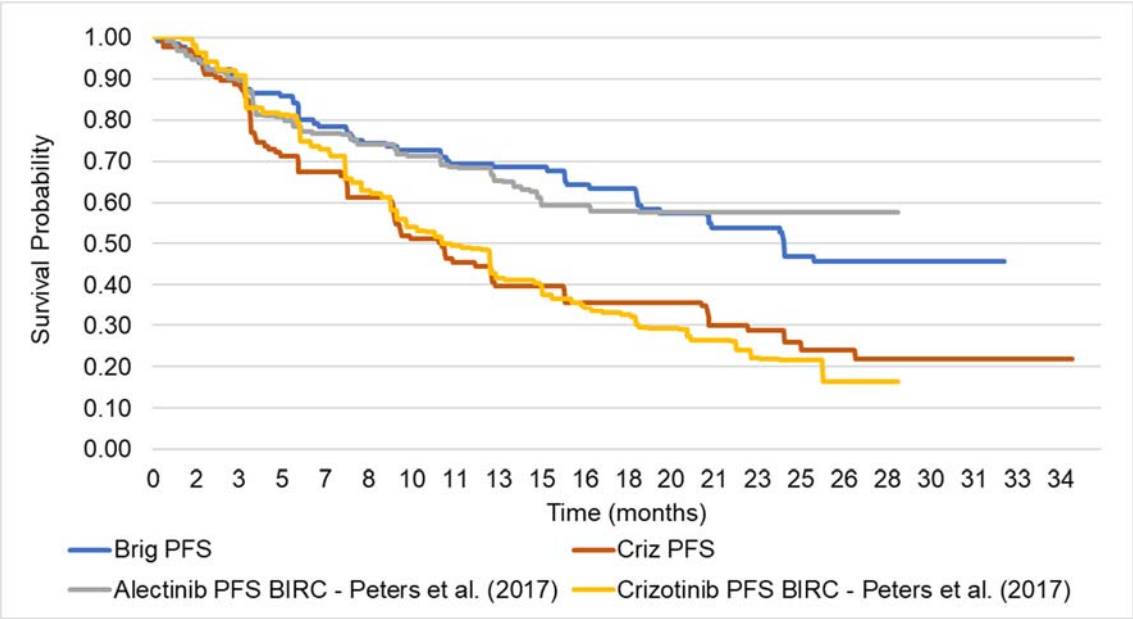
The HRs for the PFS outcomes, for which we have the most data maturity indicate estimates between 0.969-1.04 for BIRC assessed and between 0.965-1.046 for INV assessed. These support our position that brigatinib is at least as effective as alectinib. The HRs for OS outcomes are much more uncertain and are difficult to interpret due to a high level of treatment switching in the ALTA-1L trial and data immaturity. Therefore, we consider that a cost-comparison approach is appropriate for decision making in the comparison of brigatinib with alectinib (i.e. all efficacy outcomes are assumed the same for both treatments). Supporting this approach, all clinical experts consulted at the two advisory boards (see Section B.3.10) reported similar experience with brigatinib and alectinib in clinical practice. All clinical experts agreed unanimously that an assumption of clinical equivalence between brigatinib and alectinib is supported by both the clinical data and their real-world experience. Therefore, the results of a cost-comparison analysis for brigatinib vs. alectinib are presented alongside the cost-effectiveness results in Section B.3.7.

B.3.3.7.1 Progression-free survival per BIRC

Figure 44 presents a naive comparison of the Kaplan-Meier data from the ALTA-1L trial and the ALEX trial for PFS BIRC outcomes. A summary of other key outcomes for efficacy in the ALTA-1L and ALEX studies are summarised in Appendix D.1.1.8, Table 11.

The data for PFS BIRC from the ALEX trial was obtained from Peters et al. (2017); the PFS BIRC outcome was only reported in the primary analysis with a median follow-up of 18.6 months.[59] Whilst in the ALTA-1L trial there appears to be an earlier separation of curves, the trend is similar between the two trials. This supports the rationale for a cost-comparison analysis.

Figure 44: Naive comparison of BIRC-assessed PFS for brigatinib (ALTA-1L) and alectinib (ALEX)



BIRC, blinded independent review committee; Brig, brigatinib; Criz, crizotinib; PFS, progression-free survival

Table 32 presents the results for the Unweighted Bucher, the anchored MAIC analysis and the unanchored MAIC analysis for PFS BIRC outcomes. The confidence intervals are wide for each of the comparisons and they cross unity (1.0) – indicating non-statistically significant differences. Note: HRs <1.0 are in favour of brigatinib.

In the base case, the HRs derived from the unanchored MAIC are applied. This analysis makes use of all the data from ALTA-1L and aligns with the method used for OS (the unanchored MAIC is preferred for OS to avoid bias associated with treatment switching). However, as discussed in Section B.2.9, we consider that each ITC is associated with limitations and that the range of estimates produced might best be used to support the argument for a cost-comparison analysis for brigatinib vs. alectinib.

Alternative ITC analyses are explored in scenario analyses.

Table 32: Indirect treatment comparison results, brigatinib vs. alectinib, BIRC-assessed PFS

	HR (Point estimate)	95% CI	ESS (brigatinib, crizotinib)
Unweighted Bucher	1.04	0.652 – 1.66	137, 138
Anchored MAIC	0.969	0.607 – 1.545	126.78, 133.17
Unanchored MAIC	0.974	0.686 – 1.383	124.01, NA

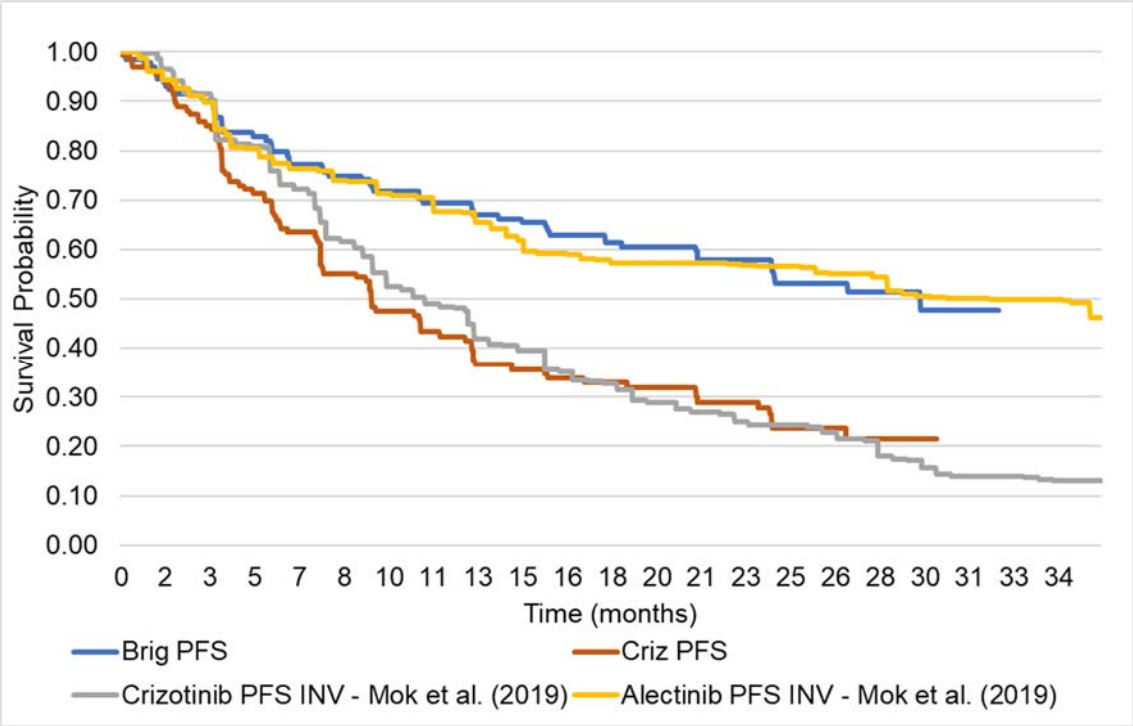
ALK, anaplastic lymphoma kinase; BIRC, blinded independent review committee; CI, confidence interval; ESS, effective sample size; HR, hazard ratio; MAIC, matched adjusted indirect comparison; PFS, progression-free survival

B.3.3.7.2 Progression-free survival per investigator

Figure 45 presents a naive comparison of the Kaplan-Meier data from the ALTA-1L trial and the ALEX trial for PFS INV outcomes. The data for PFS INV from the ALEX trial was obtained

from Mok et al. (2019)[40] – this is the latest publication with a median follow-up of 37.8 months.[40] Whilst in the ALTA-1L trial there appears to be an earlier separation of curves, the trend is similar between the two trials.

Figure 45: Naive comparison of INV-assessed data for brigatinib (ALTA-1L) and alectinib (ALEX)



Brig, brigatinib; Criz, crizotinib; INV, investigator; PFS, progression-free survival

Table 33 presents the results for the Unweighted Bucher, the anchored MAIC analysis and the unanchored MAIC analysis for PFS INV outcomes. Note: HRs <1.0 are in favour of brigatinib. The confidence intervals for the HRs are wide for each of the comparisons and they cross unity – indicating non-statistically significant differences. These outcomes closely align with those seen for PFS BIRC above.

Table 33: Indirect treatment comparison results, brigatinib vs. alectinib, INV-assessed PFS

	HR (Point estimate)	95% CI	ESS (brigatinib, crizotinib)
Unweighted Bucher	1.046	0.669 – 1.636	137, 138
Anchored MAIC	0.965	0.615 – 1.515	126.78, 133.17
Unanchored MAIC	0.969	0.68 – 1.381	124.01, NA

ALK, anaplastic lymphoma kinase; CI, confidence interval; ESS, effective sample size; HR, hazard ratio; INV, investigator; MAIC, matched adjusted indirect comparison; PFS, progression-free survival

B.3.3.7.3 Intracranial progression-free survival

The intracranial PFS variable is not publicly available from the ALEX trial. This was presented as part of the submission to NICE for alectinib (TA536[55]). However, the Kaplan-Meier curves have been redacted from the publicly available information. Therefore, the HR for intracranial PFS for brigatinib vs. alectinib is assumed to be the same as the HR for PFS.

The HR for intracranial PFS can be input on the 'Model Controls' sheet within the model. Whilst it is assumed the same as the PFS HR, it is included in the model as its own variable and is varied independently of the PFS HR in the PSA. Therefore, the PSA captures the impact of different HRs for PFS and Intracranial PFS.

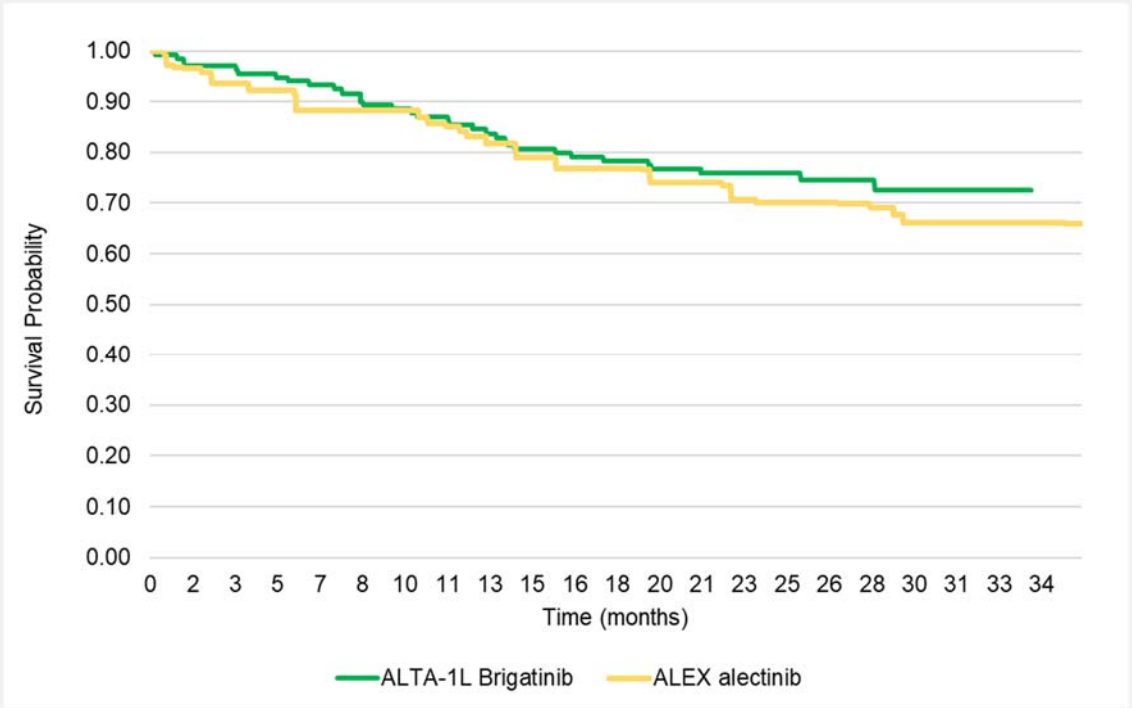
B.3.3.7.4 Overall survival

Figure 46 presents the Kaplan-Meier plot for brigatinib from the ALTA-1L data alongside the digitised OS data for alectinib from the ALEX trial publication, Camidge et al. (2018) – the latest publication showing a Kaplan-Meier plot for alectinib.[65] Based on this naïve comparison, there is no clear difference between brigatinib and alectinib. This again supports the rationale for a cost-comparison analysis.

Table 34 presents the results for the Unweighted Bucher, the anchored MAIC analysis and the unanchored MAIC analysis for OS outcomes. Note: HRs <1.0 are in favour of brigatinib.

Like the PFS outcomes, the confidence intervals are wide for each of the comparisons and cross unity – indicating non-statistically significant outcomes. However, there is a much bigger difference between the Unweighted Bucher and anchored MAIC when compared with the unanchored MAIC. These differences are still apparent even when the treatment switching adjusted data are used for crizotinib (Table 35).

Figure 46: Naive comparison of OS data for brigatinib (ALTA-1L) and alectinib (ALEX)[3,7]



OS, overall survival

To explore this further, the data sources informing the ITCs were considered. The Unweighted Bucher and anchored MAIC use data from the latest publication for ALEX – Mok et al. (2019) – 37.8 months of follow-up in the alectinib arm.[40] However, this publication only reports the

HR and confidence interval. The unanchored MAIC makes use of data from an earlier analysis and publication (Camidge et al. (2018) – 27.8 months of follow-up in the alectinib arm), where a Kaplan-Meier plot is presented for OS outcomes.[65] To explore the impact of this mismatch in data, Table 34 presents the results of the Unweighted Bucher and anchored MAIC when the earlier data cut is used (i.e. consistent with the unanchored MAIC). Whilst the point estimates for these analyses move closer to the unanchored MAIC, the data source does not fully explain the differences. Due to similarities in point estimates, the model only includes indirect analyses based on the most recent data available (i.e. uses Mok et al. (2019) for all Unweighted Bucher and anchored MAIC analyses) – the analyses based on the earlier data cut are presented here for illustrative purposes only.

None of the analyses explored fully explain the differences between the Unweighted Bucher and the anchored MAIC when compared to the unanchored MAIC. Therefore, we conclude that none of the available statistical methods succeed in removing the bias introduced through the differences between the ALTA-1L and ALEX trials. Similar to PFS, we consider that visual inspection of the Kaplan-Meier curves and the range of HRs should be considered (0.832 – 1.383) as being supportive of a cost-comparison approach.

In the base case cost-effectiveness analysis, the unanchored MAIC HR for OS (0.832) is applied. This analysis makes use of all of the data from ALTA-1L and avoids the bias in the crizotinib arm associated with treatment switching. However, as discussed in Section B.2.9, we consider that each ITC is associated with limitations and that the range of estimates produced might best be used to support the argument for a cost-comparison approach. Alternative ITC analyses are explored in scenario analyses.

Table 34: Indirect treatment comparison results, brigatinib vs. alectinib, OS

	Alectinib data source	HR (point estimate)	95% CI	ESS (brigatinib, crizotinib)
Unweighted Bucher	Mok et al. (2019)[40]	1.359	0.741 – 2.494	137, 138
Anchored MAIC	Mok et al. (2019)	1.21	0.654 – 2.238	126.781, 133.172
Unanchored MAIC	Camidge et al. (2018)[98]	0.832	0.522 – 1.325	124.014, NA
Unweighted Bucher	Camidge et al. (2018)	1.241	0.664 – 2.321	137, 138
Anchored MAIC	Camidge et al. (2018)	1.105	0.586 – 2.082	126.78, 133.17

ALK, anaplastic lymphoma kinase; CI, confidence interval; ESS, effective sample size; HR, hazard ratio; MAIC, matched adjusted indirect comparison; OS, overall survival

Table 35: Exploration of treatment switching in Unweighted Bucher and anchored MAIC analyses, brigatinib vs. alectinib, OS

	Alectinib data source	Switchers	Re-censoring?	HR (Point estimate)	95% CI
Unweighted Bucher	Mok et al. (2019)[40]	Official	No	1.291	0.703-2.369
Anchored MAIC	Mok et al. (2019)	Official	No	1.146	0.62-2.119
Unweighted Bucher	Mok et al. (2019)	Official	Yes	1.383	0.741-2.582

Anchored MAIC	Mok et al. (2019)	Official	Yes	1.231	0.655-2.312
Unweighted Bucher	Mok et al. (2019)	All	No	1.293	0.704-2.374
Anchored MAIC	Mok et al. (2019)	All	No	1.148	0.621-2.122
Unweighted Bucher	Mok et al. (2019)	All	Yes	1.191	0.636-2.229
Anchored MAIC	Mok et al. (2019)	All	Yes	1.035	0.548-1.954
Unweighted Bucher	Camidge et al. (2018)	Official	No	1.179	0.63-2.205
Anchored MAIC	Camidge et al. (2018)	Official	No	1.047	0.556-1.971
Unweighted Bucher	Camidge et al. (2018)	Official	Yes	1.263	0.664-2.402
Anchored MAIC	Camidge et al. (2018)	Official	Yes	1.124	0.587-2.15
Unweighted Bucher	Camidge et al. (2018)	All	No	1.181	0.631-2.209
Anchored MAIC	Camidge et al. (2018)	All	No	1.048	0.557-1.974
Unweighted Bucher	Camidge et al. (2018)	All	Yes	1.087	0.57-2.073
Anchored MAIC	Camidge et al. (2018)	All	Yes	0.945	0.491-1.817

ALK, anaplastic lymphoma kinase; CI, confidence interval; ESS, effective sample size; HR, hazard ratio; MAIC, matched adjusted indirect comparison; OS, overall survival

B.3.3.8 Adverse events

Treatment with ALK TKIs results in a variety of AEs. Any-cause Grade 3/4 AEs occurring in ≥3% of patients in the relevant clinical trials (ALTA-1L and ALEX) were included in the economic analysis. Adverse events from the ALTA-1L trial were sourced from Table 15.3.1.2.2.4 of the CSR.

Note: the latest publication of the ALEX trial results (Mok *et al.* [2019]) does not provide a full breakdown of AEs. However, the total number of Grade 3/4 AEs is reported as 74.[40] The second publication for the ALEX trial (Camidge *et al.* [2018]) only reports all Grade AEs that differed by ≥5% in frequency between treatment arms.[65] Therefore, the primary publication for the ALEX trial (Peters *et al.* [2017]) has been used to source Grade 3/4 AEs occurring in ≥3% of patients – this describes 63 Grade 3/4 AEs.[59] Therefore, we believe some AEs are likely missing from the alectinib arm due to lack of reporting.

Adverse events were modelled only for patients on treatment; it was assumed that AEs for all therapies cease once treatment is discontinued. It was further assumed that AEs lasted one model cycle (i.e. 28 days). Table 36 presents the number of events associated with each AE included in the model.

The number of events and the median exposure time were used to calculate a per cycle event rate (Table 37). Where AEs were not reported in specific publications, the model assumes an event rate of zero. The per cycle rate was estimated as 0.022, 0.033 and 0.007 for brigatinib, crizotinib and alectinib, respectively. As discussed earlier, the majority of AEs in the brigatinib

arm were asymptomatic laboratory abnormalities which were not associated with adverse clinical outcomes (see Section B.2.10).

Table 36: Number of adverse events for each treatment

Adverse Events	Occurrence		
	Brigatinib	Crizotinib	Alectinib
Blood creatinine phosphokinase increased	32	1	4
Amylase increased	8	1	NR
Nausea	2	3	1
Hypertension	10	0	NR
Increased AST	3	7	8
Increased ALT	2	11	7
Increased lipase level	17	5	NR
Neutropenia	0	4	0
Anaemia	2	0	7
Diarrhoea	1	4	0
Vomiting	0	1	0
Gamma-glutamyl transferase increased	1	2	1
Fatigue	0	0	1
Pneumonia	1	0	4
Urinary tract infection	NR	NR	4
Acute kidney injury	0	1	4
Weight decreased	0	0	NR
Asthenia	0	1	NR

ALT, alanine aminotransferase; AST, aspartate aminotransferase; NR, not reported

Table 37: Rate of adverse events per model cycle

Adverse events	Rate per cycle		
	Brigatinib	Crizotinib	Alectinib
Blood creatinine phosphokinase increased	0.0089	0.0008	0.0008
Amylase increased	0.0022	0.0008	0.0000
Nausea	0.0006	0.0024	0.0002
Hypertension	0.0028	0.0000	0.0000
Increased AST	0.0008	0.0056	0.0017
Increased ALT	0.0006	0.0088	0.0015
Increased lipase level	0.0047	0.0040	0.0000
Neutropenia	0.0000	0.0032	0.0000
Anaemia	0.0006	0.0000	0.0015
Diarrhoea	0.0003	0.0032	0.0000
Vomiting	0.0000	0.0008	0.0000
Gamma-glutamyl transferase increased	0.0003	0.0016	0.0002
Fatigue	0.0000	0.0000	0.0000
Pneumonia	0.0003	0.0000	0.0008

Adverse events	Rate per cycle		
	Brigatinib	Crizotinib	Alectinib
Urinary tract infection	0.0000	0.0000	0.0000
Acute kidney injury	0.0000	0.0008	0.0000
Weight decreased	0.0000	0.0000	0.0000
Asthenia	0.0000	0.0008	0.0000
Total	**0.0220**	**0.0329**	**0.0067**

ALT, alanine aminotransferase; AST, aspartate aminotransferase

B.3.4 Measurement and valuation of health effects

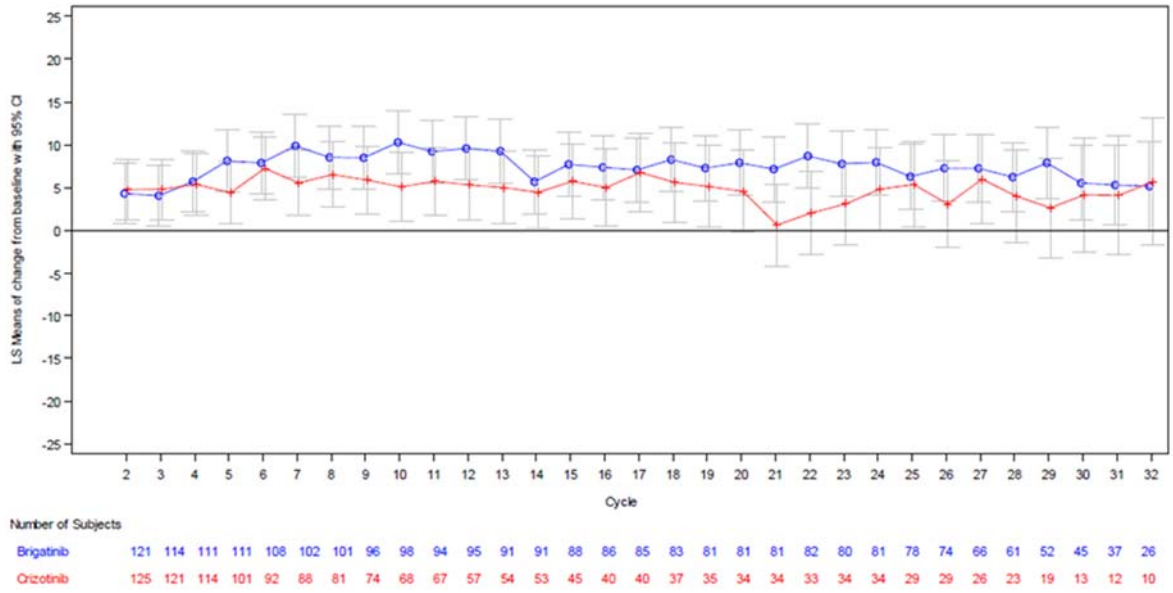
B.3.4.1 Health-related quality of life data from clinical trials

The ALTA-1L clinical trial collected HRQoL data by administering the EORTC-QLQ-C30 (v3.0) and the lung cancer specific module (the QLQ-LC13, v.3.0). The EORTC QLQ-C30 is a cancer-specific questionnaire scored for five functional scales (physical, role, cognitive, emotional and social functioning), three symptom scales (fatigue, pain, and nausea/vomiting) and a global health status/HRQoL scale. Note: the EQ-5D was not collected directly in the ALTA-1L clinical trial.

Figure 47 presents the change from baseline in GHS for EORTC QLQ-C30 and QLQ-LC13. Figure 8 and Figure 9 presents the mean change from baseline from global HRQoL, functioning and symptom scores. Brigatinib is shown to have a numeric improvement over crizotinib in all functional domains, with significant improvement in physical, emotional and cognitive functioning. In terms of symptoms subscales, scores for fatigue, nausea/vomiting, appetite loss and constipation were significantly improved with brigatinib over crizotinib. The EORTC QLQ-C30 cannot be used directly in economic evaluation as it does not incorporate preference information. Therefore, a mapping exercise was required to convert the EORTC

QLQ-C30 data into EQ-5D-3L utility scores (Section B.3.4.2). Following this, a HRQoL analysis was conducted to estimate utility values for different health states in the model (Section B.3.4.3).

Figure 47: Change from baseline in Global Health Status



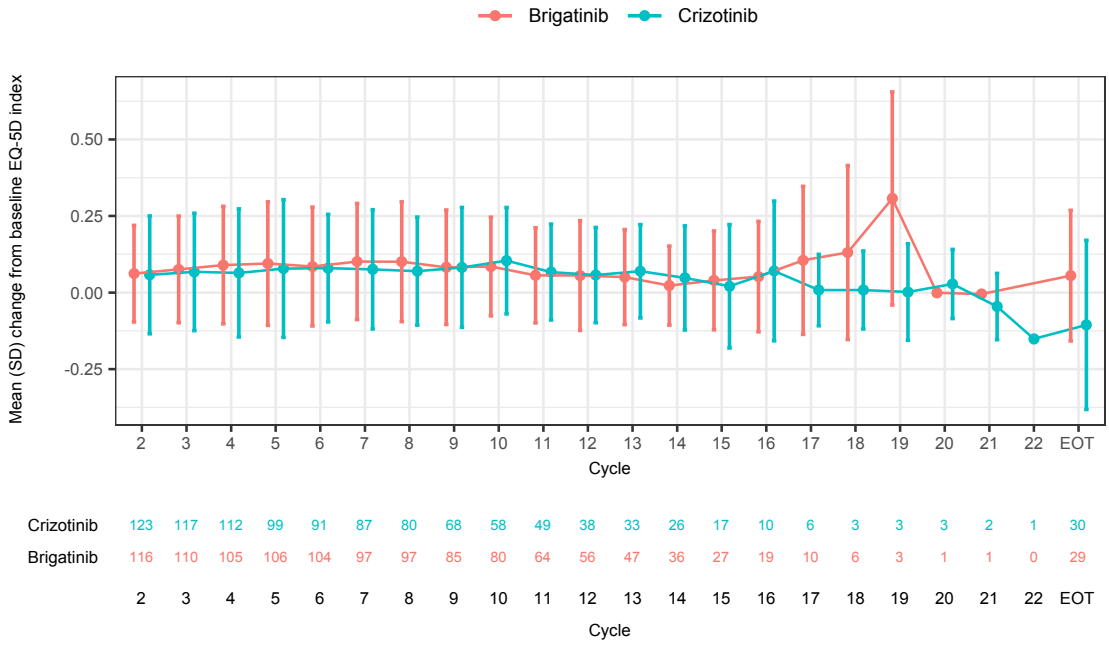
B.3.4.2 Mapping

The algorithm published in Longworth et al. (2014) was selected to map the EORTC QLQ-C30 values to EQ-5D-3L.[99] The selection was made based on appropriateness of the algorithm for the disease area (lung cancer), similarities between the index population and the patient population in the ALTA-1L trial, and performance or strengths of the methods and attributes of the algorithm. Longworth et al. (2014) included patients with a combination of different cancers, including lung cancer, and has previously been shown to perform well.

Figure 48 presents the change from baseline in EQ-5D-3L score. When this is compared to

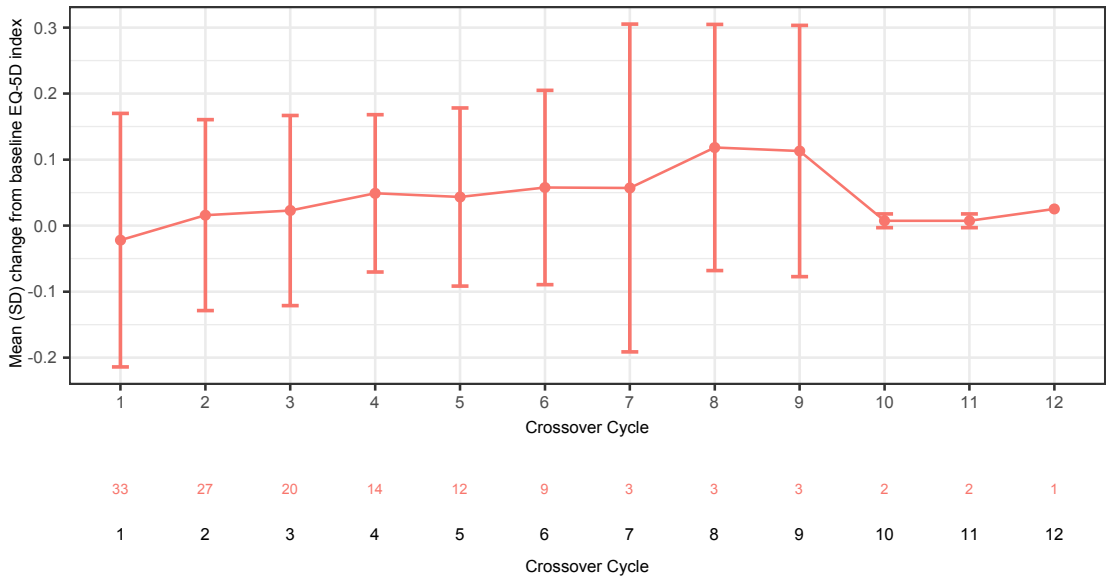
Figure 47 it can be seen that the difference between brigatinib and crizotinib HRQoL scores is much less when using the mapped EQ-5D values compared with the EORTC QLQ-C30/LC13 values. Brigatinib is shown to offer superior HRQoL when using the EORTC QLQ-C30/LC13. However, this statement cannot be sustained with the mapped EQ-5D data. This highlights that the mapped EQ-5D values may not be sensitive enough to capture all HRQoL impact for patients with ALK-positive advanced NSCLC. This has implications for the health economic modelling as it suggests that the HRQoL benefits, and hence the QALY gain, reported for brigatinib is likely to be under-estimated.

Figure 48: EQ-5D Change from Baseline Treatment Cycle



The ALTA-1L clinical trial allowed for crossover from the crizotinib arm to brigatinib upon disease progression. As well as confounding the OS outcomes, this also confounds the HRQoL outcomes. Figure 49 presents the HRQoL for patients who switch from crizotinib to brigatinib – this highlights a point estimate benefit to EQ-5D from switching to brigatinib. However, the switching population is too small to make any claims on significance. Note: no adjustments have been made to account for treatment switching in the HRQoL analysis. However, this should be considered when interpreting the results.

Figure 49: EQ-5D Change from Study Baseline in patients switching from crizotinib to brigatinib



B.3.4.3 Health-related quality of life analysis

A mixed-effects model was fitted to the data which accounts for the longitudinal nature of the data, whereby patients have multiple utility scores, measured over time. The patient was treated as a random-effect in the model due to repeated measures per patient, and the prognostic factors were included as fixed-effects.

The variables included within the mixed effects model were: baseline EQ-5D score, Grade 3/4 AE and investigator BOR – based on the availability of this variable for alectinib (this variable includes both confirmed and unconfirmed assessments). These variables were confirmed to be key drivers of HRQoL by clinical experts at an advisory board (see Section B.3.10). The categorisation of investigator BOR was based on CR or PR or SD vs. PD such that utilities could be estimated that aligned with the health states of the model.

Based on the second data cut (IA2) from the ALTA-1L trial, a total of 272 patients (out of 275) had at least one mapped EQ-5D utility value. Baseline readings were available for 263 patients. The number of patients contributing readings to the final derived mixed effects regressions was 246. The average number of EQ-5D readings from these 246 patients contributing to the analysis being 21.4, with a range of 2 to 39.

Table 38 presents the coefficients of the HRQoL analysis. Estimates are in line with expectations – utility values increase with baseline EQ-5D score and decrease with Grade 3/4 AEs and progression.

The predicted utility values based on these coefficients and a mean of covariate approach are presented in Table 39 – mean values of predictors were 0.720 for baseline EQ-5D score and 0.100 for Grade 3/4 AEs. The predicted utilities are in line with the observed utility values.

Table 38: Coefficients for HRQoL analyses applied in economic model

term	estimate	std.error	df	statistic	p.value
(Intercept)	0.527	0.028	4778.000	19.120	0.000
Baseline EQ-5D score	0.374	0.037	243.000	10.186	0.000
Grade 3/4 AE	-0.037	0.005	4778.000	-7.953	0.000
CR or PR or SD vs. PD	-0.169	0.032	243.000	-5.306	0.000

CR, complete response; df, degrees of freedom; EQ-5D, EuroQol 5-dimensions; HRQoL, health related quality of life; PD, progressive disease; PR, partial response; SD, stable disease

Table 39: Predicted utility values

Response Category	Predicted utilities	Observed utilities
CR	0.793	0.812
PR		0.795
SD		0.759
PD	0.624	0.619

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease

B.3.4.4 Health-related quality of life studies

A HRQoL SLR was conducted to identify published utility values used to determine HRQoL in patients with advanced or metastatic ALK-positive NSCLC. The original SLR was conducted in May 2018 – this was subsequently updated in May 2019. Twenty-nine publications were identified in total; 13 reporting EQ-5D data as a primary publication, six reporting mapping studies and ten papers citing utility values from the literature.

The base case economic model utilises data from ALTA-1L supplemented by Roughley et al. (2014),[46] Blackhall et al. (2014)[42] and Nafees et al. (2008).[88] As alectinib is the main comparator to brigatinib, the economic model presented in this dossier closely aligns with the alectinib NICE submission (TA536). This submission was identified as part of the SLR and also uses these publications to supplement their patient level data from the ALEX trial.

In line with the alectinib NICE submission, Roughley et al. (2014) was used to inform the CNS progression health state. This publication was not identified within our SLR as it was published as an abstract only and abstracts published before 2015 were excluded.

The alectinib NICE submission uses Blackhall et al. (2014) to inform the utility associated with subsequent chemotherapy. However, the alectinib submission uses the utility value estimated from the docetaxel arm. Whereas, this submission uses the utility value from the pemetrexed arm in line with clinical feedback – in the base case 100% of chemotherapy was pemetrexed-based. The Blackhall et al. (2014) paper was identified as part of our SLR.

Finally, in line with the alectinib NICE submission, Nafees et al. (2008) was used to inform the utility associated with BSC. This publication was not identified as part of the SLR as it was conducted using healthy participants and so was excluded based on population.

Appendix H provides the details associated with the SLR and the search strategy.

B.3.4.5 Adverse reactions

The impact of a Grade 3/4 AE on HRQoL is captured within the HRQoL analysis – a decrement of -0.037 was multiplied by the probability of a Grade 3/4 AE per cycle. It was assumed that each AE would last one cycle only (i.e. 28-days). This resulted in a utility decrement of -0.00082, -0.00123 and -0.0003 applied per cycle for brigatinib, crizotinib and alectinib, respectively.

B.3.4.6 Health-related quality of life data used in the cost-effectiveness analysis

The model includes the outputs from the HRQoL analysis – these inform the utility values for patients who are in the progression-free health state and those patients in the progressed disease health state who are receiving a subsequent line ALK inhibitor. However, HRQoL was only collected within the ALTA-1L trial until 30-days after the last dose. Therefore, there are limited data informing the progressive disease value. Therefore, multipliers were applied to account for the impact of CNS progression, chemotherapy and BSC in the progressive disease health state. The method of applying multipliers when incorporating utility values from multiple sources is in line with the NICE DSU TSD 12.[90] The alectinib NICE submission (TA536) took a similar approach i.e. used the literature to inform CNS progression, chemotherapy and BSC estimates.[55] Furthermore, the sources of utility inputs from the literature align with the sources we have used. However, they used an additive approach, whereas we have opted for a multiplicative approach in line with the NICE DSU TSD 12.

Roughley et al. (2014) evaluated the impact of brain metastases compared with other metastatic sites in terms of EQ-5D in patients with stage IV NSCLC.[46] They found that the utility value associated with brain metastases was 0.52 compared with 0.69 for contralateral lung metastases. Therefore, the multiplier of 75.36% (0.52/0.69) was applied to the progressive disease utility value to estimate the impact of brain metastases.

Blackhall et al. (2015) report the HRQoL outcomes from PROFILE 1007; the mean EQ-5D scores were 0.82 for crizotinib, 0.74 for pemetrexed and 0.66 for docetaxel.[42] The PROFILE 1007 study was in previously treated patients with ALK-positive advanced NSCLC. Therefore, a weighted utility multiplier was derived based on the assumption of 100% pemetrexed and 0% docetaxel (assumed in the base case and can be changed on the “Costs” sheet in the model). Therefore, the multiplier of 90.24% (0.74/0.82 x 100% + 0.66/0.82 x 0%) was applied to the progressive disease utility value to estimate the impact of chemotherapy. Note: the multiplier of CNS progression was applied in addition to the multiplier for chemotherapy to reflect the reduced HRQoL associated with CNS disease and chemotherapy treatment.

Nafees et al. (2008) conducted an elicitation exercise to determine utility values for different stages of NSCLC.[88] The progressive disease health state was associated with a utility value

of 0.473 compared with a responding health state utility value of 0.673. Feedback from clinical experts indicated that the value of 0.473 represented an era where progressive disease was associated with BSC. Therefore, a multiplier of 70.28% (0.473/0.673) was applied to the progression-free disease utility value to estimate the impact of BSC. Note: the multiplier of CNS progression was not applied in addition to the multiplier for BSC as the HRQoL at this stage in the pathway is expected to be similar between patients with and without CNS progression.

The economic model also includes a utility decrement associated with increasing age (-0.00026 each year), sourced from Ara and Brazier (2011).[100]

Table 40 presents the final utility values applied in the base case. Utility values applied post-progression are presented for each of the frontline treatment options (brigatinib, crizotinib and alectinib) – these may be different due to the different subsequent therapy assumptions (see Section B.3.6.2).

Table 40: Utility values applied in the base case

	Health states	Utility value	95% CI	Reference in submission/Source	Justification
Utility Values	***Pre-progression***	0.793	0.774-0.812	Section B.3.4.3, HRQoL analysis	Derived from the EORTC QLQ C30 completed by patients enrolled in the ALTA-1L clinical trial. In line with NICE Methods Guide recommendations.[89]
	Progressive disease	0.624	0.582-0.665		
	CNS Progressed				
	Brigatinib	0.543	0.528-0.558	Section B.3.4.3 and B.3.4.4, Calculation based on HRQoL analysis and multipliers from the literature. Lower and upper bounds based on the lower and upper bounds of the utility analysis. One way and probabilistic analysis varies both the utility analysis and the multipliers.	Limited follow-up beyond progression for patients enrolled in the ALTA-1L clinical trial. Therefore, incorporated utility multipliers derived from the literature. These were applied in line with recommendations in NICE DSU TSD 12.
	Crizotinib	0.532	0.511-0.552		
	Alectinib	0.539	0.523-0.554		
	Non-CNS Progressed				
	Brigatinib	0.552	0.536-0.567	Section B.3.4.3 and B.3.4.4, Calculation based on HRQoL analysis and multipliers from the literature. Lower and upper bounds based on the lower and upper bounds of the utility analysis. One way and probabilistic analysis varies both the utility analysis and the multipliers.	Limited follow-up beyond progression for patients enrolled in the ALTA-1L clinical trial. Therefore, incorporated utility multipliers derived from the literature. These were applied in line with recommendations in NICE DSU TSD 12.
	Crizotinib	0.566	0.542-0.590		
	Alectinib	0.550	0.533-0.566		
Utility multiplier	Chemotherapy multiplier	90.24%	88.49%-91.86%	Section B.3.4.4, Blackhall et al. (2014)	Limited follow-up beyond progression for patients enrolled in the ALTA-1L clinical trial. Therefore, incorporated utility multipliers derived from the literature.
	BSC multiplier	70.28%	68.96%-71.59%	Section B.3.4.4, Nafees et al. (2008)[88]	
	CNS multiplier	75.36%	73.94%-76.76%	Section B.3.4.4, Roughley et al. (2014)[46]	

	Health states	Utility value	95% CI	Reference in submission/Source	Justification
					These were applied in line with recommendations in NICE DSU TSD 12.
Utility decrements	≥1 Grade 3/4 AE	-0.037	-0.046--0.029	Section B.3.4.3 and B.3.5.5, HRQoL analysis	Derived from the EORTC QLQ C30 completed by patients enrolled in the ALTA-1L clinical trial. In line with NICE Methods Guide recommendations.
	Age	-0.0003	NA	Ara and Brazier (2011)[100]	Age decrement applied in line with the alectinib NICE submission.

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

Resource use and cost inputs are in line with the UK perspective. All costs represent the 2018/2019 cost year and have been obtained from the British National Formulary (BNF; accessed February 2020),[101] the electronic marketing information tool (eMIT; accessed February 2020),[102] the PSSRU (2019) and the NHS Reference Costs 2018/2019.[94]

B.3.5.1 Costs and resource use studies

A cost and resource use SLR was conducted to identify published cost and resource use data for ALK inhibitors in advanced or metastatic ALK-positive NSCLC. The original SLR was conducted in May 2018 – this was subsequently updated in May 2019. Nine publications were identified as reporting UK-specific costs and resources.

The economic model presented in this submission utilises resource use data presented as part of the alectinib NICE submission (TA536[55]), which was identified as part of this SLR. This was considered appropriate as alectinib is the main comparator to brigatinib and these resource use data are UK specific.

Appendix I provides the details associated with the SLR and the search strategy.

B.3.5.2 Intervention and comparators' costs and resource use

B.3.5.2.1 Treatment costs

The unit costs associated with treatment acquisition are shown in Table 41 at list price. The confidential with-PAS costs associated with brigatinib are also presented. A confidential discount of [redacted] off the list price has been accepted by NHS England and PASLU for consideration in this appraisal. The base case results use this proposed PAS discount for brigatinib and list prices for crizotinib and alectinib, both of which have confidential discounts applied in UK practice. However, as these discounts are confidential and unknown, they cannot be incorporated within our submission dossier. Discounts can easily be applied within the economic model for these treatments on the 'Model Controls' sheet.

The dose schedule of brigatinib is aligned with the ALTA-1L clinical trial and aligns with the Marketing Authorisation. The dose schedule of crizotinib aligns with both the ALTA-1L clinical trial and the Summary of Product Characteristics (SmPC).[3] The dose schedule of alectinib aligns with the ALEX clinical trial and the SmPC for alectinib.[66]

The model includes the option to account for patients who may not take the full course of doses due to dose interruption or reduction associated with AEs or non-compliance. The mean relative dose intensities are 85.51% (SD: 19.44) for brigatinib, 91.73% (SD: 13.68) for crizotinib and 95.6% for alectinib from ALTA-1L and ALEX, respectively.[39, 55] In the base case, it is assumed that half the costs associated with reduced dose intensity are saved by the UK healthcare system. This assumption is in line with the brigatinib post-crizotinib NICE submission.[103] Scenario analyses explore the impact of saving all costs and saving none of the costs.

Table 41: Unit costs associated with the technology in the economic model

	Brigatinib	Crizotinib	Alectinib
Unit dose	180mg once daily with 7-day lead-in at 90mg (one tablet, once daily)[3]	250mg twice daily (one capsule, twice-daily)[69]	600mg twice daily (four capsules, twice daily)[66]
Pack size	28 tablets (28-days)	60 capsules (30-days)	224 capsules (28-days)
Unit cost	£4,900 (180mg and starter pack) [redacted] (with PAS; 180mg and starter pack)	£4,689	£5,032
Cost per 28-days - half the costs of reduced dose intensity saved (base case)	Without current PAS £4,545 With current PAS [redacted]	£4,195	£4,921
Cost per 28-days – none of the costs of reduced dose intensity saved	Without current PAS £4,900 With current PAS [redacted]	£4,376	£5,032
Cost per 28-days – all the costs of reduced dose intensity saved	Without current PAS £4,190 With current PAS [redacted]	£4,014	£4,811
Treatment duration	Treat until progression		
Source	Takeda UK	BNF accessed February 2020	BNF accessed February 2020

B.3.5.2.2 Administration costs

Brigatinib, crizotinib and alectinib are oral therapies. Therefore, there is expected to only be a small cost of pharmacy dispensing time associated with each treatment. This was costed as 12-minutes of pharmacist time for every treatment cycle (£9.00 per treatment cycle).[94]

The model includes the option to remove the cost of treatment administration and this is explored in a scenario analysis.

B.3.5.3 Health-state unit costs and resource use

Resource use was defined by whether a patient was receiving frontline treatment (i.e. on-treatment), whether a patient had discontinued frontline treatment (i.e. off-treatment) and whether a patient had progressed in the brain. The base case assumes treat until progression for all frontline therapies. Therefore, the resource use assumptions are health state specific.

Resource use inputs were informed by the alectinib NICE submission (TA536[55]) and then validated at two later advisory boards (February 2019, January 2020 – see Section B.3.10).

B.3.5.3.1 On-treatment resource use and costs

Table 42 presents the resource use assumed for patients receiving frontline treatment. These estimates are applied irrespective of treatment arm. Table 43 presents the unit costs associated with each resource item. The total cost in the first cycle was £229. The total cost in subsequent cycles was £290.

The resource use applied for the on-treatment phase is the same as applied in the alectinib NICE submission. Clinical experts at two advisory boards confirmed that clinical practice has not changed and would not vary by choice of frontline treatment.

Table 42: Resource use associated with on-treatment

Category	Item	Frequency per month	% of patient requiring resource	Cost per month
(1) Adjustment opening cycle				
Physician visits	Oncology outpatient (f)	1.00	100%	£245
Tests and procedures	Full blood test	1.00	100%	£3
	Biochemistry	1.00	100%	£1
			Total cost per cycle:	£229
(2) On-going cycles				
Physician visits	Oncology outpatient (s)	0.75	100%	£111
	GP visit	1.00	10%	£4
	Cancer nurse	1.00	50%	£49
Tests and procedures	Full blood test	1.00	100%	£3
	Biochemistry	1.00	100%	£1
	CT scan	0.50	100%	£44
	MRI	0.20	50%	£22
	X-ray	0.30	50%	£5
	ECG	1.00	100%	£76
			Total cost per cycle:	£290

CT, computerised tomography; ECG, electro-cardiogram; GP, general practitioner; MRI, magnetic resonance imaging

Table 43: Unit costs associated with health state resource use

Resource	Unit cost	Source[94, 102]
Oncology outpatient (f)	£244.84	NHS Reference Costs (2018/19); CL. WF01B, 370, Medical Oncology Non-Admitted F2F Attendance, First.
Oncology outpatient (s)	£147.97	NHS Reference Costs (2019/19); CL, WF01C, 370, Medical Oncology Non-Admitted F2F Attendance, Follow up
GP visit	£39.00	PSSRU (2019); per surgery consultation lasting 9.22 minutes, including direct care staff costs with qualification costs
Cancer nurse	£98.74	NHS Reference Costs (2018/19); CHS, N10AF, specialist nursing, cancer related, adult face to face
Biochemistry	£1.10	NHS Reference Costs (2018/19); DAPS, DAPS04, Clinical Biochemistry

Resource	Unit cost	Source[94, 102]
Full blood test	£2.79	NHS Reference Costs (2018/19); DAPS, DAPS05, Haematology
CT scan	£88.81	NHS Reference Costs (2018/19); Total HRGs, Weighted average: RD20A, RD20b, RD20C, RD21A, RD21B, RD21C and RD22Z
X-ray	£30.59	NHS Reference Costs (2018/19); DADS, DAPF, Direct Access Plain Film
MRI	£217.49	NHS Reference Costs (2018/19); IMAGOP Outpatient RD03Z
ECG	£76.10	NHS Reference Costs (2018/19); IMAGOP Outpatient RD51A

CT, computerised tomography; ECG, electro-cardiogram; GP, general practitioner; MRI, magnetic resonance imaging; NHS, National Health Service

Concomitant medications were obtained from the ALTA-1L clinical trial for brigatinib and crizotinib, these were included if they were received by ≥10% of patients. A total of 21 clinically relevant medications were included in the model – see Appendix L.

Dosing information associated with each concomitant medication was obtained from the BNF. Costs were obtained from the eMIT where available. Where unavailable, costs were obtained from the BNF. Both accessed in February 2020. Three medications required weight-based dosing – the average of the mean weight in the brigatinib arm (68.37kg) and the crizotinib arm (68.58kg) was applied here. [101, 102]

Due to lack of comparator evidence the model assumes that the type and proportion of patients receiving concomitant medications whilst on treatment are the same for brigatinib and alectinib (i.e. concomitant medication use is assumed equal to brigatinib for alectinib). In the model, the cost of concomitant medications is only considered for patients on treatment.

The total cost per model cycle was minor at £85.67 for brigatinib and alectinib and £111.11 for crizotinib.

B.3.5.3.2 Off-treatment resource use and costs

Table 44 presents the resource use assumed for patients who have discontinued frontline therapy. These estimates are applied irrespective of treatment arm and irrespective of site of progression. Unit costs are as per the on-treatment phase. The total cost per cycle is £452.

The resource use applied for the off-treatment phase is the same as applied in the alectinib NICE submission. Clinical experts at two advisory boards confirmed that clinical practice has not changed and would not vary by choice of frontline treatment.

Table 44: Resource use associated with off-treatment

Category	Item	Frequency per month	% of patient requiring resource	Cost per month
Physician visits	Oncology outpatient (s)	1.25	100%	£185
	GP visit	1.00	50%	£20
	Cancer nurse	1.50	80%	£118
Tests and procedures	Full blood test	1.50	100%	£4
	Biochemistry	1.50	100%	£2
	CT scan	0.75	100%	£67

	MRI	0.50	80%	£87
	X-ray	0.50	60%	£9
			Total cost per cycle:	£452

CT, computerised tomography; ECG, electro-cardiogram; GP, general practitioner; MRI, magnetic resonance imaging

The model provides two options for modelling subsequent therapies: (1) includes only treatments currently recommended and used in UK clinical practice and (2) includes all treatments as per the clinical trial data. The model base case assumes option (1) in order to reflect accurately the UK base case. A scenario analysis explored option (2).

Table 45 presents the subsequent therapy distribution applied in the base case where option (1) is considered (i.e. subsequent therapies are costed based on what is recommended and used in UK clinical practice). The inputs for subsequent brigatinib and ceritinib use in the crizotinib arm have been informed by UK market share data (averages across sales from November 2019 – February 2020).[1] Inputs for other subsequent therapies in the crizotinib arm and subsequent therapies in the brigatinib and alectinib arms are informed by the assumptions underpinning the alectinib NICE submission (TA536)[55] and clinical expert judgement. These assumptions have been validated by clinical experts at an advisory board – see Section B.3.10. Note: the proportion of patients receiving subsequent therapies may not sum to 100% due to some patients not receiving active subsequent therapies (<100%) or due to some patients receiving multiple subsequent therapies (>100%).

Table 45: Subsequent therapy distribution applied in base case (Option (1) - as per UK practice)

Subsequent Anti-Cancer Treatment	Brigatinib	Crizotinib	Alectinib
ALK TKI	0%	0%	0%
Alectinib	0%	0%	0%
Brigatinib	0%	71%	0%
Ceritinib	0%	13%	0%
Crizotinib	0%	0%	0%
Lorlatinib	0%	0%	0%
Chemotherapy	50%	20%	50%
Immunotherapy	5%	5%	5%
VEGF-R	5%	5%	5%

ALK, anaplastic lymphoma kinase; TKI, tyrosine kinase inhibitor; VEGF-R, Vascular Endothelial Growth Factor

Table 7 in Section B.2.3.1 presents the subsequent therapies received following frontline treatment in ALTA-1L and ALEX. In the scenario analysis considering option 2 (i.e. including all subsequent treatments received in the clinical trials), the subsequent therapy inputs in the economic model simplify these distributions through the following assumptions:

1. Remove subsequent radiotherapy and surgery as these are captured in CNS management
2. Assume that "other ALK inhibitor" reported for the ALEX trial is lorlatinib
3. Assume other therapies are chemotherapy

Table 46 presents the subsequent therapy distribution applied when Option (2) is selected within the model (i.e. when subsequent therapies are modelled as per the clinical trial's data). At the end of the second data cut from the ALTA-1L trial, 54 patients in the brigatinib arm and 74 patients in the crizotinib arm had had a progression event (as defined by PFS BIRC).[72] Based on the ALEX trial, 41 patients in the alectinib arm had had an event.[40] Note: the subsequent therapy data for alectinib was obtained from the NICE submission and it is unclear which data cut this was from.

Note: when adjustment for treatment switching is applied (see Section B.3.3.5.2) the costs associated with brigatinib are removed from the crizotinib arm, because this scenario removes the effects of subsequent brigatinib on efficacy outcomes – this adjustment is automatically made through the clinical trial inputs. For costing purposes, it is assumed that these patients receive chemotherapy.

Table 46: Subsequent therapy distribution applied in scenario analysis (Option (2) - as per clinical trials)

Subsequent Anti-Cancer Treatment	Brigatinib	Crizotinib	Alectinib
ALK TKI	55.56%	125.68%	43.90%
Alectinib	18.52%	33.78%	0.00%
Brigatinib	1.85%	98.65%	0.00%
Ceritinib	7.41%	5.41%	9.76%
Crizotinib	20.37%	8.11%	21.95%
Lorlatinib	24.07%	14.86%	14.63%
Chemotherapy	24.07%	17.57%	95.12%
Immunotherapy	9.26%	6.76%	14.63%
VEGF-R	5.56%	5.41%	4.88%

ALK, anaplastic lymphoma kinase; TKI, tyrosine kinase inhibitor; VEGF-R, Vascular Endothelial Growth Factor

Table 47 presents the dose and cost information associated with each of the subsequent ALK inhibitors, immunotherapy (assumed atezolizumab) and VEGF-R (assumed nintedanib). Dosing schedules are based on the pivotal trials informing the efficacy in patients with previously treated ALK-positive advanced NSCLC. Note: all costs are applied based on list prices. The option is available within the model to add a simple discount to subsequent therapies on the 'Costs' sheet.

Table 47: Cost and dosing information for subsequent ALK inhibitors, immunotherapies and VEGF-Rs

Intervention	Dose	Cycle length (days)	Duration of therapy (weeks)	Pack size	mg	Cost per pack	Cost per cycle	Source
Alectinib	600mg twice daily	28	60.20	224	150	£5,032	£4,811	ALUR clinical trial[104] BNF accessed February 2020[101]
Brigatinib	180 mg once daily	28	83.49	28	180	£4,900 [redacted] (with current PAS)	£4,190 [redacted] (with current PAS)	ALTA clinical trial[39] Takeda UK
Ceritinib	750 mg once daily	28	41.89	150	150	£4,923	£4,103	ASCEND-5 clinical trial[105] BNF accessed February 2020[101]
Crizotinib	250mg twice daily	28	48.14	60	250	£4,689	£4,014	PROFILE-1005 clinical trial[106] BNF accessed February 2020[101]
Lorlatinib	100mg once daily	28	45.66	30	100	£5,283	£4,931	Study 1001[107] and NICE Committee papers[108] BNF accessed February 2020[101]
Atezolizumab	1,200mg every 3-weeks	21	33.83	20	60	£3,808	£3,808	OAK trial[109] and NICE Committee papers[110] BNF accessed February 2020[101]
Nintedanib	200mg twice daily	21	14.78	120	100	£2,151	£1,506	LUME Lung-1 clinical trial and NICE Committee papers BNF accessed February 2020[101]

ALK, anaplastic lymphoma kinase; BNF, British National Formulary; mg, milligram; PAS, patient access scheme; VEGF-R, Vascular Endothelial Growth Factor

For the chemotherapy regimen, patients are assumed to receive pemetrexed 500mg/m2 + cisplatin 75mg/m2 every 3-weeks for a maximum of four cycles followed by pemetrexed maintenance 500mg/m2 every 3-weeks – this is in line with UK clinical expert feedback. Table 48 presents the costs applied for chemotherapy.

Table 48: Chemotherapy costs

Drug	Pemetrexed powder for solution in vial	Pemetrexed powder for solution in vial	Cisplatin solution for infusion in vial
Dose (mg)/cycle	885	885	132.75
Days in cycle	21	21	21
mg/capsule/vial	100	500	50
Units	1	1	1
Tablets/vials/cycle	9	2	3
Cost/pack	£160	£800	£5
Cost per tablet/vial	£160	£800	£5
Cost/chemo cycle (21-days)	£1,440	£1,600	£15.57
Cost/model cycle (28-days)	£1,080	£1,200	£11.68
Reference	ASCEND-4[64]; BNF accessed February 2020[101]	ASCEND-4;[64] BNF accessed February 2020[101]	ASCEND-4;[64] eMIT accessed February 2020[111]

BNF, British National Formulary; eMIT, electronic marketing information tool; mg, milligram

The model assumes that all patients receive BSC following exhaustion of active therapies – in line with clinical feedback and the alectinib NICE submission TA536).[55] Table 49 provides the cost breakdown associated with BSC – the resource use is derived from the NICE submission for brigatinib in the post-crizotinib setting (TA571)[2] and was validated with clinical experts as part of this appraisal. The resultant per cycle cost of BSC is £471.

Table 49: Cost breakdown of BSC

Category	Dose	Unit cost (£)	Per cycle cost	Source
Radiotherapy	-	£142.58	£35.65	NHS Reference Costs (2018/19); Total Outpatient Attendances, 800, Clinical Oncology (previously radiotherapy)
Steroids (dexamethasone)	0.5mg daily	£2.53	£17.21	Drugs and pharmaceutical electronic market information tool (eMIT) 2020; 0.5mg tablets, 30 pack, pack cost £2.53; https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit
NSAIDs (aspirin)	75mg daily	£0.30	£0.08	Drugs and pharmaceutical electronic market information tool (eMIT) 2020; 75mg tablets, 100 pack, pack cost £0.30; https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit
Morphine	40-60mg daily (average 50mg)	£26.56	£13.28	Drugs and pharmaceutical electronic market information tool (eMIT) 2020; Morphine 50mg tablets / Packsize 56 cost £26.56; https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit
Bisphosphonate (alendronic acid)	10mg daily	£0.90	£0.90	Drugs and pharmaceutical electronic market information tool (eMIT) 2020; Alendronic acid 10mg tablets/Packsize 28, pack cost £0.90; https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit
Denosumab	120mg every 4 weeks	£183.00	£366.00	BNF Accessed February 2020; Prolia 60mg/ml solution for injection pre-filled syringes, 1 pre-filed disposable injection £183.00; https://www.medicinescomplete.com/#/content/bnf/_442118148?hspl=denosumab
Dietitian	-	£89.90	£37.76	NHS Reference Costs (2018/19); CHS, AHP, A03, Dietitian

BNF, British National Formulary; BSC, best supportive care; NHS, National Health Service

Table 50 presents the per-cycle costs related to subsequent ALK inhibitors, immunotherapies, VEGF-Rs, chemotherapies and BSC for each of the frontline treatment regimens. Based on the base case assumptions the per-cycle costs are £628 for brigatinib, £1,474 without brigatinib (second line) PAS applied, [redacted] with the brigatinib PAS applied for crizotinib and £681 for alectinib.

Table 50: Subsequent therapy per-cycle costs

Subsequent therapy	1st line treatment		
	Brigatinib	Crizotinib	Alectinib
Subsequent ALK including administration	£0	£1,045 (no PAS) [redacted] (with current PAS)	£0
Subsequent immunotherapy including administration	£32	£25	£42
Subsequent VEGF-R including administration	£5	£4	£7
Subsequent chemotherapy including administration	£154	£49	£205
Subsequent BSC	£438	£350	£427
Total	£628	£1,474 (no PAS) [redacted] (with current PAS)	£681

ALK, anaplastic lymphoma kinase; BSC, best supportive care; VEGF-R, Vascular Endothelial Growth Factor

Subsequent ALK inhibitors (i.e. brigatinib, crizotinib, alectinib, ceritinib and lorlatinib) and subsequent VEGF-R (i.e. nintedanib) are oral therapies. Therefore, the administration costs are as per the frontline therapies – 12-minutes of pharmacist time (£9.00 per treatment cycle).[94] Subsequent immunotherapies (i.e. atezolizumab) and chemotherapies incur the cost associated with more complex parenteral chemotherapy - £306.90 per treatment cycle.[102]

B.3.5.3.3 Intracranial progression resource use and costs

Additional resource use is applied for patients in the CNS progression health state to reflect the resource intensive nature of this site of progression. The management of brain metastases was discussed in depth in the alectinib NICE submission – the final distribution of therapy included: steroids (100%), stereotactic radiotherapy (SRS; 20-25%), whole brain radiotherapy (WBRT; 25%) and surgical resection (5%).

These values were presented to clinicians at the advisory board in January 2020. Clinicians indicated that the management of brain metastases is evolving in clinical practice, with a movement away from WBRT and towards SRS. It was also commented that there is a middle ground between WBRT and SRS (i.e. partial brain radiotherapy which may be used). Clinicians stated the following values were now more reflective of current UK clinical practice: steroids (10%), SRS (50%), WBRT (5%) and surgical resection (5%). Therefore, in the base case these values are used to best reflect current UK practice, while a scenario analysis explores the distribution presented in the alectinib NICE submission (TA536).

Table 51 presents the additional resource use and associated unit costs for CNS management. It is assumed that there is a lifetime exposure limit for SRS and WBRT of six sessions – in line with clinical feedback and the alectinib NICE submission. The total cost of six sessions of SRS, WBRT and surgical resection are applied as a one-off cost for patients

entering the CNS-progression health state. The cost of steroids is applied per cycle. This results in a one-off cost of £11,979 and a per cycle cost of £1.84.

Table 51: Additional resource use for CNS management

Category	Proportion of patients*	Lifetime exposure limit (dose)	Unit cost	Source
SRS	50%	6.00	£3,692	NHS Reference Costs 2018/19 Total HRGs; Stereotactic Intracranial Radiosurgery, for Neoplasms or Other Neurological Conditions, with CC Score 4+; https://www.england.nhs.uk/wp-content/uploads/2018/07/Stereotactic-ablative-body-radiotherapy-for-non-small-cell-lung-cancer-adults.pdf[102]
WBRT	5%	6.00	£972	NHS Reference Costs 2018/19 RAD; OP SC46Z Preparation for Complex Conformal Radiotherapy, with Technical Support and OP SC23Z Deliver a Fraction of Complex Treatment on a Megavoltage Machine[102]
Surgical resection	5%	NA	£12,219	NHS Reference Costs 2018/19 EL; AA82Z Intracranial Telemetry, with Cortical Mapping or Resection of Brain[102]
Steroids (dexamethasone)	10%	NA	£16.46	https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit[111]

CNS, central nervous system; NHS, National Health Service; SRS, stereotactic radiotherapy; WBRT, whole brain radiotherapy; *Proportions reflect feedback received by Takeda from UK clinical experts at an advisory board held in January 2020

B.3.6.4 Adverse reaction unit costs and resource use

Section B.3.38 describes how AEs were included in the economic model. Table 52 presents the costs applied to each AE - these were costed using the NHS Reference Costs 2018/2019.

The costs associated with laboratory abnormalities were assumed to include the cost of two medical oncology outpatient visits and two blood tests – in line with the alectinib NICE submission,[55] the brigatinib post-crizotinib NICE submission[2] and UK clinical expert feedback (see Section B.3.10). Note: this resource use represents the maximum required to manage these laboratory abnormalities, some patients may accrue far fewer costs.

The unit costs are multiplied by the rate of each AE to give the per cycle cost for each frontline treatment - £10.08 for brigatinib, £18.03 for crizotinib and £4.15 for alectinib.

Table 52: Adverse event costs

Adverse Events	Unit cost of AEs	Treatment resource use	*Sources*
Blood creatinine phosphokinase increased	£380	2 additional blood tests 2 outpatient visits	*TA500; NHS Reference Costs 2018/19; Outpatient Attendances, 370: Medical Oncology*

Adverse Events	Unit cost of AEs	Treatment resource use	*Sources*
Amylase increased	£380	2 additional blood tests 2 outpatient visits	*Assumed captured in additional blood tests and appts captured under blood creatinine phosphokinase increased*
Nausea	£1,108	Non-malignant gastrointestinal tract disorders without interventions	*NHS Reference Costs 2018/19; Total HRGs, Non-malignant gastrointestinal tract disorders without interventions with CC score 0-2, 3-4, 5-7 and 8+*
Hypertension	£599	Hypertension	*NHS Reference Costs 2018/19; Total HRGs, Hypertension, EB04Z.*
Increased AST	£380	2 additional blood tests 2 outpatient visits	*Assumed captured in additional blood tests and appts captured under blood creatinine phosphokinase increased*
Increased ALT	£380	2 additional blood tests 2 outpatient visits	*Assumed captured in additional blood tests and appts captured under blood creatinine phosphokinase increased*
Increased lipase level†	£380	2 additional blood tests 2 outpatient visits	*Assumed captured in additional blood tests and appts captured under blood creatinine phosphokinase increased*
Neutropenia	£363	As per alectinib NICE submission	*Alectinib NICE submission*
Anaemia	£657	Iron deficiency anaemia	*NHS Reference Costs 2018/19; Total HRGs, Iron deficiency anaemia with CC score 0-1, 2-5, 6-9, 10-13 and 14+*
Diarrhoea	£1,108	Non-malignant gastrointestinal tract disorders without interventions	*NHS Reference Costs 2018/19; Total HRGs, Non-malignant gastrointestinal tract disorders without interventions with CC score 0-2, 3-4, 5-7 and 8+*
Vomiting	£1,108	Non-malignant gastrointestinal tract disorders without interventions	*NHS Reference Costs 2018/19; Total HRGs, Non-malignant gastrointestinal tract disorders without interventions with CC score 0-2, 3-4, 5-7 and 8+*
Gamma-glutamyl transferase increased	£380	2 additional blood tests 2 outpatient visits	*Assumed captured in additional blood tests and appts captured under blood creatinine phosphokinase increased*
Fatigue	£0	Assumption	*Assumption*

Adverse Events	Unit cost of AEs	Treatment resource use	*Sources*
Pneumonia	£1,611	Lobar, Atypical or Viral Pneumonia, without Interventions	*NHS Reference Costs 208/19; Total HRGs, Lobar, atypical or viral pneumonia without interventions with CC score 0-3-, 4-6, 7-9, 10-13 and 14+*
Urinary tract infection	£1,454	Kidney or Urinary Tract Infections, without interventions	*NHS Reference Costs 2018/19; Total HRGs, Kidney or Urinary Tract Infections, without interventions, with CC score 0-1, 2-3, 4-7, 8-12 and 13+*
Acute kidney injury	£1,454	Kidney or Urinary Tract Infections, without interventions	*NHS Reference Costs 2018/19; Total HRGs, Kidney or Urinary Tract Infections, without interventions, with CC score 0-1, 2-3, 4-7, 8-12 and 13+*
Weight decreased	£0	Assumption	*Assumption*
Asthenia	£464	Assumption	*NHS Reference Costs 2018/19; Total HRGs, Rehabilitation for other neurological disorders*

ALT, alanine aminotransferase; AST, aspartate aminotransferase; NHS, National Health Service

B.3.6.5 Miscellaneous unit costs and resource use

The cost of end-of-life care is applied to all patients who enter the death health state as a one-off cost. This is not strictly incurred in the death state, but upon entry into the death state.

The PSSRU (2019) provides the total cost per deceased person in the last 12 months of life which is calculated as the total cost of the service divided by the number of people who died.[94] This is estimated based on costs associated with hospital care, inpatient emergency, inpatient non-emergency, outpatient, A&R, residential and nursing care, home care and other. The model provides the option to apply a lump sum cost based on 4, 8 or 12 weeks of end of life care. In the base case, 8 weeks is applied resulting in a lump sum cost of £1,772.

B.3.6.6 Costs summary

Table 53 summarises all the costs applied within the model either as a per cycle cost or as a lump sum.

Table 53: Costs summary

	Brigatinib	Crizotinib	Alectinib
Acquisition per cycle (half the costs associated with reduced dose intensity are saved)	Without proposed PAS: £4,545 With proposed PAS: [redacted]	£4,195	£4,921
Administration per cycle	£9		
Concomitant medications per cycle	£85.67	£111.11	£85.67
On-treatment resource use per cycle	First cycle = £229. Subsequent cycles = £290.		
Off-treatment resource use per cycle	£452		
CNS management lump sum	One-off cost = £11,979. Per cycle cost = £1.84		
Subsequent therapies per cycle	£628	Without current PAS: £1,474 With current PAS [redacted]	£681
Adverse events per cycle	£10.08	£18.03	£4.15
End of life lump sum cost	£1,772		

CNS, central nervous system ; PAS, patient access scheme

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

B.3.6.1 Summary of base-case analysis inputs

In line with the NICE reference case, the model considers a UK treatment provider's perspective and discounts costs and QALYs using a 3.5% discount rate. Results are presented over a lifetime horizon (30 years).

The data from the ALTA-1L clinical trial informs the clinical inputs for brigatinib vs. crizotinib. Data from ALEX informs the clinical inputs for alectinib and are used in ITCs to estimate relative efficacy of brigatinib vs. alectinib. Section B.3.3 describes the clinical parameters in more detail.

HRQoL inputs are informed by the ALTA-1L clinical trial and the literature. The literature sources are the same as those applied in the alectinib NICE submission. External utility values have been incorporated within the model through multiplicative methods as per NICE DSU TSD 12.[90] Section B.3.4 describes the HRQoL parameters in more detail.

Resource use inputs mostly align with the alectinib NICE submission (TA536) with the exception of concomitant medications, CNS management and AEs. Concomitant medications and AEs are informed by the data from the ALTA-1L clinical trial. CNS management resource use has been updated from the inputs in the alectinib NICE submission to reflect the evolving clinical practice – based on clinical expert judgement. All costs are sourced from UK specific sources. Section B.3.5 describes the costs and resource use parameters in more detail.

Where possible, the model structure and inputs align with the alectinib NICE submission (TA536) as this is the main comparator to brigatinib and also the most recent NICE appraisal

in the frontline ALK-positive NSCLC setting. All inputs and assumptions have been further validated as part of this appraisal at two advisory boards, which are detailed in Section B.3.10.

Appendix L provides a summary of variables applied in the economic model and references to the Section in the submission where it is explained in more detail.

B.3.6.2 Assumptions

Table 54 details the key assumptions used in the base case of the economic model and provides a justification for each one. A column is presented showing the scenario analyses associated with each assumption.

Table 54: Base case assumptions

Base case assumption	Justification	Scenario analysis	Reference in submission
Exponential distribution assumed for PFS outcomes	The exponential curve is selected in the base case for both brigatinib and crizotinib. This is supported by the AIC/BIC statistics, aligns with the parametric curves from which a final decision was made in the alectinib NICE submission and aligned with expert judgement from an advisory board (see Section B.3.10).	Weibull, Gompertz, log-logistic, log-normal, gamma and generalised gamma explored	Section B.3.3.3
Exponential distribution assumed for OS outcomes	The exponential curve is selected in the base case for both brigatinib and crizotinib. This is supported by the AIC/BIC statistics, aligns with the parametric curves from which a final decision was made in the alectinib NICE submission and aligned with expert judgement from an advisory board (see Section B.3.10).	Weibull, Gompertz, log-logistic, log-normal, gamma and generalised gamma explored	Section B.3.3.5
Exponential distribution assumed for intracranial PFS outcomes	The exponential curve is selected in the base case for both brigatinib and crizotinib. This is supported by the AIC/BIC statistics, aligns with the parametric curves from which a final decision was made in the alectinib NICE submission and aligned with expert judgement from an advisory board (see Section B.3.10).	Weibull, Gompertz, log-logistic, log-normal, gamma and generalised gamma explored	Section B.3.3.4
No treatment switching adjustment	Treatment switching adjustments were not considered in the base case to reflect UK clinical practice – patients often receive brigatinib following frontline crizotinib treatment in the UK	Treatment switching adjustments based on official switchers and no re-censoring, official switchers and re-censoring, all switchers and no re-censoring and all switchers and re-censoring.	Section B.3.3.5.2

Base case assumption	Justification	Scenario analysis	Reference in submission
Intracranial PFS estimated as per the standard RECIST	The modified RECIST criteria are not followed in routine clinical practice. Therefore, there are progression events captured in intracranial PFS which would not be identified in clinical practice nor in the PFS BIRC outcome from the ALTA-1L trial. Therefore, to ensure consistency the intracranial PFS variable is aligned with the standard RECIST and with PFS BIRC.	No adjustment and PFS BIRC adjusted to match intracranial PFS i.e. based on the modified RECIST criteria	Section B.3.3
Treat until progression for all frontline therapies	This is supported by the data from the ALTA-1L clinical trial and is the same method applied in the alectinib NICE submission.	Treat 1-, 2- and 3-cycles beyond progression	Section B.3.3.6
Unanchored MAIC for PFS BIRC and OS HRs of brigatinib vs. alectinib using the ITT population from the ALTA-1L trial	As discussed at the decision problem meeting, Takeda consider there to be limitations associated with all the ITC analyses. These limitations are driven by the differences between the ALTA-1L clinical trial and the ALEX trial; these are differences which cannot be totally adjusted for. We have conducted numerous analyses attempting to adjust for the different biases and we consider the evidence to highlight that brigatinib and alectinib are extremely similar. Therefore, whilst a cost-effectiveness analysis is presented alongside the brigatinib vs. crizotinib results, we consider that the cost-comparison results should be considered as the main analysis for brigatinib vs. alectinib.	Cost-comparison Unweighted Bucher, anchored MAIC (with and without treatment switching adjustments) Using ITT or treatment naïve (i.e. no prior chemotherapy) subgroup data from the ALTA-1L trial in the ITCs. Using PFS INV data rather than PFS BIRC.	Section B.3.3.7
Utility for progression-free and progressed receiving subsequent ALK inhibitor based on the ALTA-1L clinical trial	As per the NICE Methods Guide.	NA	Section B.3.4
Administration costs of oral therapies included	As per the alectinib NICE submission[55] and the brigatinib post-crizotinib NICE submission.[2]	No administration costs applied for oral therapies.	Section B.3.5.2.2
Half the costs associated with reduced dose intensity saved	As per the brigatinib post-crizotinib NICE submission.[2]	All costs saved. None of the costs saved.	Section B.3.6.2.1
Subsequent therapy informed by real-world market share data for crizotinib and based on real-world estimates for brigatinib and alectinib	To align the model with UK clinical practice. This is also aligned with the alectinib NICE submission.	Subsequent therapy distribution based on clinical trial data. Note: this is incomplete for alectinib and so this scenario should be	Section B.3.6

Base case assumption	Justification	Scenario analysis	Reference in submission
		interpreted with caution.	

BIRC, blinded independent review committee; CNS, central nervous system; INV, investigator assessed; ITC, indirect treatment comparison; NICE, National Institute for Health and Care Excellence; OS, overall survival; PFS, progression-free survival

B.3.7 Base-case results

3.7.1 Base-case incremental cost-effectiveness analysis results

The base case cost-effectiveness results for brigatinib vs. crizotinib and vs. alectinib are shown in Table 55. The incremental analysis of all three interventions is presented in Table 56. The cost-comparison of brigatinib vs. alectinib is presented in Table 57. All results are presented using the list prices for crizotinib and alectinib and the proposed PAS discount for frontline brigatinib ([redacted]); the current PAS discount is applied for subsequent use of brigatinib in the crizotinib arm ([redacted])).

For brigatinib vs. crizotinib, brigatinib is associated with a gain of 0.26 life years and [redacted]) QALYs per patient, with a decrease in costs of [redacted] per patient. This results in brigatinib dominating crizotinib. Note: the total QALY gain attributed to the crizotinib arm is much higher than observed in the alectinib NICE submission (TA536) due to the high rate of treatment switching from crizotinib to brigatinib that occurred in the ALTA-1L trial but not in the ALEX trial ([redacted])vs. 2.84, respectively). Hence, the crizotinib arm in ALTA-1L represents a sequence of treatments (i.e. crizotinib followed by brigatinib). By contrast, the crizotinib arm in the alectinib NICE submission isolated the frontline therapy as no treatment switching was officially permitted in the ALEX trial protocol (a very small number of patients did switch unofficially). Conversely, the total QALYs accrued in the brigatinib arm are similar to those accrued in the alectinib arm of the alectinib NICE submission ([redacted])vs. 3.79, respectively).

For brigatinib vs. alectinib, brigatinib is associated with a gain of 0.80 life years and [redacted]) QALYs per patient. However, as discussed in Section B.2.9 and B.3.3.7, the choice of ITC method can quickly change these results. As discussed at the decision problem meeting, Takeda consider there to be limitations associated with all the ITC analyses – particularly for OS. These limitations are driven by the differences between the ALTA-1L clinical trial and the ALEX trial, differences in design and conduct of the trials which cannot be totally adjusted for. We have conducted numerous analyses attempting to adjust for the different biases and we consider the evidence to highlight that brigatinib and alectinib are extremely similar. Therefore, whilst a cost-effectiveness analysis is presented alongside the brigatinib vs. crizotinib results, we consider that the cost-comparison results should be considered as the main analysis for brigatinib vs. alectinib. The cost-comparison analysis assumes OS, PFS and intracranial PFS outcomes are identical between brigatinib and alectinib. These results indicate that brigatinib is cost saving compared with alectinib – saves £104,579 per patient based on the proposed PAS for brigatinib and the list price for alectinib.

Appendix J presents the clinical outcomes and disaggregated life years, QALYs and costs.

Table 55: Base case results

Intervention	Total costs	Total Life Years	Total QALYs	Inc. costs	Inc. Life Years	Inc. QALYs	ICER
Brigatinib	[redacted]	5.868	[redacted]	N/A	N/A	N/A	N/A
Crizotinib	[redacted]	5.610	[redacted]	[redacted]	0.26	[redacted]	Brigatinib is dominant
Alectinib	[redacted]	5.072	[redacted]	[redacted]	0.80	[redacted]	Brigatinib is dominant

ICER, incremental cost-effectivness ratio; Inc, incremental; QALYs, quality-adjusted life years

Table 56: Incremental analysis

Intervention	Total Costs	Total Life Years	Total QALYs	Inc. Costs	Inc. Life Years	Inc. QALYs	ICER
Brigatinib	[redacted]	5.868	[redacted]	[redacted]	0.796	[redacted]	-£201,195
Alectinib	[redacted]	5.072	[redacted]	[redacted]	-0.538	[redacted]	£4,487,716
Crizotinib	[redacted]	5.610	[redacted]	N/A	N/A	N/A	N/A

ICER, incremental cost-effectivness ratio; Inc, incremental; QALYs, quality-adjusted life years

Table 57: Cost-comparison results for brigatinib vs. alectinib

Intervention	Total Costs	Inc. Costs
Brigatinib	[redacted]	N/A
Alectinib	[redacted]	-£104,579

Inc, incremental

B.3.8 Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

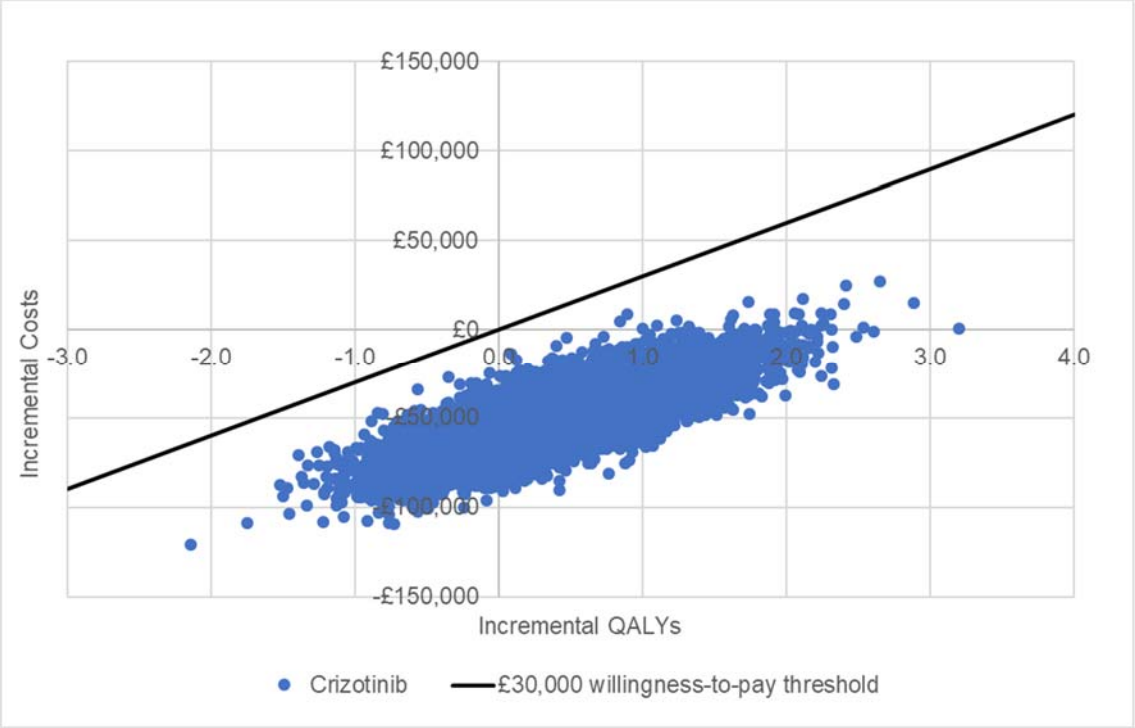
To characterise uncertainty in model inputs a PSA was performed. A PSA varies all inputs simultaneously, based upon their distributional information (see Appendix L1.2) and records a resulting ICER which may conceivably be the "true" underlying ICER.

The results of 10,000 PSA iterations are presented in Figure 50 for brigatinib vs. crizotinib and in Figure 51 for brigatinib vs. alectinib, depicted as a cost-effectiveness scatter plot. All iterations for both comparisons fall under the £30,000 willingness-to-pay threshold shown on the graph. Mean probabilistic incremental QALYs gained from brigatinib were [redacted] (SD: [redacted]) and [redacted] (SD: [redacted]) vs. crizotinib and vs. alectinib, respectively. Mean probabilistic incremental costs were [redacted] (SD: [redacted]) and [redacted] (SD: [redacted]), respectively. These results indicate that brigatinib remained dominant in the PSA, aligning with the results of the deterministic analysis.

Figure 52 presents the cost-effectiveness acceptability curve (CEAC) including all three treatments. As expected, given that the proposed PAS discount has been applied to brigatinib and list prices were used for alectinib and crizotinib, brigatinib has 100% chance of being cost-effective at a willingness-to-pay thresholds of £30,000/QALY.

As stated in Section B.3.7.1, we consider that a cost-comparison analysis provides a more suitable approach for comparing brigatinib with alectinib. Therefore, the PSA has been conducted within this framework. Probabilistic differences in costs (-£104,904) align with those in the deterministic base case (-£104,579).

Figure 50: Cost-effectiveness plane from 10,000 iterations, brigatinib vs. crizotinib

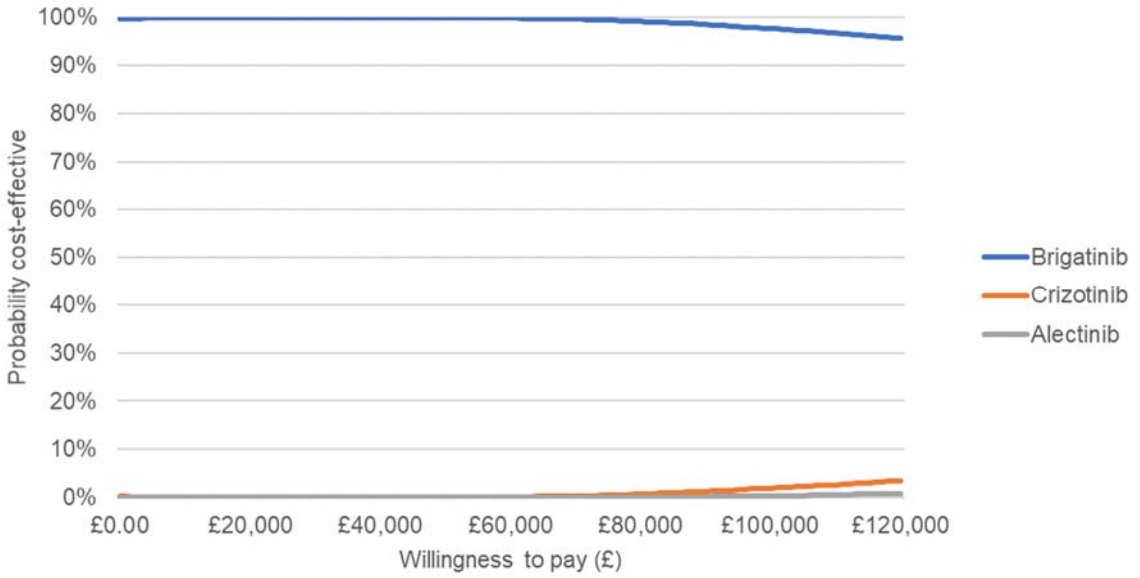


QALYs, quality adjusted life years

Figure 51: Cost-effectiveness plane from 10,000 iterations, brigatinib vs. alectinib

QALYs, quality adjusted life years

Figure 52: CEAC curve



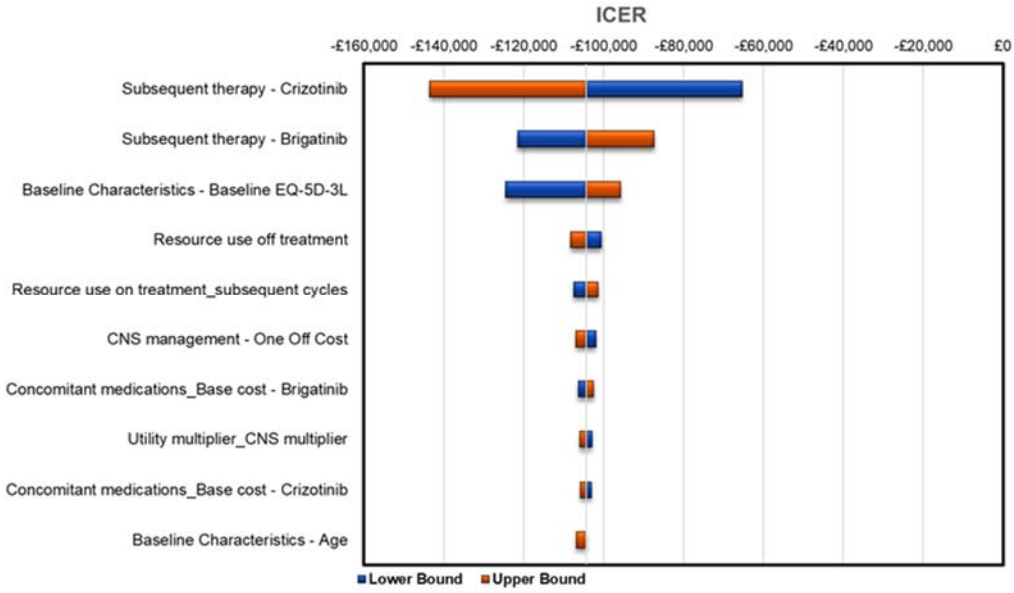
CEAC, cost-effectiveness acceptability curve

B.3.8.2 Deterministic sensitivity analysis

One-way sensitivity analyses were performed to evaluate the sensitivity of the model ICER to individual inputs, holding all else constant. Distributional information associated with each parameter is presented in Appendix L1.2. Model results were recorded after changing each input to its upper and lower bound value in turn.

Figure 53 presents a Tornado diagram, with the ten most influential parameters shown in descending order of ICER sensitivity for the brigatinib vs. crizotinib comparison. Table 58 displays this information in a tabular format. Figure 54 and Table 66 provide outcomes based on an NMB outcome, using a willingness-to-pay threshold of £30,000/QALY. The biggest driver of results are the costs of subsequent therapy in the brigatinib and crizotinib treatment arms – this is to be expected, particularly for crizotinib, as the subsequent treatment pathway consists of brigatinib and other ALK inhibitor(s). Brigatinib remains dominant in all scenarios.

Figure 53: Tornado diagram, brigatinib vs. crizotinib (ICER)



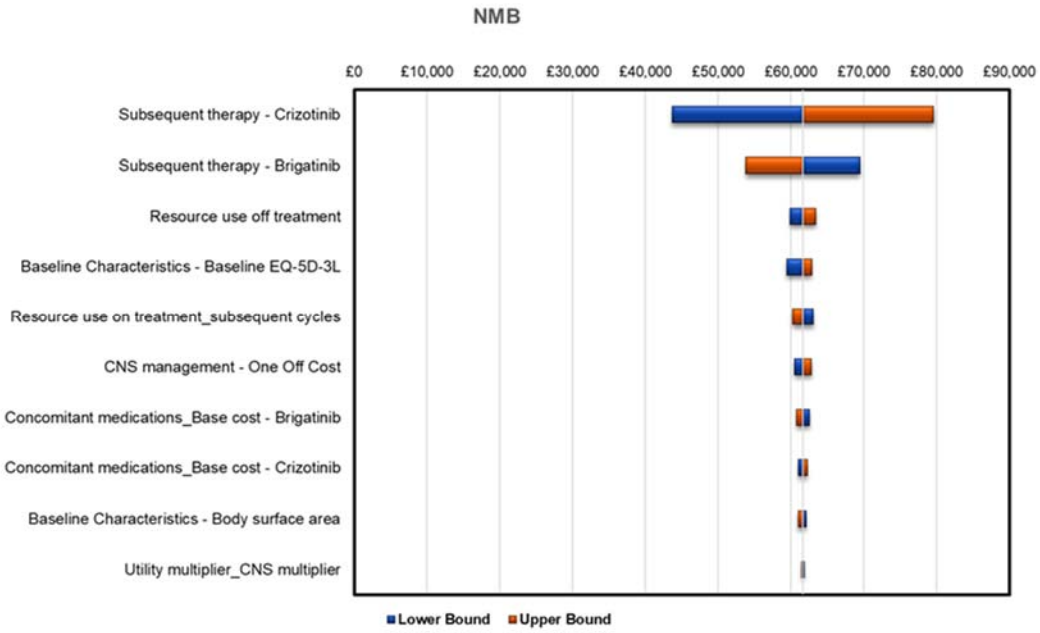
CNS, central nervous system; ICER, incremental cost-effectiveness ratio

Table 58: Numerical results of the one-way sensitivity analysis, brigatinib vs. crizotinib (ICER)

Rank	Parameter	Lower Bound	Upper Bound	Difference
1	Subsequent therapy - Crizotinib	-£65,216	-£143,548	£78,331
2	Subsequent therapy - Brigatinib	-£121,501	-£87,263	£34,239
3	Baseline Characteristics - Baseline EQ-5D-3L	-£124,529	-£95,670	£28,858
4	Resource use off treatment	-£100,505	-£108,259	£7,754
5	Resource use on treatment_subsequent cycles	-£107,500	-£101,265	£6,235
6	CNS management - One Off Cost	-£101,830	-£106,934	£5,104
7	Concomitant medications_Base cost – Brigatinib	-£106,361	-£102,403	£3,958
8	Utility multiplier_CNS multiplier	-£102,867	-£105,913	£3,046
9	Concomitant medications_Base cost – Crizotinib	-£103,011	-£105,753	£2,743
10	Baseline Characteristics - Age	-£104,209	-£106,870	£2,661

CNS, central nervous system; ICER, incremental cost-effectiveness ratio

Figure 54: Tornado diagram, brigatinib vs. crizotinib (NMB)



CNS, central nervous system; NMB, net monetary benefit

Table 59: Numerical results of the one-way sensitivity analysis, brigatinib vs. crizotinib (NMB)

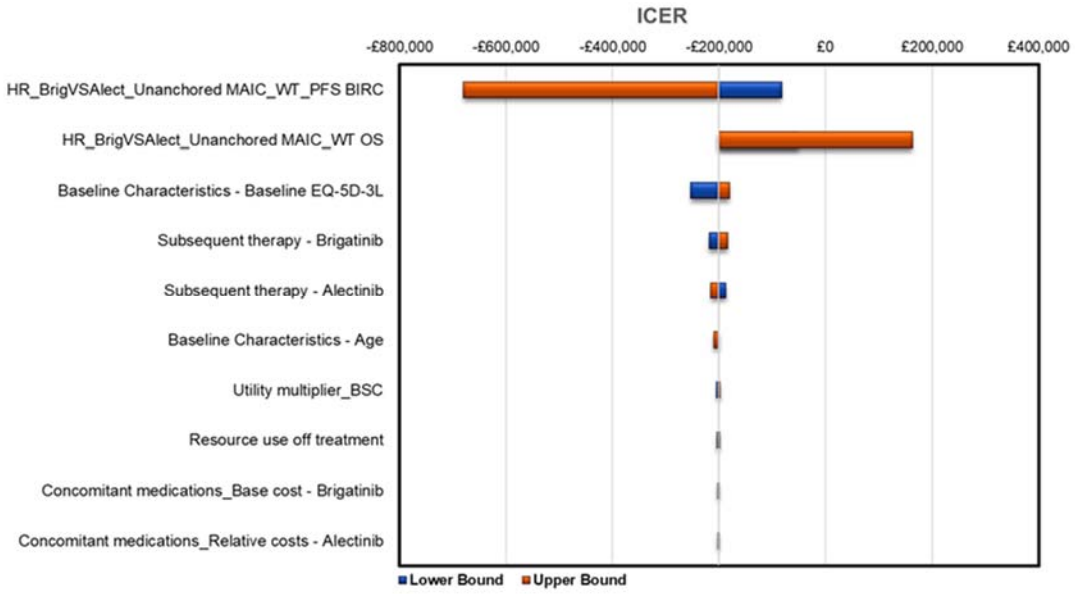
Rank	Parameter	Lower Bound	Upper Bound	Difference
1	Subsequent therapy – Crizotinib	£43,673	£79,602	£35,928
2	Subsequent therapy – Brigatinib	£69,490	£53,785	£15,704
3	Resource use off treatment	£59,859	£63,416	£3,557
4	Baseline Characteristics - Baseline EQ-5D-3L	£59,411	£62,890	£3,479
5	Resource use on treatment_subsequent cycles	£63,067	£60,208	£2,860
6	CNS management - One Off Cost	£60,467	£62,808	£2,341
7	Concomitant medications_Base cost – Brigatinib	£62,545	£60,730	£1,815
8	Concomitant medications_Base cost – Crizotinib	£61,008	£62,266	£1,258
9	Baseline Characteristics - Body surface area	£62,080	£60,976	£1,104
10	Utility multiplier_CNS multiplier	£61,840	£61,439	£402

CNS, central nervous system; NMB, net monetary benefit

Figure 55 presents a Tornado diagram with the ten most influential parameters shown in descending order of ICER sensitivity for the brigatinib vs. alectinib comparison. Table 60 displays this information in a tabular format. Figure 56 and Table 61 provide outcomes based on an NMB outcome, using a willingness-to-pay threshold of £30,000/QALY. The biggest

drivers of results for brigatinib vs. alectinib are the relative efficacy estimates associated with PFS BIRC and OS. The model includes a number of options in terms of methods used to calculate these estimates which are explored in Section B.3.8.1. It should be noted that no one scenario is preferred, and we consider that the overall data are supportive of equivalence between brigatinib and alectinib. Therefore, OWSA has been conducted within a cost-comparison framework (Figure 57 and Table 62). These results align with the brigatinib vs. crizotinib comparison, in that the cost of subsequent therapies in the brigatinib and alectinib arms are the key drivers of results.

Figure 55: Tornado diagram, brigatinib vs. alectinib (ICER)



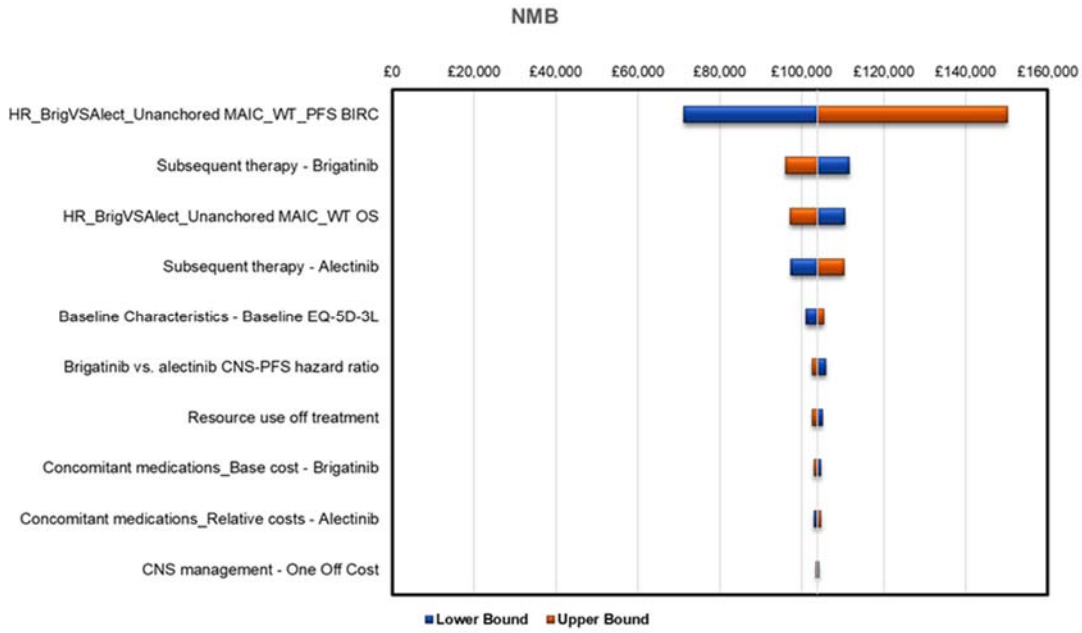
CNS, central nervous system; ICER, incremental cost-effectiveness ratio

Table 60: Numerical results of the one-way sensitivity analysis, brigatinib vs. alectinib (ICER)

Rank	Parameter	Lower Bound	Upper Bound	Difference
1	HR_BrigVSAlect_Unanchored MAIC_WT_PFS BIRC	-£82,347	-£679,843	£597,496
2	HR_BrigVSAlect_Unanchored MAIC_WT OS	-£51,246	£163,489	£214,735
3	Baseline Characteristics - Baseline EQ-5D-3L	-£253,548	-£180,247	£73,301
4	Subsequent therapy - Brigatinib	-£218,675	-£183,714	£34,961
5	Subsequent therapy - Alectinib	-£186,601	-£215,788	£29,187
6	Baseline Characteristics - Age	-£200,147	-£210,204	£10,057
7	Utility multiplier_BSC	-£204,817	-£197,741	£7,077
8	Resource use off treatment	-£204,086	-£198,303	£5,783
9	Concomitant medications_Base cost - Brigatinib	-£203,215	-£199,174	£4,041
10	Concomitant medications_Relative costs - Alectinib	-£199,220	-£203,169	£3,949

CNS, central nervous system; ICER, incremental cost-effectiveness ratio

Figure 56: Tornado diagram, brigatinib vs. alectinib (NMB)



CNS, central nervous system; NMB, net monetary benefit

Table 61: Numerical results of the one-way sensitivity analysis, brigatinib vs. alectinib (NMB)

Rank	Parameter	Lower Bound	Upper Bound	Difference
1	HR_BrigVSAlect_Unanchored MAIC_WT_PFS BIRC	£71,186	£150,198	£79,012
2	Subsequent therapy – Brigatinib	£111,705	£96,001	£15,704
3	HR_BrigVSAlect_Unanchored MAIC_WT OS	£110,631	£97,167	£13,464
4	Subsequent therapy – Alectinib	£97,298	£110,409	£13,111
5	Baseline Characteristics - Baseline EQ-5D-3L	£101,071	£105,419	£4,349
6	Brigatinib vs. alectinib intracranial PFS hazard ratio	£105,987	£102,524	£3,463
7	Resource use off treatment	£105,152	£102,554	£2,598
8	Concomitant medications_Base cost – Brigatinib	£104,761	£102,945	£1,815
9	Concomitant medications_Relative costs – Alectinib	£102,966	£104,740	£1,774
10	CNS management - One Off Cost	£104,240	£103,467	£773

CNS, central nervous system; NMB, net monetary benefit

Figure 57: Tornado diagram, brigatinib vs. alectinib (difference in costs)

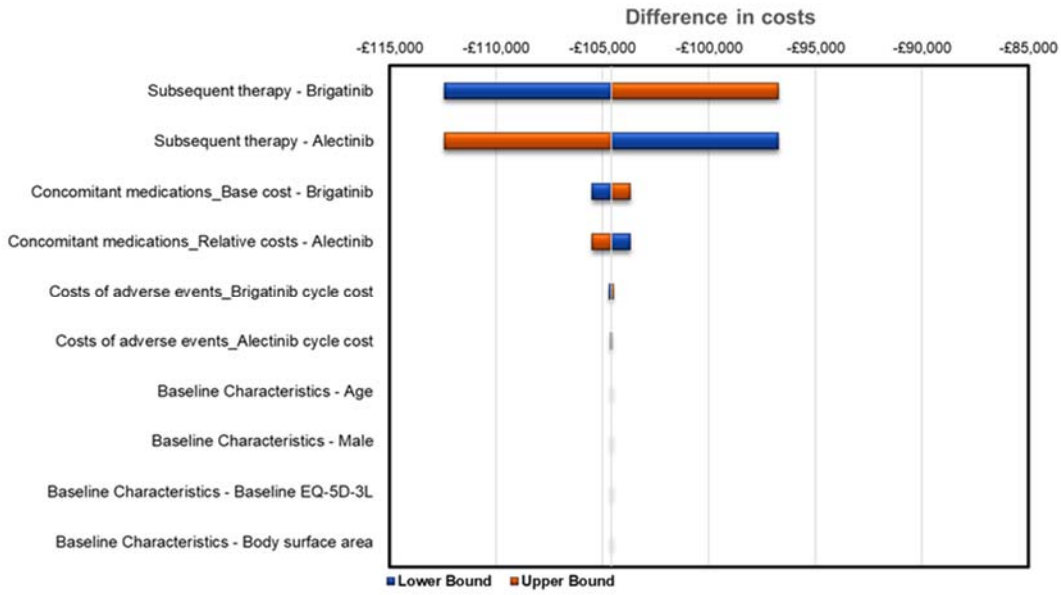


Table 62: Numerical results of the one-way sensitivity analysis, brigatinib vs. alectinib (difference in costs)

Rank	Parameter	Lower Bound	Upper Bound	Difference
1	Subsequent therapy – Brigatinib	-£112,431	-£96,727	£15,704
2	Subsequent therapy – Alectinib	-£96,727	-£112,431	£15,704
3	Concomitant medications_Base cost – Brigatinib	-£105,487	-£103,671	£1,815
4	Concomitant medications_Relative costs – Alectinib	-£103,671	-£105,487	£1,815
5	Costs of AEs_Brigatinib cycle cost	-£104,686	-£104,472	£214
6	Costs of AEs_Alectinib cycle cost	-£104,535	-£104,623	£88
7	Baseline Characteristics – Age	-£104,579	-£104,579	£0
8	Baseline Characteristics – Male	-£104,579	-£104,579	£0
9	Baseline Characteristics - Baseline EQ-5D-3L	-£104,579	-£104,579	£0
10	Baseline Characteristics - Body surface area	-£104,579	-£104,579	£0

B.3.8.3 Scenario analysis

Table 54 describes the key assumptions in the model and the scenario analyses. Results from each of these scenarios are presented in Table 63.

Brigatinib remains dominant across all comparisons with crizotinib. In the comparison with alectinib, brigatinib remains dominant across all comparisons except where the methodology

underpinning the ITCs are varied. In these ITC scenarios, the ICER often falls in the south-west quadrant of the cost-effectiveness plane where brigatinib is less costly yet less efficacious than alectinib. Therefore, the NMB based on a willingness-to-pay threshold of £30,000/QALY is also presented – all scenarios result in a positive NMB.

As discussed in Section B.2.9 and B.3.3.7, there are a number of flaws with each of the ITCs conducted, particularly for OS. The outcomes of the PFS ITCs are all generally aligned and indicate brigatinib is at least as good as alectinib (HRs varying from 0.964–1.046). However, the outcomes of the OS ITCs are much more varied, ranging from 0.832–1.383, which has a large impact on results. Due to the equivalence demonstrated by the PFS ITCs and feedback from clinical experts, we consider that a cost-comparison approach is more suitable for the comparison of brigatinib with alectinib – as presented in Table 57. Therefore, Table 64 presents the scenario analysis results when a cost-comparison is conducted, assuming all efficacy outcomes between brigatinib and alectinib are identical. Note: brigatinib remains cost-saving across all scenarios with minimal variation across the scenarios.

Table 63: Cost-effectiveness scenario analysis results

	Brigatinib vs. Crizotinib			Brigatinib vs. Alectinib		
	Incremental costs	**Incremental QALYs**	**ICER**	**Incremental costs**	**Incremental QALYs**	**ICER**
Clinical effectiveness scenarios						
Parametric model fits for OS						
Weibull	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	Brigatinib is dominant
Gompertz	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	Brigatinib is dominant
Log-logistic	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	Brigatinib is dominant
Log-normal	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	Brigatinib is dominant
Gamma	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	Brigatinib is dominant
Gen. Gamma	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	Brigatinib is dominant
Exponential (base case)	[redacted]	[redacted]	**Brigatinib is dominant**	[redacted]	[redacted]	**Brigatinib is dominant**
Parametric model fits for PFS BIRC						
Weibull	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	Brigatinib is dominant
Gompertz	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	Brigatinib is dominant
Log-logistic	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	Brigatinib is dominant
Log-normal	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	Brigatinib is dominant
Gamma	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	Brigatinib is dominant
Gen. Gamma	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	Brigatinib is dominant
Exponential (base case)	[redacted]	[redacted]	**Brigatinib is dominant**	[redacted]	[redacted]	**Brigatinib is dominant**

	Brigatinib vs. Crizotinib			Brigatinib vs. Alectinib		
	Incremental costs	**Incremental QALYs**	**ICER**	**Incremental costs**	**Incremental QALYs**	**ICER**
Parametric model fits for intracranial PFS						
Weibull	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	Brigatinib is dominant
Gompertz	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	Brigatinib is dominant
Log-logistic	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	Brigatinib is dominant
Log-normal	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	Brigatinib is dominant
Gamma	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	Brigatinib is dominant
Gen. Gamma	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	Brigatinib is dominant
Exponential (base case)	[redacted]	[redacted]	**Brigatinib is dominant**	[redacted]	[redacted]	**Brigatinib is dominant**
Treatment switching adjustments						
No switching adjustment (base case)	[redacted]	[redacted]	**Brigatinib is dominant**	[redacted]	[redacted]	**Brigatinib is dominant**
Adjusted for official switchers, no re-censoring	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	Brigatinib is dominant
Adjusted for official switchers, re-censoring	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	Brigatinib is dominant
Adjusted for all switchers, no re-censoring	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	Brigatinib is dominant
Adjusted for all switchers, re-censoring	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	Brigatinib is dominant
Approach to match intracranial PFS and PFS data						
PFS adjusted to intracranial PFS	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	Brigatinib is dominant
Unadjusted	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	Brigatinib is dominant

	Brigatinib vs. Crizotinib			Brigatinib vs. Alectinib		
	Incremental costs	**Incremental QALYs**	**ICER**	**Incremental costs**	**Incremental QALYs**	**ICER**
Intracranial PFS adjusted to PFS (base case)	[redacted]	[redacted]	**Brigatinib is dominant**	[redacted]	[redacted]	**Brigatinib is dominant**
Treatment waning						
No waning (base case)	[redacted]	[redacted]	**Brigatinib is dominant**	[redacted]	[redacted]	**Brigatinib is dominant**
Mortality rate equal at 5-years	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	Brigatinib is dominant
Mortality rate equal at 10-years	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	Brigatinib is dominant
Mortality rate equal at 20-years	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	Brigatinib is dominant
Cap approach based on the lifetables						
Cap using absolute survival	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	Brigatinib is dominant
No cap	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	Brigatinib is dominant
Cap using conditional survival (base case)	[redacted]	[redacted]	**Brigatinib is dominant**	[redacted]	[redacted]	**Brigatinib is dominant**
ITCs brigatinib vs. alectinib						
Unweighted Bucher (ITT, OS and PFS BIRC), no adjustment for switching	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	£154,416 (NMB: £104,159)
Unweighted Bucher (ITT, OS and PFS BIRC), treatment switching all switchers, no re-censoring	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	£180,236 (NMB: £105,039)
Unweighted Bucher (ITT, OS and PFS BIRC), treatment switching all switchers, re-censoring	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	£253,215 (NMB: £106,415)
Unweighted Bucher (ITT, OS and PFS BIRC), treatment switching official switchers only, no re-censoring	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	£181,280 (NMB: £105,069)
Unweighted Bucher (ITT, OS and PFS BIRC), treatment switching official switchers only, re-censoring	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	£147,222 (NMB: £103,844)

	Brigatinib vs. Crizotinib			Brigatinib vs. Alectinib		
	Incremental costs	**Incremental QALYs**	**ICER**	**Incremental costs**	**Incremental QALYs**	**ICER**
Anchored MAIC (ITT, OS and PFS BIRC), no adjustment for switching	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	£236,174 (NMB: £98,083)
Anchored MAIC (ITT, OS and PFS BIRC), treatment switching all switchers, no re-censoring	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	£324,078 (NMB: £98,944)
Anchored MAIC (ITT, OS and PFS BIRC), treatment switching all switchers, re-censoring	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	£1,520,162 (NMB: £100,532)
Anchored MAIC (ITT, OS and PFS BIRC), treatment switching official switchers only, no re-censoring	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	£328,305 (NMB: £98,973)
Anchored MAIC (ITT, OS and PFS BIRC), treatment switching official switchers only, re-censoring	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	£217,284 (NMB: £97,791)
Unanchored MAIC (ITT, OS and PFS BIRC) (base case)	[redacted]	[redacted]	**Brigatinib is dominant**	[redacted]	[redacted]	**Brigatinib is dominant (NMB: £103,853)**
Unweighted Bucher (ITT, OS and PFS INV), no adjustment for switching	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	£154,686 (NMB: £104,824)
Unweighted Bucher (ITT, OS and PFS INV), treatment switching all switchers, no re-censoring	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	£180,425 (NMB: £105,703)
Unweighted Bucher (ITT, OS and PFS INV), treatment switching all switchers, re-censoring	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	£252,942 (NMB: £107,075)
Unweighted Bucher (ITT, OS and PFS INV), treatment switching official switchers only, no re-censoring	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	£181,466 (NMB: £105,732)
Unweighted Bucher (ITT, OS and PFS INV), treatment switching official switchers only, re-censoring	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	£147,507 (NMB: £104,510)
Anchored MAIC (ITT, OS and PFS INV), no adjustment for switching	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	£236,262 (NMB: £97,677)
Anchored MAIC (ITT, OS and PFS INV), treatment switching all switchers, no re-censoring	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	£324,784 (NMB: £98,539)

	Brigatinib vs. Crizotinib			Brigatinib vs. Alectinib		
	Incremental costs	**Incremental QALYs**	**ICER**	**Incremental costs**	**Incremental QALYs**	**ICER**
Anchored MAIC (ITT, OS and PFS INV), treatment switching all switchers, re-censoring	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	£1,564,117 (NMB: £100,130)
Anchored MAIC (ITT, OS and PFS INV), treatment switching official switchers only, no re-censoring	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	£329,049 (NMB: £98,568)
Anchored MAIC (ITT, OS and PFS INV), treatment switching official switchers only, re-censoring	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	£217,285 (NMB: £97,384)
Unanchored MAIC (ITT, OS and PFS INV)	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	Brigatinib is dominant (NMB: £103,281)
Cost scenarios						
Time on treatment						
Treat until progression (base case)	[redacted]	[redacted]	**Brigatinib is dominant**	[redacted]	[redacted]	**Brigatinib is dominant**
Treat one cycle post-progression	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	Brigatinib is dominant
Treat two cycles post-progression	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	Brigatinib is dominant
Treat three cycles post-progression	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	Brigatinib is dominant
Administration costs						
Exclude pharmacy administration costs	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	Brigatinib is dominant
Include pharmacy administration costs (base case)	[redacted]	[redacted]	**Brigatinib is dominant**	[redacted]	[redacted]	**Brigatinib is dominant**
Relative dose intensity						
All costs saved	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	Brigatinib is dominant
Half costs saved (base case)	[redacted]	[redacted]	**Brigatinib is dominant**	[redacted]	[redacted]	**Brigatinib is dominant**
No costs saved	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	Brigatinib is dominant

	Brigatinib vs. Crizotinib			Brigatinib vs. Alectinib		
	Incremental costs	**Incremental QALYs**	**ICER**	**Incremental costs**	**Incremental QALYs**	**ICER**
						Source of subsequent therapy
Source from ALTA-1L and relevant clinical trials	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	Brigatinib is dominant
User defined (base case)	[redacted]	[redacted]	**Brigatinib is dominant**	[redacted]	[redacted]	**Brigatinib is dominant**
Discount rate scenarios						
Discount rate used in the model						
No discount rate applied to costs and health outcomes	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	Brigatinib is dominant
Discount rate of 3.5% for both cost and health outcomes (base case)	[redacted]	[redacted]	**Brigatinib is dominant**	[redacted]	[redacted]	**Brigatinib is dominant**
Time horizon scenarios						
Time horizon						
5-years	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	Brigatinib is dominant
10-years	[redacted]	[redacted]	Brigatinib is dominant	[redacted]	[redacted]	Brigatinib is dominant
30-years (base case)	[redacted]	[redacted]	**Brigatinib is dominant**	[redacted]	[redacted]	**Brigatinib is dominant**

Table 64: Cost-comparison scenario analyses of brigatinib vs. alectinib

Scenario	Incremental costs
Parametric model fits to OS	
Weibull	-£104,579
Gompertz	-£104,579
Log-logistic	-£104,579
Log-normal	-£104,579
Gamma	-£104,579
Gen. Gamma	-£104,579
Exponential (base case)	**-£104,579**
Parametric model fits to PFS BIRC	
Weibull	-£109,177
Gompertz	-£137,022
Log-logistic	-£143,867
Log-normal	-£148,681
Gamma	-£107,185
Gen. Gamma	-£137,167
Exponential (base case)	**-£104,579**
Parametric model fits to intracranial PFS	
Weibull	-£104,579
Gompertz	-£104,579
Log-logistic	-£104,579
Log-normal	-£104,579
Gamma	-£104,579
Gen. Gamma	-£100,243
Exponential (base case)	**-£104,579**
Treatment switching adjustments	
No switching adjustment (base case)	**-£104,579**
Adjusted for official switchers, no re-censoring	-£104,579
Adjusted for official switchers, re-censoring	-£104,579
Adjusted for all switchers, no re-censoring	-£104,579
Adjusted for all switchers, re-censoring	-£104,579
Approach to match intracranial PFS and PFS data	
PFS adjusted to intracranial PFS	-£96,153
Unadjusted	-£104,579
Intracranial PFS adjusted to PFS (base case)	**-£104,579**
Cap approach based on the lifetables	
Cap using absolute survival	-£104,579
No cap	-£104,579
Cap using conditional survival (base case)	**-£104,579**
Time on treatment	
Treat until progression (base case)	**-£104,579**
Treat one cycle post-progression	-£106,761

Scenario	Incremental costs
Treat two cycles post-progression	-£108,943
Treat three cycles post-progression	-£111,125
Administration costs	
Exclude pharmacy administration costs	-£104,579
Include pharmacy administration costs (base case)	**-£104,579**
Relative dose intensity	
All costs saved	-£106,060
Half costs saved (base case)	**-£104,579**
No costs saved	-£103,097
Source of subsequent therapy	
Source from ALTA-1L and relevant clinical trials	-£101,630
User defined (base case)	**-£104,579**
Discount rate	
No discount rate applied to costs and health outcomes	-£114,998
Discount rate of 3.5% for both cost and health outcomes (base case)	**-£104,579**
Time horizon	
5-years	-£88,870
10-years	-£102,151
30-years (base case)	**-£104,579**

B.3.8.4 Summary of sensitivity analyses results

The sensitivity analyses demonstrate that brigatinib remains dominant in all scenarios compared to crizotinib, with a 100% probability of being cost-effective at a £30,000/QALY willingness-to-pay threshold. Note: these results are based on the proposed PAS discount being applied for brigatinib and the list price being applied for crizotinib.

The biggest drivers of the brigatinib vs. crizotinib results are: the choice of parametric curve for OS, PFS BIRC and whether treatment switching analyses are applied. The extrapolated curves applied in the base case have been validated with clinicians (see Section B.3.10) and compared to those used in the alectinib NICE submission. For OS, clinical experts considered that the exponential curve, which was the most pessimistic of the standard parametric curves, was the only plausible curve fit given real-world outcomes at 10 or 20 years. Including treatment switching adjustment methods also has a large impact on results, this is because the costs of subsequent brigatinib use which are removed from the crizotinib arm are not being outweighed by the reduction in efficacy. However, it is important to note that the treatment switching analyses produced results which were either implausible or did not align with clinical expectations. Therefore, it is likely that the data from IA2 are too immature to be able to conduct a robust treatment switching analysis. Given that brigatinib is used routinely following crizotinib in UK clinical practice, these scenarios are considered hypothetical and not reflective of current clinical practice.

The sensitivity analyses demonstrate that brigatinib remains dominant or has a positive NMB in all scenarios compared to alectinib, with a 100% probability of being cost-effective at a

£30,000/QALY willingness-to-pay threshold. Note: these results are based on the proposed PAS discount being applied for brigatinib and the list price being applied for alectinib. Additionally, in the cost-comparison framework, brigatinib is shown to be cost-saving across all scenarios with minimal variation.

B.3.9 Subgroup analysis

No subgroup analyses have been explored.

B.3.10 Validation

B.3.10.1 Validation of clinical inputs

Two clinical expert advisory boards were conducted to validate the clinical assumptions underpinning the economic model: (1) February 2019 advisory board and (2) January 2020 advisory board. Both are summarised in Table 65.

Table 65: Summary of advisory boards supporting this submission

	February 2019	January 2020
Number of clinical experts	6	11
Geographical spread	Leicester London Suffolk Wales Manchester x2	London x4 Manchester x2 Wales Glasgow Suffolk Birmingham Merseyside

The following topics were discussed in detail at the advisory boards:

- The overall management of ALK-positive advanced NSCLC in the UK
- The treatment pathway, including subsequent therapies
- Prognostic or treatment effect modifying factors for OS, PFS and HRQoL
- Definition of progression in clinical practice (RECIST vs. modified RECIST)
- Real-world experience of brigatinib and alectinib
- Duration of treatment and decision to discontinue
- Resource use associated with frontline therapies vs. subsequent therapies
- Management of Grade 3/4 AEs classed as laboratory abnormalities

Validation of extrapolated outcomes was also discussed in detail – this is discussed in Section B.3.10.2.

<u>Prognostic or treatment effect modifying factors for OS, PFS and HRQoL</u>

Statistical analyses explored factors driving the prognosis or treatment effect using the candidate list of: gender, age, smoking status, race (Asian vs. non-Asian), baseline brain

metastases and ECOG score (0/1 vs. 2). This list was informed by clinical expert consultation conducted as part of the brigatinib post-crizotinib NICE submission[2] and was confirmed by clinical experts at both advisory boards to be independent of treatment line (i.e. there are no additional prognostic or treatment effect modifiers to consider in the frontline setting vs. the post-crizotinib setting). This list was also used as part of the MAIC analyses.

Similarly, the variables considered to be influential on HRQoL were baseline EQ-5D score, AEs and response. Therefore, these variables were included in the HRQoL analysis.

Definition of progression in clinical practice (RECIST vs. modified RECIST)

Clinical advisors considered the ALTA-1L trial as robust largely due to the use of BIRC-assessed PFS and the inclusion of radiotherapy to the CNS in the definition of the primary outcome. It was also noted that the need for radiotherapy to the brain due to the development of new CNS lesions indicated disease progression in routine clinical practice.

Clinical experts at the January 2020 advisory board specified that the RECIST measurement tool is used in clinical practice and that the modified RECIST measurement tool is not representative of clinical practice (including practice within specialist centres). There was agreement that the modified RECIST tool is very sensitive and so it is understandable that there are more events identified using this tool vs. the standard RECIST measure. Therefore, the intracranial PFS variable was adjusted to reflect RECIST only measurements in order to reflect real world practice in the base case. Note: this is also in line with the method used in the alectinib NICE submission (TA536).[55]

Real-world experience of brigatinib and alectinib

This was discussed in more detail at the later advisory board (January 2020), so that clinicians had more experience of using alectinib or brigatinib in the frontline setting. Ten out of the 11 advisors had used alectinib in the frontline setting; the remaining clinician had not been able to access alectinib due to its unavailability in patients who receive prior chemotherapy.

Three clinicians had experienced frontline brigatinib use through the ALTA-1L clinical trial. Clinicians who had had experience of both alectinib and brigatinib in the frontline reported similar experiences with each treatment. All clinicians considered that, given the outcomes from the ALTA-1L study and the ALEX study, brigatinib and alectinib have a similar efficacy profile. Clinicians' impression of the trial data was that: brigatinib demonstrates similar extracranial efficacy to alectinib and it appears to be more effective than alectinib in patients with brain metastases at baseline. The differences between the trial designs and baseline characteristics were discussed at length and it was concluded that a robust ITC was not possible. Therefore, conclusions were mainly based off the comparison of Kaplan-Meier curves (Figure 44, Figure 46). Furthermore, it was discussed that the presence of brain metastases is often unknown at baseline. Therefore, brigatinib was seen as an attractive frontline treatment option because it performs well both extracranially and intracranially.

Given their real-world experience and the clinical trial data, clinical experts were supportive of the statement: "brigatinib is at least as effective as alectinib" and they all supported the rationale for a simple cost-comparison analysis to compare the two agents. In addition to

improved intracranial efficacy, clinicians considered brigatinib may offer the following real-world benefits over alectinib:

- a more manageable AE profile because most of the AEs seen with brigatinib in ALTA-1L were asymptomatic laboratory abnormalities that were of no clinical consequence,
- potential for improved patient compliance with brigatinib as it can be taken as one tablet, once-daily whereas alectinib requires four capsules to be taken twice-daily. Some clinical experts have real-world experience of patients treated with alectinib self-modifying their dose by taking fewer tablets than prescribed if they experience side-effects. As a single tablet, this is more difficult to do with brigatinib,
- Improved HRQoL because the EORTC QLQ C-30 collected in the ALTA-1L clinical trial found significant improvements with brigatinib vs. crizotinib; such an improvement in HRQoL was not seen in the ALEX trial of alectinib vs. crizotinib.

The health economic model captures AEs and compliance (through applying the relative dose intensity (RDI). Contrary to clinician feedback, in the model managing AEs appears to be more costly for brigatinib than alectinib. Furthermore, the relative dose intensity reported for alectinib in the ALEX trial was higher than that reported for brigatinib in ALTA-1L. These model outcomes are not considered to be reflective of real-world clinical experience and may be largely due to the way in which the relevant trials were conducted (e.g. the protocol for screening for laboratory abnormalities was particularly rigorous in the ALTA-1L trial). Therefore, this should be noted when considering the model outcomes. Furthermore, whilst the EORTC QLQ C-30 showed a significant difference in favour of brigatinib over crizotinib in ALTA-1L, this was not maintained when results were mapped to EQ-5D – which is then applied within the model. Therefore, the model does not adequately capture treatment specific HRQoL. It is important to note that, of the three benefits of brigatinib over alectinib that were identified by clinical experts, it is uncertain whether these are adequately captured in the health economic model.

Duration of treatment and decision to discontinue

At both clinical expert advisory boards, it was considered that patients would, on average, be treated until progression in the frontline setting. The feedback from the later advisory board emphasised this further as with the availability of efficacious subsequent therapies, patients would not be kept on treatment after progression. This is supported by the data from the ALTA-1L clinical trial. Clinicians commented that it was unusual for patients to discontinue treatment prior to progression, unless there were tolerability issues. It was further agreed that these conclusions would apply to all frontline therapies.

Therefore, the base case assumes that all patients are treated until progression. This assumption is also in line with the alectinib NICE submission (TA536).

Resource use associated with frontline therapies vs. subsequent therapies

The resource use assumptions associated with pre-progression and progressed disease in the alectinib NICE submission were presented to clinicians. It was considered that these inputs have not changed in the last two years. However, the resource use associated with CNS

management is considered to have evolved since the alectinib appraisal (TA536).[55] Table 66 presents the differences in resource use; notably, the use of SRS has increased and the use of WBRT has decreased.

To align with current clinical practice, the economic model assumes the resource use validated at the advisory board in the base case. A scenario analysis considers the inputs from the alectinib NICE submission.

Table 66: CNS management resource use (Inputs from alectinib NICE submission vs. feedback from January 2020 advisory board)

	Alectinib NICE submission (TA536)	Feedback from clinical experts
SRS	20-25%	50%
WBRT	25%	5%
Surgical resection	5%	5%
Steroids (dexamethasone)	100%	10%

SRS, stereotactic radiosurgery; WBRT, whole brain radiotherapy

The treatment pathway including subsequent therapies

Clinicians were asked to map out the clinical pathway based on treatments that were currently reimbursed within the UK. Alectinib was identified by all the clinicians to be the standard of care in the UK whereas ceritinib was considered irrelevant in the frontline (as it has been displaced by alectinib). Table 67 presents the output of this exercise for subsequent treatment. The estimates for subsequent brigatinib and ceritinib use following frontline crizotinib align with UK market share data (average across sales from November 2020 – February 2020); 71% of progressed patients receive brigatinib and 13% receive ceritinib.

Table 67: Clinical pathway as mapped out by clinicians at January 2020 advisory board

Frontline	Brigatinib/alectinib	Crizotinib
Second line	Chemotherapy: 50-60% BSC: 40-50%	Brigatinib: 70-80% Ceritinib: 5-10% Chemotherapy: 0% BSC: 20-30%
Third line	BSC: 100%	Chemotherapy: 30% BSC: 70%
Fourth line	NA	BSC: 100%

The base case inputs were informed by the market share data and supported by this clinical feedback. The alectinib NICE appraisal featured a lot of discussion about subsequent therapies. Two scenarios were considered for decision making, presented in Table 68. The base case in that submission aligns with the proportion of patients receiving chemotherapy after alectinib (and brigatinib) i.e. 50%. However, this submission assumes that all patients who receive frontline alectinib or brigatinib will eventually receive BSC at some point – based on clinical feedback. The base case in this submission following crizotinib approximates the

proportion of patients receiving another ALK inhibitor in the alectinib NICE appraisal (71% vs. 75%, respectively). However, our submission considers subsequent brigatinib as well as ceritinib[112] – after the reimbursement of brigatinib in this setting in February 2019.[2] Furthermore, it is assumed that a proportion of patients will receive chemotherapy at third line in the crizotinib arm (30%), in line with clinical feedback. It is also assumed that all patients will eventually receive BSC at some point, following frontline crizotinib. Finally, this submission also considers a small proportion of patients receiving VEGF-R or immunotherapies – clinicians considered this would be a small proportion (<5%) across all treatment arms.

Table 68: Subsequent therapy assumptions from alectinib NICE submission

	Post-alectinib		Post-crizotinib	
	Chemotherapy	BSC	Ceritinib	BSC
"Middle ground"	50%	50%	75%	25%
"Conservative"	50%	50%	70%	30%

Treatment of Grade 3/4 adverse events classed as laboratory abnormalities

A number of the Grade 3/4 AEs reported in the ALTA-1L clinical trial were asymptomatic laboratory abnormalities (e.g. increased blood creatinine phosphokinase, increased amylase, increased AST, increased ALT etc.). At the advisory boards, we asked how these abnormalities are managed in clinical practice. It was confirmed that these laboratory abnormalities would be managed through dose interruptions or modifications – the additional resource use would be limited to, at most, two medical oncology outpatient visits and two additional blood tests for monitoring. Therefore, the model includes these costs.

B.3.10.2 Validation of extrapolated outcomes

All parametric curves based on the IA2 data from ALTA-1L were presented to clinical experts at the January 2020 advisory board – this was done at the later advisory board only because the second data cut was unavailable at the time of the earlier advisory board. Clinicians considered that the exponential appeared to be the most reasonable for PFS, intracranial PFS and OS outcomes. Clinicians felt strongly that brigatinib and alectinib were very similar in terms of PFS and OS (unknown about intracranial PFS for alectinib), and that the same parametric curve as applied in the alectinib submission (exponential) should be considered in this appraisal.

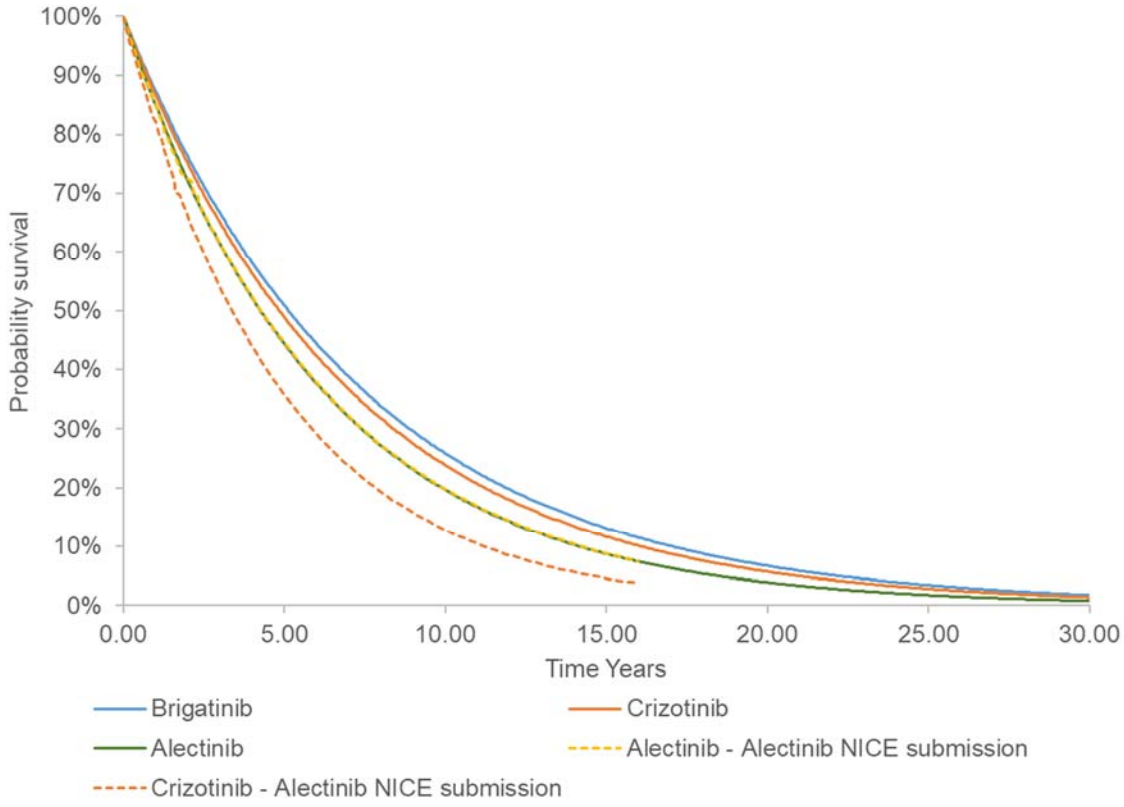
The OS modelling was discussed further, because these data are immature and are a key driver of the model outcomes. It was considered that, whilst the exponential provides the lowest estimates of survival over time, these estimates still appear higher than would be expected. However, it was considered difficult to predict the exact proportion alive at 15- or 20-years given the rapidly evolving treatment landscape. Given the lack of long-term data following frontline ALK inhibitors, it was considered that the exponential curve predicting the worst outcomes was appropriate as a base case choice.

Unfortunately, the extrapolated OS curves using the later data cut from the ALEX trial are redacted in the alectinib NICE submission dossier. Only the extrapolated curves using the first

data cut from ALEX are available for validation purposes – these have been digitised and are presented alongside the extrapolated curves from this submission in Figure 58. Note: Figure 58 presents the base case cost-effectiveness curves (i.e. the HR from the unanchored MAIC is applied to estimate OS associated with alectinib). As discussed in Section B.3.3.7, we consider that a cost-comparison analysis is also an appropriate (and in our opinion a preferable) approach to compare brigatinib with alectinib (i.e. brigatinib and alectinib are assumed equally effective).

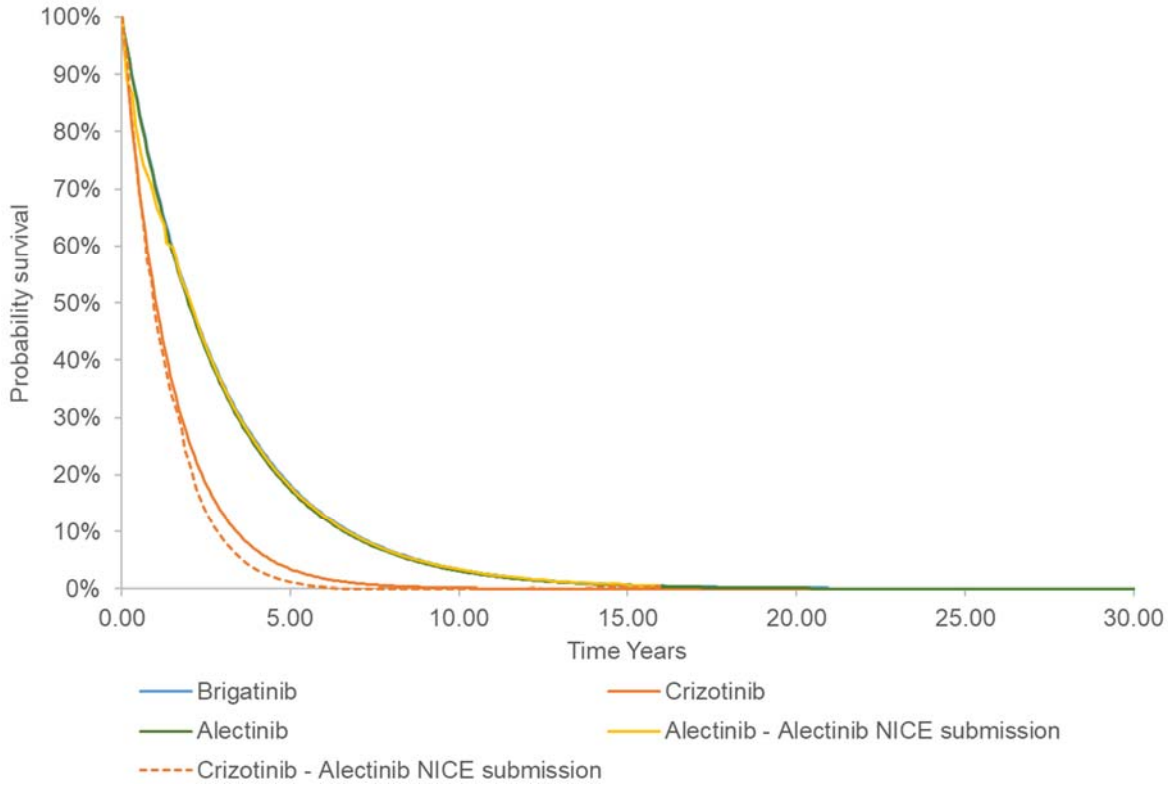
The extrapolated outcomes for alectinib appear identical between the base case in our submission and the alectinib NICE submission (first data cut, TA536). However, as noted above, we consider a cost-comparison to be a preferred approach. In this scenario, the OS outcomes for alectinib are better than those seen in the alectinib NICE submission. There is a big difference between the extrapolated outcomes for crizotinib in this appraisal and those in the alectinib appraisal. As discussed earlier, this is driven by confounding due to the high rate of subsequent therapies and crossover from crizotinib to brigatinib that occurred in the ALTA-1L trial; hence, the data for the crizotinib arm in the ALTA-1L trial represents a sequence of ALK inhibitors which is not comparable with the crizotinib arm in the ALEX trial, where crossover from crizotinib to alectinib was not allowed per protocol. These differences make validation difficult. However, the difference between the crizotinib arms is understandable. This comparison confirms a similar shape in curves across the two submission dossiers.

Figure 58: Extrapolated OS outcomes from the alectinib NICE submission vs. this submission



In the alectinib NICE submission, a preference was given to PFS BIRC, rather than PFS INV. However, the extrapolated curves informing PFS BIRC do not appear to be publicly available, only PFS INV from the first data cut seems to be presented in the Committee papers. Therefore, these data have been digitised and compared with the extrapolated PFS BIRC curves in this submission (Figure 59). A high level of congruence is observed between PFS outcomes for both alectinib and crizotinib. Therefore, validating our base case choice of parametric curves.

Figure 59: Extrapolated PFS outcomes from the alectinib NICE submission vs. this submission



B.3.10.3 Validation of cost-effectiveness analysis

B.3.10.3.1 Internal validity

The economic model was quality-assured through the NICE PRIMA review process and through external quality checking processes. The NICE PRIMA review process was concluded in May 2019. Note: this was based on the first data cut from the ALTA-1L clinical trial. The overall assessment was that:

> *"The partitioned survival modelling approach and model structure for the brigatinib CEA model were consistent with previous NSCLC models appraised by NICE. The methods within the CEA model were generally consistent with NICE methods, with some discrepancies in utility score measurement methods. The inclusion of a wide variety of survival curve choices was a good feature of the model. The CEA model was*

> *generally laid out well but would benefit from further navigation aids and explanatory text."*

In relation to the utility score measurement methods, the PRIMA report advised that utility decrements derived from multiple sources with different methods of measuring HRQoL should be combined using multiplicative methods – this advice has been adhered to in the updated economic model.

As part of the PRIMA process, Takeda submitted a separate cost-comparison model. Feedback indicated that the cost-comparison model was highly dependent on inputs and assumptions underpinning the cost-effectiveness model. Furthermore, it was considered non-sensical to be able to set different inputs and assumptions in both models. Therefore, following this feedback, a cost-comparison approach was implemented within the cost-effectiveness model – which is presented within this dossier.

All other findings from the PRIMA review were addressed during the subsequent update of the economic model with the second data cut (IA2). Due to time restrictions, a PRIMA review of the update economic model (based on the IA2 data) was not feasible. However, to ensure the rigour of the final model, external health economists not involved in model building reviewed the model for coding errors, inconsistencies and the plausibility of inputs. These included 'black box' testing, including (but not limited to): setting all the costs equal to zero and expecting this to be reflected in the results, setting utilities equal to one and expecting QALYs to equal life years, setting efficacy equal between treatment arms and expecting the efficacy results to be identical. At this stage, few inconsistencies were identified in the model. These have been addressed prior to submitting to NICE.

B.3.10.3.2 External validity

To assess external validity of the model outcomes, total discounted life years and total discounted QALYs are compared across the literature – see

Table **69**. Note: only 11 of the 25 cost-effectiveness models identified as part of the economic SLR reported these outcomes for brigatinib, alectinib or crizotinib. No studies were identified within the economic SLR that considered cost-effectiveness outcomes for brigatinib (the search was conducted May 2019).

Five studies were identified as reporting life years and QALYs for alectinib, these ranged from 3.31-5.69 and 2.33-3.79, respectively. These estimates align with the outcomes predicted by our economic model in the base case cost-effectiveness setting – 5.072 and 3.424, respectively. However, in the cost-comparison scenario it is assumed that alectinib has identical outcomes to brigatinib (i.e. 5.868 and 3.874, respectively). These are the highest outcomes across the identified literature and may represent the more efficacious subsequent therapies used in the brigatinib arm compared with what was used in ALEX.

Ten studies were identified as reporting life years and QALYs for crizotinib; these ranged from 1.26-4.56 and 0.68-2.84, respectively. These estimates are much lower than the outcomes

predicted by our economic model – 5.610 and 3.417, respectively. This is because, as described earlier, the data for crizotinib from ALTA-1L which informs our economic model comprises a sequence of ALK inhibitors. By contrast, historical cost-effectiveness analyses for crizotinib have been based on data from trials where there was limited access to effective subsequent therapies. As OS outcomes are much better in the crizotinib arm of the ALTA-1L trial than in historical data, the ICER will naturally be much higher for brigatinib vs. crizotinib using the ALTA-1L data than it would be if brigatinib were compared with the same crizotinib data that was used in the alectinib NICE submission (TA536). This is a direct result of the ALTA-1L trial design allowing for crossover from crizotinib on progression, whereas the ALEX clinical trial did not allow this.

Table 69: Comparison of life years and QALYs across the literature

	Total discounted life years*	Total discounted QALYs*
This submission		
Brigatinib	5.868	[redacted]
Crizotinib	5.610	[redacted]
Alectinib	5.072	[redacted]
Alectinib NICE submission (TA536)		
Alectinib	5.14	3.79
Crizotinib	4.32	2.84
Crizotinib NICE submission (TA406)		
Crizotinib	2.42	CiC
Guan et al. (2019)		
Alectinib	5.69	3.26
Crizotinib	4.56	2.23
Lu et al. (2018)		
Crizotinib	1.45	0.78
Oksuz et al. (2018)		
Alectinib	3.31	2.33
Crizotinib	2.74	1.70[113]
Carlson et al. (2018)		
Alectinib	5.21	3.51
Crizotinib	4.30	2.64
Kourkoulas et al. (2017)		
Alectinib	5.01	3.74
Xie et al. (2018)		
Crizotinib	3.85	2.68
Zhou et al. (2018)		
Crizotinib	2.73	2.41
Lu et al. (2016)		
Crizotinib	1.447-1.45	0.764-0.766
Djalalov et al. (2014)		
Crizotinib	1.26	0.681

**Where it is unclear whether outcomes are discounted, it is assumed that they are discounted*

B.3.11 Interpretation and conclusions of economic evidence

We have developed a health economic model to assess the cost-effectiveness of brigatinib in patients with ALK-positive advanced NSCLC previously untreated with an ALK inhibitor. The model structure and inputs closely align with the model informing the alectinib NICE submission (TA536) which was considered appropriate given alectinib is the main comparator to brigatinib and the alectinib appraisal is the most recent of the frontline ALK inhibitors to go through the NICE process.

The cost-effectiveness model clearly demonstrates the advantages of brigatinib when compared to crizotinib, even when the crizotinib arm includes subsequent brigatinib. This highlights the advantages of using the more effective treatment upfront. Brigatinib accrues more life years (+0.26) and more QALYs (+0.46) over a lifetime horizon, compared with crizotinib. Although the confidential PAS discount is not known for crizotinib, cost savings are clearly demonstrated in terms of reduced CNS management (-£3,945) and reduced use of expensive subsequent therapies (-£33,707). The uncertainty associated with the inputs informing the economic model are explored in scenario analyses – these demonstrate that the results are most sensitive to the parametric curves underpinning extrapolations and the treatment switching assumptions. Whilst it is to be expected that these are the biggest drivers in the model, the assumptions underpinning the base case have been validated using the literature and two advisory boards – described in detail in Section B.3.10.

The cost-effectiveness model indicates that brigatinib accrues more life years (+0.80) and QALYs (+0.45) than alectinib. Whilst a cost-effectiveness analysis is presented, in line with NICE's preference for the base case, we consider that a cost-comparison analysis provides the best approach for comparing brigatinib with alectinib. We believe that the ITCs (Section B.2.9) conducted using the data from ALTA-1L and ALEX indicate that brigatinib and alectinib have an extremely similar efficacy profile. The estimated HRs for PFS range from 0.965 to 1.046. The OS results encompass much more uncertainty, hindered by: immature data, differences between trial populations and differences between trial design – most notably, due to treatment switching (crossover), which was permitted in the protocol of the ALTA-1L trial from crizotinib to brigatinib on progression, but was not allowed by the ALEX trial protocol. A range of analyses has been presented using the OS data to explore these differences; however, none are able to fully adjust for all of these.

We consider the most robust analysis to be the one using the unanchored MAIC methodology, because this avoids using data from the crizotinib arms (from both ALTA-1L and ALEX) and thus avoids the introduction of bias due to treatment crossover. However, whilst this method is used in the base case cost-effectiveness analysis, given the similarities in the PFS results, we would expect the "true" relative OS effect to also be similar between brigatinib and alectinib (i.e. brigatinib is at least as good as alectinib). The cost-comparison framework aligns with NICE's preferred methodology when an intervention offers at least the same health benefits as a comparator – we believe such equivalence is supported by naïve comparisons of the data, the ITCs and feedback from real-world use of brigatinib and alectinib in UK clinical practice. This framework assumes that the OS, PFS and intracranial PFS driving the model structure are identical between brigatinib and alectinib. In the base case, brigatinib is shown

to be cost-saving. However, the alectinib confidential price discount (PAS) is unknown thus making conclusive statements impossible.

The strengths of our analyses include:

- The ALTA-1L clinical trial is a randomised, Phase III multi-centre, international, open-label comparative study, offering a robust comparison between brigatinib and crizotinib in patients who have been previously untreated with an ALK inhibitor. Feedback from clinicians has been that this trial is highly representative of real-world clinical practice, particularly in relation to these factors: some patients had received prior chemotherapy, the proportion of patients with baseline CNS metastases and that treatment crossover from crizotinib to brigatinib was allowed on progression.
- The assumptions underpinning the results (i.e. the extrapolation of the time-to-event outcomes) have been validated using the literature and at an advisory board – the most pessimistic survival curves (exponential) have been applied in the base case, predicting the poorest survival at 10, 20 and 30 years.
- All outcomes have been compared with the alectinib NICE submission (TA536) which our appraisal largely mirrors. The PFS outcomes are almost identical between the appraisals for the crizotinib arms, and very similar between the brigatinib and alectinib arms. The OS outcomes differ; however, this is to be expected given the difference between the trials in the rate of treatment crossover that occurred.
- The HRQoL data have been obtained from the patients in the ALTA-1L clinical trial where possible – in line with the NICE Methods Guide.[89] Where these data are insufficient (e.g. following progression), multiplicative methods have been used to incorporate external data sources – in line with NICE DSU TSD 12.[90]
- Extensive sensitivity and scenario analyses explore the assumptions and uncertainty associated with different data sources and different methods.

The main limitations associated with the cost-effectiveness analyses are:

The ALTA-1L clinical trial is not directly comparable to other clinical trials in the frontline setting, such as the ALEX trial of alectinib vs. crizotinib. Therefore, validating clinical outcomes by comparing across the literature has been extremely challenging. This is largely driven by the timing of the ALTA-1L clinical trial and the rapidly evolving treatment pathway which now includes subsequent ALK inhibitors following treatment with crizotinib. The ALTA-1L clinical trial is the first RCT where the overall survival outcomes in the crizotinib arm reflects that of a sequence of ALK inhibitors. Additional differences such as the inclusion of patients with prior chemotherapy and how a PFS event is defined also make cross-trial comparisons difficult. However, feedback from clinicians indicates that these aspects of the ALTA-1L trial are reflective of UK clinical practice and so it provides generalisable, meaningful outcomes that they can relate to. Nevertheless, ITCs attempting to obtain estimates of relative efficacy between brigatinib and alectinib have been hindered by these differences.

A further limitation relates to the relative immaturity of the overall survival data; the analyses have been based on data with a median follow-up of 24.9 months (in the brigatinib arm; IA2), where only 33 and 37 OS events have occurred in the brigatinib and crizotinib arms, respectively. Therefore, there is some uncertainty associated with the extrapolated OS

outcomes and the treatment switching analyses. The OS extrapolations have undergone extensive validation, and we consider the base case to be reflective of expected outcomes in clinical practice. However, the available treatment switching analyses do not appear to be able to fully adjust for the impact of treatment switching on OS outcomes. Therefore, the isolated overall survival benefit of brigatinib vs. crizotinib (without bias from subsequent brigatinib in the crizotinib arm) is unknown.

Finally, the lack of trial-based utility values for the progressed disease health states result in utility values being sourced from the literature. However, these have been incorporated as per the guidance in NICE DSU TSD documents.

Conclusion

Brigatinib is an innovative, next-generation ALK inhibitor that has shown an improved efficacy profile, both intracranially and extracranially, and improved HRQoL when compared to crizotinib. The benefits of treating patients upfront with brigatinib, rather than waiting to use brigatinib at a later line, are demonstrated in the ALTA-1L clinical trial. Brigatinib is considered to be at least as effective as the current standard of care, alectinib. However, patients treated with brigatinib only require one tablet to be taken once-daily, offering a reduced pill burden compared with alectinib (which requires four capsules to be taken twice daily with food). Additionally, we have submitted a revised PAS which improves further the cost effectiveness of brigatinib.

The AEs associated with brigatinib are manageable and are mostly laboratory abnormalities which can be addressed through dose modification. These AEs do not lead to a deterioration in HRQoL in most patients.

A positive NICE recommendation for brigatinib would provide patients and clinicians with a welcome additional treatment option in the frontline setting.

B.4 References

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B.5 List of Appendices

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Technical engagement response form

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

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **5.00pm on 1 October 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	Eugene Benson
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	Takeda UK Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Response from Evidence Review Group	Liverpool Reviews and Implementation Group (LRiG)

Questions for engagement

<table>
<tr><th colspan="2">Issue 1: Comparators</th></tr>
<tr><td>1. Which ALK-inhibitors are typically used in routine NHS practice for patients with confirmed ALK-positive untreated NSCLC? Please provide details of which are most commonly used, e.g. Treatment 1: 60% of patients, Treatment 2: 10% of patients, and so on.</td><td>Alectinib is the main ALK inhibitor that is routinely used in NHS practice for untreated patients with confirmed ALK-positive NSCLC. Crizotinib and ceritinib are also available for use in untreated patients with ALK-positive NSCLC. However, both are less commonly used in the NHS in this setting due to the availability of alectinib which is considered by clinicians to be superior in efficacy and safety. This is reflected in the recent market research data (July 2020) presented below on the use of ALK inhibitors in the UK:

<table><tr><td>Treatment 1</td><td>Alectinib</td><td>85%</td><td rowspan="3">Source: Takeda UK Ltd presentation of Medimix LiveTrackerTM data of July 2020</td></tr><tr><td>Treatment 2</td><td>Crizotinib</td><td>7%</td></tr><tr><td>Treatment 3</td><td>Ceritinib</td><td>1%</td></tr></table>
Please note that the estimates above do not add up to 100% because chemotherapy is excluded as per question 1.</td></tr>
<tr><td>ERG response</td><td>The ERG has no further comment</td></tr>
<tr><td>2. Which ALK-inhibitors are typically used in routine NHS practice for patients with confirmed ALK-positive NSCLC who have previously received treatment with chemotherapy (before confirmation of ALK status)? Please provide details of which are most commonly used, e.g. Treatment 1: 60% of patients, Treatment 2: 10% of patients, and so on.</td><td>For patients with confirmed ALK-positive advanced NSCLC who have previously been treated with chemotherapy, the only available subsequent ALK inhibitor recommended by NICE for use in the NHS is crizotinib. There is no existing evidence and no funding in place for treatment with alectinib or ceritinib in ALK-positive patients who initially received chemotherapy.</td></tr>
</table>

ERG response	The ERG has no further comment
Issue 2: **Indirect Treatment Comparison**	
3. *Is the population of the ALESIA trial (Asian population) generalisable to clinical practice in the NHS in England?* a) *Does race (Asian versus non-Asian) impact prognosis in patients with ALK+ NSCLC?* b) *Is race (Asian versus non-Asian) a treatment effect modifier? If yes, please provide details*	No, the population of the ALESIA study is not generalisable to clinical practice in England. The individuals recruited into the ALESIA study were exclusively east Asian specifically from China, South Korea and Thailand only. The most recent census by the Office of National Statistics showed that less than 2% of the UK population is likely to be from China, South Korea and Thailand. Therefore, the population of patients in the ALESIA study is not at all representative of the UK demographic. a) We believe this is really a question for clinical experts to answer. However, in addition to just focusing on race, we would suggest that NICE also seeks clinical expert input on the potential impact of the healthcare system itself (e.g. there may be significant regional differences in health systems and pathways of care, and these may impact patient outcomes). Such differences would again argue against the inclusion of the ALESIA trial within the ITCs. b) See our response to Question 3a).
ERG response	The ERG has no further comment
Issue 3: **Overall survival**	
4. *What percentage of people with ALK-positive advanced NSCLC seen in the NHS would likely to be alive at 1-year, 2-years, 5-years, 10-years if treated with brigatinib? How would this compare to the OS expected for alectinib?*	We are unable to comment on the first question and we see this as one for clinical experts to address. Regarding the second question, as per our submission (and assuming all other things are equal) we would expect OS outcomes to be the same for patients treated with brigatinib or alectinib.

ERG response	The ERG has no further comment
Issue 4: Cost-comparison/minimisation versus alectinib	
5. *Please describe similarities and differences seen with brigatinib and alectinib within clinical practice.*	**Similarities** • Brigatinib and alectinib are both oral, second-generation tyrosine kinase inhibitors with similar mechanisms of action which involves the inhibition of anaplastic lymphoma kinase (ALK). • Both have demonstrated an increased potency in inhibiting ALK compared to crizotinib. This has translated clinically, as both have shown improved efficacy vs. crizotinib in their respective head-to-head trials in the frontline setting. • Brigatinib and alectinib were both designed to penetrate the blood-brain barrier effectively and have demonstrated improved intracranial efficacy compared to crizotinib. • Both have good activity against ALK mutations that confer resistance to crizotinib. **Differences** • Brigatinib and alectinib are both administered orally. However, brigatinib has a more convenient dosing regimen of one tablet taken once-daily with or without food, whereas alectinib requires four capsules to be taken twice-daily with food. • Brigatinib has demonstrated efficacy in patients regardless of whether they have been previously treated with chemotherapy or not; alectinib has no evidence supporting its efficacy in patients who were initially treated with chemotherapy. • Brigatinib is the only ALK inhibitor in the frontline setting to have demonstrated clinically relevant and statistically significant quality of life improvements compared to crizotinib (in the ALTA-1L trial). Please see the company response to ERG clarification question 15 for more detailed information.

ERG response	Thank you for providing the detail of the similarities and differences between brigatinib and alectinib. For a cost-comparison to be undertaken, the assumption is made that an intervention and comparator are 'similar enough' in terms of all relevant outcomes that any differences are minimal and do not impact on the economic assessment. Pharmacological and trial-based statistical evidence should be presented to support an assumption of 'similar enough', as failure to properly assess similarity poses the risk of recommending treatments that are inferior to current standard of care.
Issue 5: Duration of treatment	
6. *How long do people typically spend on ALK-inhibitors such as brigatinib, alectinib and crizotinib? Is duration of treatment likely to be the same for patients receiving alectinib and patients receiving brigatinib?*	We believe clinical experts are best placed to answer the first question. Our understanding is that the decision to continue treatment beyond progression (or not) is affected by the availability (or not) of efficacious subsequent therapies. If there are limited options available for a patient after progression, a clinician may opt to continue treatment beyond progression provided that the patient is still receiving some clinical benefit. Given that this is an area of some uncertainty, our health economic model explores a number of scenarios, including: treat until progression or treat 1, 2 or 3 cycles beyond progression. Regarding the second question, we would expect this to be the same for either brigatinib or alectinib in the frontline setting.
ERG response	The ERG has no further comment
7. *What percentage of patients stop treatment before disease progression? For what reasons is treatment stopped in these patients?*	The majority of patients in the ALTA-1L and ALEX clinical trials continued treatment until they experienced progressive disease, failed to gain any clinical benefit or had intolerable toxicity. This is considered to be reflective of clinical practice. In the most recent ALTA-1L analyses, 13% of patients treated with brigatinib discontinued treatment before disease progression due to adverse events (compared with 9% of patients in the crizotinib arm). This is comparable with the alectinib arm in the ALEX study (also from the latest

	safety data), where 15% of patients treated with alectinib discontinued treatment due to adverse events, compared with 15% of patients treated with crizotinib. As we understand it, the major reasons for stopping treatment before disease progression would be adverse events or patient choice.
ERG response	The ERG has no further comment
8. *What percentage of patients continue treatment after progression of disease? For what reason would patients continue treatment after progression of disease*	We believe clinical experts are best placed to answer these questions. Please also see our answer to question 6.
ERG response	The ERG has no further comment
Issue 6: Partitioning progressed disease by CNS progression	
9. Are there any other forms of extrapulmonary progression (e.g. bone metastasis) that may incur very specific costs and QALYs? If yes, please specify.	With the exception of progression in the CNS, we are not aware of any other forms of extrapulmonary progression that incur very specific costs and QALYs. Clinician input has highlighted that the most significant of site-specific costs and health-related quality of life (HRQoL) impacts in advanced ALK-positive NSCLC are in patients with brain or CNS metastases. The CNS is a known and key sanctuary site for progression in advanced ALK-positive NSCLC. In the presence of CNS metastases, patients may experience greater symptom burden in the form of confusion, drowsiness, weakness in the limbs and severe headaches which can negatively impact their HRQoL. Additionally, everyday activities (such as driving) can be affected by CNS metastases. In relation to costs, CNS metastases are commonly associated with severe morbidity and increased economic burden resulting from frequent hospital visits and inpatient stays, increased medical treatment, imaging and radiotherapy.

	Because of these very specific impacts, CNS progression has been modelled separately within the cost-effectiveness model. This approach aligns with the methodology used in the alectinib NICE submission (TA536) – the key comparator to brigatinib. A practical consideration adds to this argument as studies of ALK-inhibitors have only reported CNS progression endpoints alongside PFS and OS data – this emphasises the relevance of intracranial endpoints to clinicians, patients and the overall healthcare system.
ERG response	The ERG has no further comment
10. The company used data from an abstract by Roughley et al. (2014) to compare differences in health-related quality of life between patients with and without CNS-progression. 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). Does it appear to be clinically feasible for this difference in health-related quality of life to be due to CNS-progression? *a) If not, what other factors could be contributing to a difference in health-related quality of life?*	Yes, we believe this is clinically feasible given the significant increase in symptom burden due to CNS metastases (see our answer to Question 9 above). The utility decrement published by Roughley et al. (2014) provides the best available data for the impact of CNS metastases in this patient population. This is the same source which was used in the alectinib NICE submission (TA536). In line with the NICE Decision Support Unit Technical Support Documents, we have applied this using a multiplicative method to reflect the relative change in HRQoL (a 75.4% decrease in utility value). Based on the feedback we have received as part of this appraisal, we consider that a 75.4% decrease in utility is in line with patients' experience. Regarding Question 10 a), we are not aware of any other factors that could be contributing to this difference in health-related quality of life.
ERG response	The ERG has no further comment
Issue 7: Excluding PFS and intracranial PFS within treatment waning	
11. *Do you consider it acceptable for treatment waning to include PFS and intracranial PFS?*	We do not think it is relevant to include treatment waning for PFS and intracranial PFS outcomes. On average, patients receive treatment until progression – based on the ALTA-1L clinical data and

	the feedback from the real-world setting. It is counter-intuitive to discontinue the treatment effect associated with brigatinib whilst patients are on treatment. It is important to note that the model discontinues the treatment effect completely in these scenarios and does not wane it over time – this is the same for OS endpoints. Therefore, scenarios looking at treatment waning for PFS and intracranial PFS remove the brigatinib treatment effect such that the probability of progression is in line with patients treated with crizotinib. This is considered clinically implausible whilst patients are still receiving brigatinib.
ERG response	The ERG has no further comment
12. *What duration do you think is suitable for modelling treatment-waning?*	We would like to hear the feedback from the clinical experts in relation to this question. The duration of treatment effect beyond drug discontinuation is unknown for all ALK inhibitors. However, we consider that whilst patients are receiving treatment, the treatment effect would be expected to be maintained. Therefore, we consider that the application of treatment waning at 3- and 5-years is unlikely and conservative as approximately 37% and 19% of patients remain on treatment with brigatinib, respectively. As previously stated, the model discontinues the treatment effect completely in these scenarios and does not wane it over time. This simplification has been made due to the difficulty in reflecting this complex phenomenon in the model structure. Nevertheless, we consider that these scenarios show an unrealistic lower bound for the duration of the treatment effect. The scenarios presented in the company submission explored treatment waning at 7, 10 and 20 years: • By 7 years, <10% of patients remain on treatment. • By 10 years, <4% of patients remain on treatment. • By 20 years, approximately all patients have discontinued treatment.

	Please see Section B.3.8.3 and Table 63 in the company submission for a more detailed outline of the scenario analyses regarding treatment waning. It is important to note that this phenomenon affects the brigatinib vs. crizotinib comparison only. As the OS profiles for brigatinib and alectinib are considered to be the same, treatment waning does not impact the relative difference nor the cost-effectiveness results for the brigatinib vs. alectinib comparison.
ERG response	The ERG has no further comment

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Post-Appraisal Committee Meeting Submission by Takeda

(as requested by Appraisal Committee D)

10th November 2020

Abbreviations

ALK	Anaplastic lymphoma kinase
CNS	Central nervous system
ERG	Evidence Review Group
FE	Fixed effects
HR	Hazard ratio
ICER	Incremental cost-effectiveness ratio
ITC	Indirect treatment comparison
LY	Life year
MAIC	Matched adjusted indirect comparison
NICE	National Institute for Health and Care Excellence
NMB	Net monetary benefit
NSCLC	Non-small-cell lung cancer
OS	Overall survival
PAS	Patient access scheme
PFS	Progression-free survival
QALY	Quality adjusted life year
RE	Random effects
TSD	Technical support document
WTP	Willingness to pay

Introduction

This document was prepared at the request of NICE Appraisal Committee D and it aims to address some of their concerns with regards to cost-effectiveness under different OS scenarios.

The first NICE Appraisal Committee meeting for brigatinib for the treatment of ALK-positive advanced non-small-cell lung cancer (NSCLC) that has not been previously treated with an ALK inhibitor [ID1468] was held on Wednesday 4th November 2020. During this meeting, there was extensive discussion regarding the indirect treatment comparisons (ITCs) that estimate the relative effect of brigatinib compared with alectinib – particularly in terms of the overall survival (OS) endpoint.

To recap briefly, our base case was presented using an unanchored matched adjusted indirect comparison (MAIC) in an attempt to account for the differences in subsequent therapies observed between the crizotinib arms in the ALTA-1L and ALEX clinical trials – driven by the high rate of protocol-specified treatment crossover in ALTA-1L and the quickly evolving treatment landscape. This resulted in a hazard ratio for OS of 0.832 (95% CI: 0.522 – 1.325) for brigatinib relative to alectinib, which was applied within a cost-effectiveness framework to provide an incremental cost-effectiveness ratio (ICER) in which brigatinib dominated alectinib based on the simple patient access scheme (PAS) applied to brigatinib and the list price for alectinib.

We are aware that the unanchored MAIC approach is contrary to the guidance specified in the NICE Technical Support Document (TSD) 18 – as stated on Slide 17 of the Appraisal Committee slides – when an anchored approach is possible.[4] However, we explored the unanchored MAIC approach as an alternative method due to challenges that were encountered within an anchored MAIC framework when seeking to adjust for the high levels of treatment switching/crossover that were seen in the ALTA-1L trial. This was discussed in detail with the NICE Technical Team during the Decision Problem Meeting (held on March 25th 2020) and was explained within our submission dossier (see Section B.2.9 on page 65 and Section B.3.3.7 on page 107). We recognise the limitations with the unanchored analysis, which is why we have presented it alongside the other 20 analyses we conducted on the OS endpoint. Note: Slide 21 of the Appraisal Committee slides indicates that there were 12 hazard ratios estimated by Takeda for OS, we would like to clarify that there were actually 21 hazard ratios for OS presented in Table 34 and Table 35 of the submission dossier (pages 112-113).

Notably, the base case reflects a cost-effectiveness framework as agreed in discussions with NICE and the ERG during the NICE Decision Problem Meeting held on March 25th 2020. During these discussions, both NICE and the ERG advised that Takeda should undertake a cost utility analysis (vs. alectinib and crizotinib) as the base case, and that a

cost comparison vs. alectinib alone could also be included as an important scenario analysis. This is what was submitted by Takeda and we provided a full justification for our approach in the submission dossier. We continue to believe that there is value in the cost-comparison approach, in which a hazard ratio of 1.0 is applied for the PFS, CNS-PFS and OS endpoints (i.e. brigatinib is assumed to be the same as alectinib across these endpoints).

The ERG's feedback on the relative OS estimates was summarised at the Appraisal Committee meeting – see Slide 21: *"The ERG has not used alternative OS estimates for brigatinib due to markedly high uncertainty in the ITCs conducted by the company (98.6% cross-over with crizotinib in ALTA-1L)"*, *"Of the 12 OS HRs for brigatinib versus alectinib considered by the company, only the unanchored MAIC chosen by the company resulted in a point estimate where brigatinib OS was numerically better than alectinib. The ERG considers the unanchored MAIC to be unsuitable for decision making"* and *"of the 11 other OS HR considered by the company, whilst the ERG considers none are robust enough to be used in favour of the unanchored MAIC, all would suggest that brigatinib would result in ICERs of over £100k per QALY gained compared to alectinib."*

Therefore, it was summarised that there is significant uncertainty in the relative OS estimates for brigatinib vs. alectinib. During the Appraisal Committee meeting, we clarified that the other 11 hazard ratios which the ERG referred to all put the ICER in the South-West quadrant of the cost-effectiveness plane (i.e. brigatinib is less efficacious and less costly compared with alectinib), where the ICER should be interpreted as *savings per QALY lost* (a higher ICER in the South-West quadrant implies a larger cost saving associated with each unit of forgone benefit) and it is the Net Monetary Benefit (NMB) that should be considered (rather than the ICER as stated incorrectly on Slide 21).

Within this document we discuss the impact of OS uncertainty on the cost-effectiveness results and highlight that even across the most extreme of these scenarios, brigatinib remains a cost-effective use of NHS resources at both a £20,000 willingness-to-pay (WTP) threshold and a £30,000 WTP threshold.

Scenario analyses

Table 1 presents the cost-effectiveness results for the 21 OS hazard ratios reported in the submission dossier (see Tables 34 and 35 of the dossier), as well as the four additional scenarios conducted by the ERG exploring the latest data cut for ALEX and the ALESIA clinical trial – see Slide 18 of the Appraisal Committee slides. Note: the latest data for ALEX were presented on 11th May 2020, the same week as the submission date for this indication and so were not included in our analyses. Secondly, for reasons presented at the clarification stage and during the NICE Appraisal Committee meeting, we consider that the most relevant data for alectinib are from the ALEX clinical trial which

are the most representative and generalisable to UK clinical practice. However, the scenarios including the ALESIA trial are presented for completeness in Table 1.

The scenarios demonstrate that across all of the OS analyses, brigatinib dominates alectinib when the ICER is in the South East quadrant of the cost-effectiveness plane. Brigatinib is also shown to have a positive NMB at a WTP threshold of £30,000 and £20,000 when the ICER is in the South West quadrant of the cost-effectiveness plane. These results indicate that brigatinib is cost effective in all of these scenarios. Note: these results are based on the simple PAS being applied to brigatinib and the list price for alectinib.

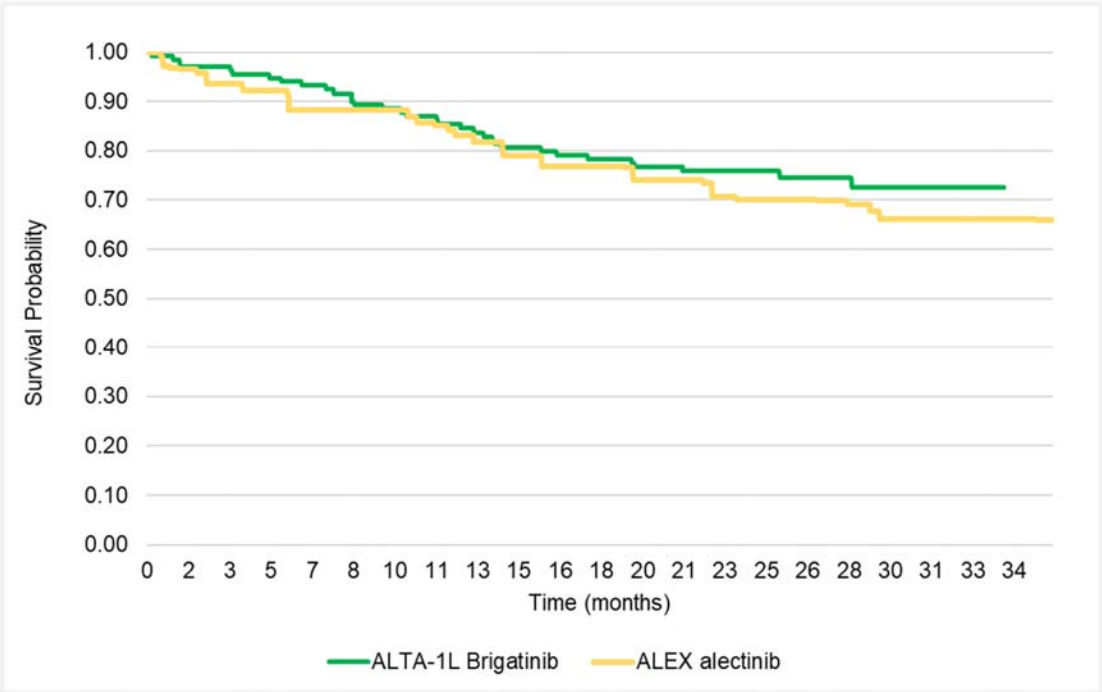
When interpreting the results, we consider it vital that the external validity and clinical plausibility of the scenarios are considered. We recognise the uncertainty associated with the relative OS outcomes between brigatinib and alectinib and the challenge to conclusively demonstrate equivalence based on statistical non-inferiority tests. As stated in the clarification questions and discussed during the Appraisal Committee meeting, the differences in the design of the ALTA-1L and ALEX clinical trials (particularly in relation to treatment switching/crossover), the differences in study populations and the indirect nature of the comparison hinder the ability to estimate meaningful results from these tests. Whilst the exact relative difference on the OS endpoint between brigatinib and alectinib is uncertain, we consider the scale of the difference in life years (LYs) estimated between brigatinib and alectinib in some scenarios to be clinically implausible. For example, some of these scenarios predict up to 3.3 additional LYs gained for alectinib compared with brigatinib. In fact, 18 of the 25 scenarios presented in Table 1 predict more than 6 months of additional OS for alectinib compared with brigatinib. While we recognise some uncertainty associated with the OS comparisons, we believe that neither the clinical data nor the clinical expert opinion already provided to NICE support such a large difference in OS between two medicines that are from the same pharmacological class and which have an identical mechanism of action.

Given the equivalence demonstrated across a range of ITC analyses conducted on the PFS endpoints (both blinded independent review committee [BIRC] and investigator [INV] assessed) – hazard ratio estimates range from 0.97 to 1.05 – and the identical management of patients post-brigatinib or post-alectinib (a point that was re-iterated by clinical experts during the Appraisal Committee meeting), we would also anticipate similar OS profiles. This was supported by the clinical expert feedback we received at two advisory boards before the Appraisal Committee meeting and during the Appraisal Committee meeting by the two clinical experts who participated at the request of NICE. Both clinical experts clearly stated at the Appraisal Committee meeting, and in their submissions to NICE prior to the meeting, that they consider brigatinib to be at least

equivalent to alectinib in clinical efficacy and that they would not expect to see any significant differences between the two medicines in relation to either PFS or OS.

In addition to the detailed ITC analyses that were undertaken, we note that a naïve comparison of the Kaplan Meier plots for OS taken from the ALTA-1L and ALEX trials (see Figure 46 from the company submission dossier) also supports a conclusion of equivalence between brigatinib and alectinib. For ease of reference, Figure 46 from the company submission dossier is reproduced here as Figure 1.

Figure 1 Naive comparison of OS data for brigatinib (ALTA-1L)[1] and alectinib (ALEX)[2]



With respect to the assumption of clinical equivalence between brigatinib and alectinib, it is also worth considering, as recommended by the ERG, the biological/pharmacological plausibility that supports such an assumption:

- Brigatinib and alectinib are both oral, second-generation tyrosine kinase inhibitors with similar mechanisms of action which involves the inhibition of anaplastic lymphoma kinase (ALK).

• Both have demonstrated an increased potency in inhibiting ALK compared to crizotinib. This has translated clinically, as both have shown improved efficacy vs. crizotinib in their respective head-to-head trials in the frontline setting.

• Brigatinib and alectinib were both designed to penetrate the blood-brain barrier effectively and have demonstrated improved intracranial efficacy compared to crizotinib.

• Both medicines have good activity against ALK mutations that confer resistance to crizotinib.

Table 1: Results of scenario analyses exploring uncertainty associated with OS

		OS HR	LYs brigatinib	LYs alectinib	Inc LYs	Savings per QALY lost	NMB at £30K***	NMB at £20K***
Company - 1	Unweighted Bucher - No treatment switching adjustment	1.36	5.87	7.35	-1.48	£150,950*	£96,698	£104,693
Company - 2	Anchored MAIC - No treatment switching adjustment	1.21	5.87	6.77	-0.90	£235,878*	£98,752	£103,548
Company – 3**	**Unanchored MAIC - No treatment switching adjustment (Base Case)**	**0.832**	**5.87**	**5.07**	**0.80**	**Brigatinib is dominant**	**£103,853**	**£99,361**
Company - 4	Company - 1 (Camidge data)	1.241	5.87	6.89	-1.02	£209,435*	£98,322	£103,802
Company - 5	Company - 2 (Camidge data)	1.105	5.87	6.33	-0.46	£448,219*	£100,217	£102,613
Company - 6	Unweighted Bucher - Official switchers - No Re-censoring	1.291	5.87	7.09	-1.22	£178,914*	£97,635	£104,191
Company - 7	Anchored MAIC - Official switchers - No Re-censoring	1.146	5.87	6.50	-0.64	£327,472*	£99,644	£102,994
Company - 8	Unweighted Bucher - Official switchers - Yes Re-censoring	1.383	5.87	7.43	-1.57	£143,905*	£96,390	£104,853
Company - 9	Anchored MAIC - Official switchers - Yes Re-censoring	1.231	5.87	6.85	-0.98	£217,167*	£98,460	£103,721
Company - 10	Unweighted Bucher - All switchers - No Re-censoring	1.293	5.87	7.09	-1.23	£177,914*	£97,607	£104,206
Company - 11	Anchored MAIC - All switchers - No Re-censoring	1.148	5.87	6.51	-0.64	£323,362*	£99,616	£103,012
Company - 12	Unweighted Bucher - All switchers - Yes Re-censoring	1.191	5.87	6.69	-0.82	£256,464*	£99,016	£103,388
Company - 13	Anchored MAIC - All switchers - Yes Re-censoring	1.035	5.87	6.03	-0.16	£1,436,066*	£101,191	£101,911
Company - 14	Company - 6 (Camidge data)	1.179	5.87	6.64	-0.77	£271,793*	£99,183	£103,285
Company - 15	Company - 7 (Camidge data)	1.047	5.87	6.08	-0.21	£1,028,771*	£101,025	£102,036
Company - 16	Company - 8 (Camidge data)	1.263	5.87	6.98	-1.11	£194,543*	£98,019	£103,976
Company - 17	Company - 9 (Camidge data)	1.124	5.87	6.41	-0.54	£381,855*	£99,951	£102,792
Company - 18	Company - 10 (Camidge data)	1.181	5.87	6.65	-0.78	£269,092*	£99,155	£103,303
Company - 19	Company - 11 (Camidge data)	1.048	5.87	6.08	-0.21	£1,005,266*	£101,011	£102,047
Company - 20	Company - 12 (Camidge data)	1.087	5.87	6.25	-0.39	£539,709*	£100,468	£102,439

		OS HR	LYs brigatinib	LYs alectinib	Inc LYs	Savings per QALY lost	NMB at £30K***	NMB at £20K***
Company - 21	Company - 13 (Camidge data)	0.945	5.87	5.62	0.25	Brigatinib is dominant	£102,418	£100,891
ERG - 1	ERG analysis FE ITC + ALESIA	1.54	5.87	7.98	-2.12	£112,073*	£94,350	£105,846
ERG - 2	ERG analysis RE ITC + ALESIA	1.91	5.87	9.10	-3.24	£80,950*	£90,029	£107,699
ERG - 3	ERG analysis FE ITC + ALESIA + updated OS from ALEX	1.57	5.87	8.08	-2.22	£108,012*	£93,973	£106,019
ERG - 4	ERG analysis RE ITC + ALESIA + updated OS from ALEX	1.93	5.87	9.16	-3.29	£79,983*	£89,815	£107,785

The results in this table indicate that brigatinib is cost effective in all of these OS scenarios.

Abbreviations: ERG, Evidence Review Group; FE, fixed effects; ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; HR, hazard ratio; LYs, life years; MAIC, matched adjusted indirect comparison; NMB, net monetary benefit; OS, overall survival; QALY, quality adjusted life year; RE, random effects

* These ICERs are in the South-West quadrant of the cost-effectiveness plane and should be interpreted as the savings per quality adjusted life year (QALY) lost. In this quadrant the Net Monetary Benefit (NMB) should be interpreted and not the ICER.

** Company base case

*** The NMB is calculated as (incremental QALYs x WTP threshold) – incremental costs. A positive NMB indicates that the intervention is cost-effective based on the pre-specified WTP threshold.

Discussion and Conclusion

While we acknowledge the uncertainty associated with the relative OS treatment effect between brigatinib and alectinib, we consider that the equivalence demonstrated by all of the ITCs on the PFS endpoints and the feedback provided by clinical experts who have real-world experience of brigatinib and alectinib support the assumption of a similar OS profile between the two agents. This is also supported by the pharmacological similarity between the two medicines.

Previous NICE appraisals that included cost-comparison frameworks have not had to demonstrate statistical equivalence through non-inferiority tests when assessing the applicability of the cost-comparison framework. In terms of precedence, we note in particular the recent case of venetoclax plus rituximab for previously treated chronic lymphocytic leukaemia CLL [TA561][3] which received a positive recommendation from Appraisal Committee C. We have attached an assessment of TA561, in which we point out the similarities and differences between that appraisal and this current one (see Appendix 1). When considering precedence, we would ask that NICE looks at decisions across all four of its Appraisal Committees.

Across all of the scenarios exploring the uncertainty in the relative OS benefit (see Table 1), brigatinib remains a cost-effective treatment when compared to alectinib for patients with ALK-positive advanced NSCLC that has not been previously treated with an ALK inhibitor– at WTP thresholds of £30,000 and £20,000. The NMBs are all positive and consistent across these scenarios (with savings per QALY lost of £99,361 - £107,785, based on the £20,000 WTP threshold). There are some extreme scenarios that predict a greater than 6-month OS gain with alectinib compared to brigatinib. However, we do not consider these scenarios to be clinically plausible based on the available clinical data and the known similarities between the two medicines. We also do not believe that clinical experts would regard these scenarios as clinically plausible. Nevertheless, even under these clinically implausible scenarios, brigatinib remains a cost-effective use of NHS resources.

Considering all of the evidence presented to NICE we believe it would be reasonable for the Committee to issue a positive recommendation for brigatinib for ALK-positive advanced NSCLC that has not been previously treated with an ALK inhibitor. Such a recommendation would provide patients and clinicians with a welcome additional treatment option in this setting.

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Appendix 1

Venetoclax with rituximab for previously treated chronic lymphocytic leukaemia (CLL) – [TA561]

SUMMARY

- Company: AbbVie
- Outcome: Recommended
- Publication Date: 27 February 2019
- Initial negative ACD issued: October 2018
- NICE Appraisal Committee: C
- Two committee meetings held
- In the ACD, the NICE committee requested a cost-comparison vs. the SoC
- Deemed ineligible for End of Life or Cancer Drugs Fund
- No head-to-head evidence to standard of care (SoC), Ibrutinib

CLINICAL

- No direct evidence; comparator in the phase 3 MURANO trial was "bendamustine plus rituximab" which was rarely used in current practice.
- The committee requested a cost-comparison in the negative ACD- *"because of uncertainties in the company's modelling, a cost comparison of venetoclax plus rituximab and ibrutinib is requested from the company, which might address these uncertainties"*.
- Request for a cost-comparison was based on several factors:

  o Although there was no head-to-head evidence, clinical experts maintained that venetoclax plus rituximab had similar efficacy to ibrutinib

  o The MAIC conducted by both AbbVie and the ERG were both deemed to be 'limited' by the committee – in some scenarios venetoclax plus rituximab was more efficacious and in others, ibrutinib was more efficacious.

COST-EFFECTIVENESS

- NICE stated that 'there is no one plausible ICER' due to limitations in the efficacy data
- Reliance on limited and biased (patients in the comparator arm were healthier) ITCs to estimate the clinical benefits.
- Mismatch between modelled costs and benefits – stopping rule applied after two years (consistent with trial treatment duration) but benefits accrued over 20 years.

COMPARISON WITH BRIGATINIB APPRAISAL [ID1468]

Similarities to brigatinib vs. alectinib

a) there were no head-to-head studies;

b) the data was fairly immature;

c) venetoclax was considered 'at least as good' as the existing SoC ibrutinib and physicians 'welcomed a range of options';

d) there were no superiority/non-inferiority studies or tests presented to support equivalence;

e) the unanchored MAIC had significant limitations;

f) clinical expert opinion supported the equivalence claim to the SoC.

Differences to brigatinib vs. alectinib

a) company did not present a scenario or make a case for a cost-comparison - the committee requested this;

b) a cost-comparison was accepted despite the following:

• venetoclax and ibrutinib are from different pharmacological classes

• the two agents have a very different mechanism of action – venetoclax is a B-cell lymphoma-2 (BCL-2) inhibitor that targets a specific protein, BCL-2;while ibrutinib is a B-cell receptor antagonist which targets the Bruton's tyrosine kinase (BTK) protein with the aim of disrupting cell growth signals.

• the cost comparison is comparing two medicines (venetoclax plus rituximab) with one medicine (ibrutinib).

c) there were significant mismatches between the modelling and the clinical trial;

d) the company's long-term extrapolation of benefits was a limitation.

NICE CONCLUSIONS

- The Committee concluded that neither the company's MAIC nor the ERG's network meta-analysis were ideal but, because there were no other analyses, it agreed that they can be used for decision making.
- Committee agreed that because of the lack of trial data directly comparing venetoclax plus rituximab with ibrutinib, and limitations in the MAIC and the network meta-analysis, it could not decide which analysis was more appropriate for decision making.
- Therefore, it was not able to determine the most plausible ICER.
- The Committee concluded that even though the relative treatment effect of venetoclax plus rituximab compared with ibrutinib was uncertain, both sets of analyses produced ICERs within the range considered to be an acceptable use of NHS resources based on the cost per QALY lost or gained.
- The cost-comparison analysis provides supporting evidence that venetoclax plus rituximab is a cost-effective use of NHS resources.
- The company based the cost-comparison analysis on the assumption of equal efficacy between venetoclax plus rituximab and ibrutinib.
- The Committee concluded that this was appropriate based on the clinical experts' opinion and because there was no evidence of a difference in treatment effect.

PRECEDENCE POINTS (RELEVANT TO ID1468)

- Cost comparison was proposed by Committee C as part of the 'solution' to the lack of head-to-head evidence and a highly uncertain unanchored MAIC output.
- The cost-comparison analysis was based on an assumption of equal efficacy between venetoclax plus rituximab and ibrutinib.
- Committee C concluded that a cost-comparison analysis was appropriate based on clinical experts' opinion and because there was no evidence of a difference in treatment effect.
- Cost-comparison was accepted between two medicines that are not even from the same pharmacological class – by comparison brigatinib and alectinib are almost identical in all key respects.
- Cost comparison compared two medicines with only one medicine.
- The Committee was not able to determine the most plausible ICER.
- FAD contains no ICERs, just a statement that *"both sets of analyses (MAIC and NMA) produced ICERs within the range considered to be an acceptable use of NHS resources".*

ERG STA REPORT Addendum 1

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]

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number 128262

Completed 16th November 2020

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

1 INTRODUCTION

As part of the National Institute for Health and Care Excellence (NICE) Single Technology Appraisal (STA) process to consider the clinical and cost effectiveness of brigatinib for the treatment of anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) in patients who have not previously received an ALK inhibitor, the NICE Appraisal Committee asked the company (Takeda) to provide incremental cost effectiveness ratios (ICERs) per quality adjusted life year (QALYs) for all of the 21 overall survival (OS) hazard ratios (HRs) that had been presented in the original company submission (CS, Table 34 and Table 35).

The ERG was asked by NICE to:

- replicate the company's ICERs and net monetary benefit (NMB) analyses with the inclusion of the confidential Patient Access Scheme (PAS) for alectinib
- confirm if the ICERs, with the inclusion of the confidential PAS for alectinib, still fall into the South-West quadrant
- confirm if the net monetary benefit analyses results remain positive when the alectinib PAS is incorporated.

The ERG was not able to produce results that exactly matched the company results. Further, the company did not correct the utility algorithm model error identified by the ERG in the original report. The ERG's cost effectiveness results, after correcting the utility algorithm error and using the proposed PAS price for brigatinib and current list prices for alectinib and subsequent therapies, are presented in Table 1. The ERG also included cost effectiveness results using OS HRs generated using data from the ALESIA trial (ERG report, Section 9.3, Table 40).

Results showed that use of two of the 25 OS HRs generated ICERs per QALY gained that did not fall in the South-West quadrant (company base case [scenario 3] and company scenario 21). For all 25 OS HRs considered, the NMB for brigatinib versus alectinib was positive at £20,000 and £30,000 per QALY gained.

Table 1 Results of scenario analyses exploring uncertainty associated with OS (ERG corrected base case, proposed PAS price for brigatinib and list prices for alectinib and subsequent therapies)

		OS HR	LYs brigatinib	LYs alectinib	Inc LYs	Savings per QALY lost	NMB at £30K***	NMB at £20K***
Company - 1	Unweighted Bucher - No treatment switching adjustment	1.36	5.87	7.35	-1.48	*£158,157	£104,753	£112,927
Company - 2	Anchored MAIC - No treatment switching adjustment	1.21	5.87	6.77	-0.90	*£241,847	£98,418	£103,063
Company – 3**	**Unanchored MAIC - No treatment switching adjustment (Base Case)**	**0.832**	**5.87**	**5.07**	**0.80**	**Brigatinib is dominant**	**£103,539**	**£99,152**
Company - 4	Company - 1 (Camidge data)	1.241	5.87	6.89	-1.02	*£214,477	£98,709	£104,059
Company - 5	Company - 2 (Camidge data)	1.105	5.87	6.33	-0.46	*£458,884	£100,384	£102,725
Company - 6	Unweighted Bucher - Official switchers - No Re-censoring	1.291	5.87	7.09	-1.22	*£185,666	£105,561	£112,342
Company - 7	Anchored MAIC - Official switchers - No Re-censoring	1.146	5.87	6.50	-0.64	*£336,151	£99,205	£102,445
Company - 8	Unweighted Bucher - Official switchers - Yes Re-censoring	1.383	5.87	7.43	-1.57	*£150,791	£104,473	£113,122
Company - 9	Anchored MAIC - Official switchers - Yes Re-censoring	1.231	5.87	6.85	-0.98	*£222,510	£98,159	£103,257
Company - 10	Unweighted Bucher - All switchers - No Re-censoring	1.293	5.87	7.09	-1.23	*£184,596	£105,535	£112,361
Company - 11	Anchored MAIC - All switchers - No Re-censoring	1.148	5.87	6.51	-0.64	*£331,825	£99,180	£102,466
Company - 12	Unweighted Bucher - All switchers - Yes Re-censoring	1.191	5.87	6.69	-0.82	*£259,326	£106,752	£111,407
Company - 13	Anchored MAIC - All switchers - Yes Re-censoring	1.035	5.87	6.03	-0.16	*£1,554,871	£100,577	£101,236
Company - 14	Company - 6 (Camidge data)	1.179	5.87	6.64	-0.77	*£278,810	£98,799	£102,770
Company - 15	Company - 7 (Camidge data)	1.047	5.87	6.08	-0.21	*£1,083,683	£100,426	£101,379
Company - 16	Company - 8 (Camidge data)	1.263	5.87	6.98	-1.11	*£199,087	£97,764	£103,546
Company - 17	Company - 9 (Camidge data)	1.124	5.87	6.41	-0.54	*£393,152	£99,479	£102,218
Company - 18	Company - 10 (Camidge data)	1.181	5.87	6.65	-0.78	*£276,016	£98,774	£102,789

		OS HR	LYs brigatinib	LYs alectinib	Inc LYs	Savings per QALY lost	NMB at £30K***	NMB at £20K***
Company - 19	Company - 11 (Camidge data)	1.048	5.87	6.08	-0.21	*£1,058,026	£100,414	£101,391
Company - 20	Company - 12 (Camidge data)	1.087	5.87	6.25	-0.39	*£558,709	£99,936	£101,826
Company - 21	Company - 13 (Camidge data)	0.945	5.87	5.62	0.25	Brigatinib is dominant	£101,646	£100,119
ERG - 1	ERG analysis FE ITC + ALESIA	1.54	5.87	7.98	-2.12	*£114,450	£94,486	£105,675
ERG - 2	ERG analysis RE ITC + ALESIA	1.91	5.87	9.10	-3.24	*£82,633	£90,606	£107,820
ERG - 3	ERG analysis FE ITC + ALESIA + updated OS from ALEX	1.57	5.87	8.08	-2.22	*£110,294	£94,149	£105,874
ERG - 4	ERG analysis RE ITC + ALESIA + updated OS from ALEX	1.93	5.87	9.16	-3.29	*£81,647	£90,414	£107,920

ERG=Evidence Review Group; FE=fixed effects; ICER=incremental cost effectiveness ratio; ITC=indirect treatment comparison; HR=hazard ratio; LYs=life years; MAIC=matching adjusted indirect comparison; NMB=net monetary benefit; OS=overall survival; QALY=quality adjusted life year; RE=random effects; WTP=willingness to pay

* These ICERs are in the South-West quadrant of the cost effectiveness plane and should be interpreted as the savings per QALY lost. A value above the normally accepted willingness to pay threshold for a QALY gained indicates a treatment is cost effective

** Company base case

*** The NMB is calculated as (incremental QALYs x WTP threshold) – incremental costs. A positive NMB indicates that the intervention is cost effective based on the pre-specified WTP threshold

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Clarification questions

June 2020

File name	Version	Contains confidential information	Date
ClarificationResponses_ID1468_BrigatinibFL_NSCLC_v1.0_REDACTED	1.0	Yes	19/06/2020

Section A: Clarification on effectiveness data

ALTA-1L trial

A1. <u>Priority Question:</u> Are the versions of the trial protocol (version 2, dated 21 September 2016) and the statistical analysis plan (version 3, dated 27 March 2018), available as supplementary material to the Camidge et al publication, the most up to date versions of the ALTA-1L trial protocol and statistical analysis plan? If more recent versions are available, please provide these.

<u>Response</u>: No, these are not the most recent versions. The most up-to-date versions of the trial protocol and statistical analysis plan for ALTA-1L are available and provided in separate files, along with these clarification responses.

A2. In the company submission (CS), Table 13 of Appendix D (RCT Risk of bias for the ALTA-1L trial of brigatinib), it is stated that: “Specific instructions for randomisation were supplied in a study reference manual.” Please provide this study reference manual or specific details of the random sequence generation and allocation concealment methods.

<u>Response</u>: The sequence of randomisation was generated using Medidata RSTM (formerly balance) integrated with electronic data capture (EDC). Patients were randomly assigned (1:1) using an interactive web-based response system which randomly assigned patients by study arms with consideration to the stratification factors (presence of brain metastases and completion of at least one cycle of previous chemotherapy).

Regarding allocation concealment, ALTA-1L is an open-label study; patients and the investigators were unblinded to treatment assignment. However, the blinded independent review committee (BIRC), responsible for evaluating the radiographic images collected during the study for the primary and all intracranial endpoints, were blinded to treatment assignment and all patient information.

Assessment of proportional hazards in the ALTA-1L trial

A3. <u>Priority Question</u>: It is stated (CS, page 40) that blinded independent review centre (BIRC)-assessed progression-free survival (PFS) was analysed using the "Cox regression model with the stratification factors as covariates."

a. **Is the Schoenfeld residual plot and test of BIRC-assessed PFS (CS, Figure 26) also based on this Cox model with the stratification factors as covariates?**

<u>Response:</u> The Schoenfeld residual plot and test of BIRC-assessed PFS was based on a Cox model with only treatment arm included as an explanatory variable – no covariates or stratification factors were considered. This aligned with the parametric modelling approach adopted within the economic model (i.e. independent curves fit to each treatment arm, with no covariates). These analyses were conducted in R using the function cox.zph in the Survival package.[1, 2] Proportional hazard tests and diagnostics were based on weighted residuals.

b. **Similarly, please clarify which analysis model the Schoenfeld residual plot and test of overall survival (OS) (CS, Figure 39) was based on.**

<u>Response:</u> The same methods were employed for OS as per BIRC-assessed PFS (see response to A3a).

A4. <u>Priority Question</u>: Please provide log cumulative hazard plots, Schoenfeld residuals plots and Schoenfeld Test p-values for the following analyses, with exact details of which analysis models the Schoenfeld residual plot and test are based on:

a. **Subgroup analysis of BIRC-assessed PFS for patients with or without brain metastases**

b. **Subgroup analysis of BIRC-assessed PFS for patients treated or not treated with prior chemotherapy**

c. **PFS by investigator assessment**

d. **Intracranial PFS**

e. **Duration of response.**

Response: The same methodology described in the response to question A3a above was employed to derive the requested analyses. The log cumulative hazard plots are depicted below on the left and the Schoenfeld residuals to the right, including the relevant p-values.

a. Subgroup analysis of BIRC-assessed PFS for patients with or without brain metastases

Patients with baseline brain metastases

Patients without baseline brain metastases

b. Subgroup analysis of BIRC-assessed PFS for patients treated or not treated with prior chemotherapy

Patients treated with prior chemotherapy

Patients not treated with prior chemotherapy

c. PFS by investigator assessment

d. Intracranial PFS

BIRC-assessed intracranial PFS

e. Duration of response

BIRC-assessed confirmed response

ALEX trial

A5. The source of subsequent therapies described in Table 7 of the CS for the ALEX trial is stated to be the alectinib NICE submission (TA536). It is stated in the TA536 committee papers (Pre-Meeting Briefing, slide 43) that subsequent therapies were only documented for 41% of the ALEX population. Please clarify whether the data in Table 7 are based on this 41% of the ALEX trial population or whether additional information was available for the whole ALEX trial population.

Response: The data presented in Table 7 of the CS are based on the data that were available as part of the TA536 process. In relation to subsequent therapies, this includes only the 41% of the ALEX population for which such information is available. To our knowledge, no further information was available for incorporation within our submission.

Systematic literature review search results

A6. The numbers in the text describing the study selection process (CS, Appendix D, Section D.1.1.5) differ from the numbers included in the accompanying PRISMA diagram (Figure 1). Please clarify which numbers are correct.

Response: The accompanying PRISMA diagram reflects the accurate numbers for the original and all subsequent updated literature searches.

A7. In the PRISMA diagram (CS, Appendix D, Section D.1.1.5) it is stated that 18 interventional trials were eligible for inclusion in the systematic literature review (SLR). However, nine trials are listed in Table 4 (Publications identified in the SLR for randomised clinical trials) and 15 trials are listed in Table 5 (References associated with each included trial). Please explain the differences in numbers between the PRISMA diagram, Table 4 and Table 5.

Response: The studies listed in Table 4 in the CS excluded randomised combination trials identified in the SLR. The information from both Table 4 and 5 in the CS have been consolidated and updated in Table 1 below to align with the PRISMA diagram (CS, Figure 1, Appendix D.1.1.5). Table 1 accurately reflects the outputs from the most up-to-date literature review (i.e. 18 identified interventional studies); the references associated with each trial are also presented as requested.

Table 1: Interventional studies identified in the original 2018 SLR and the subsequent 2019 and 2020 updates

Study intervention	Trial ID/ identifier	References
1. Brigatinib	ALTA-1L	Tiseo, M.; Popat, S.; Gettinger, S. N.; Peters, S.; Haney, J.; Kerstein, D.; Camidge, D. R. Design of ALTA-1 L (ALK in lung cancer trial of brigatinib in first-line), a randomized phase 3 trial of brigatinib (BRG) versus crizotinib (CRZ) in tyrosine kinase inhibitor (TKI)-naive patients (pts) with advanced anaplastic lymphoma kinase (ALK)positive non-small cell lung cancer (NSCLC). Journal of Clinical Oncology 2017;35(): Popat, S; Tiseo, M; Gettinger, S; Peters, S; Haney, J; Kerstein, D; Camidge, R. ALTA-1L (ALK in lung cancer trial of BrigAtinib in 1st Line): a randomized, phase 3 trial of brigatinib (BRG) versus crizotinib (CRZ) in tyrosine kinase inhibitor (TKI)-naive, advanced anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC). Annals of oncology. Conference: 41st European society for medical oncology congress, ESMO 2016. Denmark. 2016;27(no pagination): ALTA-1L Study: A Phase 3 Study of Brigatinib Versus Crizotinib in ALK-positive Advanced Non-Small Cell Lung Cancer Patients (ALTA-1L). NCT02737501. Clinical Trials registry. https://clinicaltrials.gov/ct2/show/NCT02737501 A Phase 3 Multicenter Open-label Study of Brigatinib versus Crizotinib in ALK-positive Advanced Lung Cancer patients. EUCTR2015-003447-19-GB. https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2015-003447-19 A Phase 3 Multicenter Open-label Study of Brigatinib (AP26113) Versus Crizotinib in Patients With ALK-positive Advanced Lung Cancer. DRKS00011682. http://www.drks.de/DRKS00011682 Takeda Pharmaceuticals: ALTA-1L: Data on file
2. Alectinib	ALEX	Camidge, D Ross; Peters, Solange; Mok, Tony; Gadgeel, Shirish M; Cheema, Parneet K; Pavlakis, Nick; De Marinis, Filippo; Stroyakovskiy, Daniil L; Cho, Byoung Chul; Zhang, Li. Updated efficacy and safety data from the global phase III ALEX study of alectinib (ALC) vs crizotinib (CZ) in untreated advanced ALK+ NSCLC. 2018;(): American Society of Clinical Oncology 2018 Perol, M.; Peters, S.; Pavlakis, N.; Levchenko, E.; Platania, M.; Oliveira, J.; Novello, S.; Karagiannis, T.; Zeaiter, A.; Dziadziuszko, R. Patient-reported outcomes (PROs) in ALEX: A phase III study of alectinib (ALEC) vs crizotinib (CRIZ) in non-small-cell lung cancer (NSCLC). Journal of Thoracic Oncology 2018;13 (4 Supplement 1)():S80-S81. Peters, S; Camidge, Dr; Shaw, At; Gadgeel, S; Ahn, Js; Kim, Dw; Ou, Si; Pérol, M; Dziadziuszko, R; Rosell, R; Zeaiter, A; Mitry, E; Golding, S; Balas, B; Noe, J; Morcos, Pn; Mok, T. Alectinib versus Crizotinib in Untreated ALK-Positive Non-Small-Cell Lung Cancer. New England journal of medicine 2017;377(9):829-838 Shaw, At; Peters, S; Mok, T; Gadgeel, Sm; Ahn, Js;

Study intervention	Trial ID/ identifier	References
		Ignatius, Ou S-H; Perol, M; Dziadziuszko, R; Kim, D-W; Rosell, R; Zeaiter, Ah; Liu, T; Golding, S; Balas, B; Noe, J; Morcos, Pn; Camidge, R. Alectinib Versus Crizotinib in Treatment-Naive Advanced ALK Positive Non-Small Cell Lung Cancer (NSCLC): primary Results of the Global Phase III ALEX Study. Journal of clinical oncology. Conference: 2017 Annual Meeting of the American society of clinical oncology, ASCO. United states 2017;35(15 Supplement 1) (no pagination): A Study Comparing Alectinib With Crizotinib in Treatment-Naive Anaplastic Lymphoma Kinase-Positive Advanced Non-Small Cell Lung Cancer Participants (ALEX). NCT02075840. https://clinicaltrials.gov/ct2/show/NCT02075840
3. Alectinib	J-ALEX	Hida, T.; Nokihara, H.; Kondo, M.; Kim, Y. H.; Azuma, K.; Seto, T.; Takiguchi, Y.; Nishio, M.; Yoshioka, H.; Imamura, F.; Hotta, K.; Watanabe, S.; Goto, K.; Satouchi, M.; Kozuki, T.; Shukuya, T.; Nakagawa, K.; Mitsudomi, T.; Yamamoto, N.; Asakawa, T.; Asabe, R.; Tanaka, T.; Tamura, T. 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(10089):29-39. Kim, Y.; Hida, T.; Nokihara, H.; Kondo, M.; Azuma, K.; Seto, T.; Takiguchi, Y.; Nishio, M.; Yoshioka, H.; Imamura, F.; Hotta, K.; Watanabe, S.; Goto, K.; Nakagawa, K.; Mitsudomi, T.; Yamamoto, N.; Kuriki, H.; Asabe, R.; Tanaka, T.; Tamura, T. Alectinib (ALC) versus crizotinib (CRZ) in ALK-positive non-small cell lung cancer (ALK+ NSCLC): Primary results from phase III study (J-ALEX). Journal of Thoracic Oncology 2017;12 (1 Supplement 1)():S378-S379. Nishio, M.; Nakagawa, K.; Mitsudomi, T.; Yamamoto, N.; Tanaka, T.; Kuriki, H.; Zeaiter, A.; Tamura, T. Analysis of central nervous system efficacy in the J-ALEX study of alectinib versus crizotinib in ALK-positive non-small-cell lung cancer. Lung Cancer 2018;121():37-40. Nokihara, H.; Hida, T.; Kondo, M.; Hak Kim, Y.; Azuma, K.; Seto, T.; Takiguchi, Y.; Nishio, M.; Yoshioka, H.; Imamura, F.; Hotta, K.; Watanabe, S.; Goto, K.; Nakagawa, K.; Mitsudomi, T.; Yamamoto, N.; Kuriki, H.; Asabe, R.; Tanaka, T.; Tamura, T. Alectinib (ALC) versus crizotinib (CRZ) in ALK-inhibitor naive ALK-positive non-small cell lung cancer (ALK+ NSCLC): Primary results from the J-ALEX study. Journal of Clinical Oncology. Conference 2016;34(Supplement 15): Takiguchi, Y; Hida, T; Nokihara, H; Kondo, M; Kim, Yh; Azuma, K; Seto, T; Nishio, M; Yoshioka, H; Imamura, F; Hotta, K; Watanabe, S; Goto, K; Nakagawa, K; Mitsudomi, T; Yamamoto, N; Kuriki, H; Inagaki, N; Tanaka, T; Tamura, T. Updated efficacy and safety of the j-alex study comparing alectinib (ALC) with crizotinib (CRZ) in ALK-inhibitor naive ALK fusion positive non-small cell lung cancer (ALK+ NSCLC). Journal of clinical oncology. Conference: 2017 annual meeting of the american society of clinical oncology, ASCO. United

Study intervention	Trial ID/ identifier	References
		states 2017;35(15 Supplement 1) (no pagination): J-ALEX study. JPRN-JapicCTI-132316. http://www.clinicaltrials.jp/user/showCteDetailE.jsp?japicId=JapicCTI-132316
4. Alectinib	ALESIA	Zhou, C.; Kim, S. W.; Reungwetwattana, T.; Zhou, J.; Zhang, Y.; He, J.; Yang, J. J.; Cheng, Y.; Lee, S. H.; Bu, L.; Xu, T.; Yang, L.; Wang, C.; Liu, T.; Morcos, P. N.; Lu, Y.; Zhang, L. Alectinib versus crizotinib in untreated Asian patients with anaplastic lymphoma kinase-positive non-small-cell lung cancer (ALESIA): a randomised phase 3 study. The Lancet Respiratory Medicine 2019;7(5):437-446. Zhou, C.; Lu, Y.; Kim, S. W.; Reungwetwattana, T.; Zhou, J.; Zhang, Y.; He, J.; Yang, J. J.; Cheng, Y.; Lee, S. H. Primary results of ALESIA: Phase III, randomised openlabel study of alectinib (ALC) vs crizotinib (CRZ) in Asian patients (pts) with treatment-naive ALK+ advanced non-small-cell lung cancer (NSCLC). Annals of Oncology. Conference: European Society for Medical Oncology Asia Congress, ESMO 2018;29(Supplement 9): Zhou, C.; Lu, Y.; Kim, S. W.; Reungwetwattana, T.; Zhou, J.; Zhang, Y.; He, J.; Yang, J. J.; Cheng, Y.; Lee, S. H.; Bu, L.; Xu, T.; Yang, L.; Wang, C.; Morcos, P. N.; Mitry, E.; Liu, T.; Zhang, L. Primary results of ALESIA: A randomised, phase III, open-label study of alectinib vs crizotinib in Asian patients with treatment-naive ALK plus advanced NSCLC. Annals of Oncology 2018;29:740-740.
5. Ceritinib	ASCEND-1	Kim D-W, Mehra R, Tan DSW, Felip E, Chow LQM, Camidge DR, et al. Activity and safety of ceritinib in patients with ALK -rearranged non-small-cell lung cancer (ASCEND-1): updated results from the multicentre, open-label, phase 1 trial. The Lancet Oncology. 2016;17(4):452-63. Kim D-W, Mehra R, Tan D. Correction to Lancet Oncol 2016; 17: 456. The Lancet Oncology. 2016;17(5). Tan D, Felip E, Chow LQ, Sharma S, Urban P, Malet I, et al. P3.02a-015 Ceritinib as First-Line Therapy in Patients with ALK-Rearranged Non-Small Cell Lung Cancer: ASCEND-1 Subgroup Analysis. Journal of Thoracic Oncology. 2017;12(1):S1169-S70. A Dose Escalation/Expansion Study of LDK378 in Patients With Tumors Characterized by Genetic Abnormalities in Anaplastic Lymphoma Kinase. NCT01283516. Clinical Trials Registry. https://clinicaltrials.gov/ct2/show/NCT01283516
6. Ceritinib	ASCEND-4	De Castro, G.; Shao-Weng Tan, D.; Crino, L.; Wu, Y. L.; Paz-Ares, L.; Wolf, J.; Geater, S.; Orlov, S.; Cortinovis, D.; Yu, C. J.; Hochmair, M.; Cortot, A.; Tsai, C. M.; Moro-Sibilot, D.; Campelo, R. G.; Branle, F.; Sen, P.; McCulloch, T.; Soria, J. C. First-line ceritinib versus chemotherapy in patients with ALK-rearranged (ALK+) NSCLC: A randomized, phase 3 study (ASCEND-4). Journal of Thoracic Oncology 2017;12 (1 Supplement 1)():S7

Study intervention	Trial ID/ identifier	References
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7. Ceritinib	ASCEND-7	L.Q. Chow, F. Barlesi, E.M. Bertino, M.J. van den Bent, H. Wakelee, P.Y. Wen, C. Chiu, S. Orlov, M. Majem, R. Chiari, M. McKeage, C. Yu, F.K. Hurtado, P. Cazorla Arratia, Y. Song, F. Branle, M. Shi, D. Kim. Results of the ASCEND-7 phase II study evaluating ALK inhibitor (ALKi) ceritinib in patients (pts) with ALK+ non-small cell lung cancer (NSCLC) metastatic to the brain. 2019
8. Ceritinib	ASCEND-8	Cho, B. C.; Kim, D. W.; Bearz, A.; Laurie, S. A.; McKeage, M.; Borra, G.; Park, K.; Kim, S. W.; Ghosn, M.; Ardizzoni, A.; Maiello, E.; Greystoke, A.; Yu, R.; Osborne, K.; Gu, W.; Scott, J. W.; Passos, V. Q.; Lau, Y. Y.; Wrona, A. ASCEND-8: A Randomized Phase 1 Study of Ceritinib, 450 mg or 600 mg, Taken with a Low-Fat Meal versus 750 mg in Fasted State in Patients with Anaplastic Lymphoma Kinase (ALK)-Rearranged Metastatic Non-Small Cell Lung Cancer (NSCLC). Journal of Thoracic Oncology 2017;12(9):1357-1367 Cho, Bc; Obermannova, R; Bearz, A; Kim, D; Orlov, S; Borra, G; Kim, S; Postmus, Pe; Laurie, S; Park, K; Geater, S; Bettini, Ac; Osborne, K; Passos, Vq; Chen, Z; Dziadziuszko, R. Efficacy and updated safety of ceritinib (450 Mg or 600 Mg) with Low-Fat Meal vs 750 Mg Fasted in ALK+ metastatic NSCLC. Journal of thoracic oncology. Conference: 18th world conference on lung cancer of the international association for the study of lung cancer, IASLC 2017. Japan 2017;12(11 Supplement 2):S1757 Dziadziuszko, R.; Kim, D. W.; Bearz, A.; Laurie, S.; McKeage, M.; Park, K.; Kim, S. W.; Passos, V. Q.; Osborne, K.; Lau, Y. Y.; Gu, J.; Cho, B. C. Phase 1 study of ceritinib 450 mg or 600 mg taken with a low-fat meal versus 750 mg in fasted state in ALK+ metastatic NSCLC. Journal of Thoracic Oncology 2017; 12 (1 Supplement 1)():S1184.

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9. Crizotinib	PROFILE 1001	Camidge, D. R.; Bang, Y. J.; Kwak, E. L.; Iafrate, A. J.; Varella-Garcia, M.; Fox, S. B.; Riely, G. J.; Solomon, B.; Ou, S. H.; Kim, D. W.; Salgia, R.; Fidias, P.; Engelman, J. A.; Gandhi, L.; Janne, P. A.; Costa, D. B.; Shapiro, G. I.; Lorusso, P.; Ruffner, K.; Stephenson, P.; Tang, Y.; Wilner, K.; Clark, J. W.; Shaw, A. T. Activity and safety of crizotinib in patients with ALK-positive non-small-cell lung cancer: updated results from a phase 1 study. Lancet Oncology 2012; 13 (10): 1011-9 A Study Of Oral PF-02341066, A C-Met/Hepatocyte Growth Factor Tyrosine Kinase Inhibitor, In Patients With Advanced Cancer (PROFILE 1001). NCT00585195. Clinical Trials Registry. https://clinicaltrials.gov/ct2/show/NCT00585195
10. Crizotinib	PROFILE 1005	Blackhall, F.; Ross Camidge, D.; Shaw, A. T.; Soria, J. C.; Solomon, B. J.; Mok, T.; Hirsh, V.; Janne, P. A.; Shi, Y.; Yang, P. C.; Pas, T.; Hida, T.; Carpeno, J. C.; Lanzalone, S.; Polli, A.; Iyer, S.; Reisman, A.; Wilner, K. D.; Kim, D. W. 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(3):e000219 An Investigational Drug, PF-02341066, Is Being Studied In Patients With Advanced Non-Small Cell Lung Cancer With A Specific Gene Profile Involving The Anaplastic Lymphoma Kinase (ALK) Gene. NCT00932451. Clinical Trials Registry. https://clinicaltrials.gov/ct2/show/NCT00932451
11. Crizotinib	PROFILE 1007	Blackhall, F.; Kim, D. W.; Besse, B.; Nokihara, H.; Han, J. Y.; Wilner, K. D.; Reisman, A.; Iyer, S.; Hirsh, V.; Shaw, A. T. Patient-Reported Outcomes and Quality of Life in PROFILE 1007: A Randomized Trial of Crizotinib Compared with Chemotherapy in Previously Treated Patients with ALK-Positive (vol 9, pg 1625, 2014). Journal of Thoracic Oncology 2015;10(11):1657-1657 Blackhall, F.; Kim, D. W.; Besse, B.; Nokihara, H.; Han, J. Y.; Wilner, K. D.; Reisman, A.; Iyer, S.; Hirsh, V.; Shaw, A. T. Patient-reported outcomes and quality of life in PROFILE 1007: a randomized trial of crizotinib compared with chemotherapy in previously treated patients with ALK-positive advanced non-small-cell lung cancer.[Erratum appears in J Thorac Oncol. 2015 Nov;10(11):1657]. Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer 2014;9(11):1625-33 An Investigational Drug, PF-02341066 Is Being Studied Versus Standard Of Care In Patients With Advanced Non-Small Cell Lung Cancer With A Specific Gene Profile

Study intervention	Trial ID/ identifier	References
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12. Crizotinib	PROFILE 1014	Blackhall, F.; Mok, T.; Nishio, M.; Kim, D. W.; Wilner, K. D.; Reisman, A.; Iyer, S.; Solomon, B. J. Quality of life for crizotinib vs. Chemotherapy in Asian ALK-Positive NSCLC Patients. Journal of Thoracic Oncology 2015;2)():S378-S379 A Clinical Trial Testing The Efficacy Of Crizotinib Versus Standard Chemotherapy Pemetrexed Plus Cisplatin Or Carboplatin In Patients With ALK Positive Non Squamous Cancer Of The Lung (PROFILE 1014). CTRI/2012/01/002323. http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=3905 Felip, E; Blackhall, Fh; Mok, T; Cappuzzo, F; Wilner, Kd; Reisman, A; Iyer, S; Solomon, Bj. Impact of crizotinib on patient-reported general health status compared with chemotherapy in patients with no prior systemic treatment

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14. Lorlatinib	NCT01970865	Felip1, E; T Bauer, Benjamin Solomon, B Besse, L James, J Clancy, K; Klamerus; J-F Martini; A Abbattista, A Shaw. MA07.11 Safety and efficacy of lorlatinib (PF-06463922) in patients with advanced ALK+ or ROS1+ non-small-cell lung cancer (NSCLC). Vienna, Austria 2016 Solomon, B. J.; Bauer, T. M.; Felip, E.; Besse, B.; James, L. P.; Clancy, J. S.; Klamerus, K. J.; Martini, J. F.; Abbattista, A.; Shaw, A. T. Safety and efficacy of lorlatinib (PF-06463922) from the dose escalation component of a study in patients with advanced ALK+ or ROS1+ non-small cell lung cancer (NSCLC). Journal of Clinical Oncology. Conference 2016;34(Supplement 15): Solomon, B.; Shaw, A.; Ou, S.; Besse, B.; Felip, E.; Bauer, T.; Soo, R.; Bearz, A.; Lin, C.; Clancy, J.; Abbattista, A.; Thurm, H.; Peltz, G.; Masters, E.; Martini,

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15. Alectinib	BFAST (NCT03178552)	S.M. Gadgeel, T.S.K. Mok, S. Peters, J.A.A. Alexander, N.B. Leighl, V. Sriuranpong, M. Perol, G. De Castro Jr., E. Nadal, F. De Marinis, J. Han, M. Yan, T. Riehl, E. Schleifman, S.M. Paul, S. Mocci, D. Shames, M.S. Mathisen, R. Dziadziuszko. Phase II/III Blood First Assay Screening Trial (BFAST) in patients (pts) with treatment-naïve NSCLC: initial results from the ALK+ cohort. 2019;():
Combination trials		
16. Crizotinib + Nivolumab	CHECKMATE 370	Spigel, D. R.; Reynolds, C.; Waterhouse, D.; Garon, E. B.; Chandler, J.; Babu, S.; Thurmes, P.; Spira, A.; Jotte, R.; Zhu, J.; Lin, W. H.; Blumenschein, G., Jr. Phase 1/2 Study of the Safety and Tolerability of Nivolumab Plus Crizotinib for the First-Line Treatment of Anaplastic Lymphoma Kinase Translocation - Positive Advanced Non-Small Cell Lung Cancer (CheckMate 370). Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer. 2018; 13(5): 682-688 A Study of Nivolumab in Advanced Non-Small Cell Lung Cancer (NSCLC) (CheckMate370). NCT02574078. Clinical Trials Registry. https://clinicaltrials.gov/ct2/show/NCT02574078
17. Crizotinib + Bevacizumab	NCT02946359	Yang, Bo; Cui, Zhi; Meng, Xianyang; Huang, Ziwei; Hu, Yi. Crizotinib with bevacizumab as first-line therapy in patients with advanced non-small-cell lung cancer harboring EML4-ALK fusion variant mutation: A prospective exploratory study. 2018;(): American Society of Clinical Oncology 2018 A+C in Metastatic Lung Adenocarcinoma Cancer. NCT02946359. Clinical Trials Registry. https://clinicaltrials.gov/ct2/show/NCT02946359
18. Alectinib + Atezolizumab	NCT02013219	Kim, Dong-Wan; Gadgeel, Shirish M; Gettinger, Scott N; Riely, Gregory J; Oxnard, Geoffrey R; Mekhail, Tarek; Schmid, Peter; Dowlati, Afshin; Heist, Rebecca Suk; Wozniak, Antoinette J. Safety and clinical activity results from a phase Ib study of alectinib plus atezolizumab in ALK+ advanced NSCLC (aNSCLC) 2018;(): American Society of Clinical Oncology 2018 A Phase 1b Study of Atezolizumab in Combination With Erlotinib or Alectinib in Participants With Non-Small Cell Lung Cancer (NSCLC). NCT02013219. Clinical Trials Registry. https://clinicaltrials.gov/ct2/show/NCT02013219

Indirect treatment comparisons (ITCs) and treatment switching methods

A8. <u>Priority Question:</u> It is stated in the CS (page 21) that: *"J-ALEX and ALESIA were excluded from the ITCs as these studies are not representative of the UK population (Asian populations only)."*

Substantial proportions of the ALTA-1L (39.3%, CS Table 9) and the ALEX (45.8%, Peter et al 2017) trial populations are Asian and yet these trials were included in the company's ITC. Furthermore, only 36 patients (13%) in the ALTA-1L trial and only 1% of from the ALEX trial were enrolled from the UK ([CS, Section B.2.3.1] and [TA536 committee papers, Pre-Meeting briefing, slide 5]).

In light of the characteristics of the ALTA-1L and ALEX trial populations, please explain why the J-ALEX and ALESIA trial populations were not considered representative of the UK population. Alternatively, please provide other reasons for excluding the J-ALEX and ALESIA trials from the ITCs.

<u>Response</u>: ALTA-1L and ALEX are both global, registration-enabling studies which had recruitment sites in Europe, Asia, USA and Canada. As the key pivotal trials that provided the evidence on which the European marketing authorisation (MA) is based, it is essential that these are included in the ITCs.

In contrast, the J-ALEX and ALESIA trials were regional studies which exclusively recruited Japanese and Asian populations, respectively. As a result, outcomes from the J-ALEX and ALESIA studies (each of which compared alectinib to crizotinib) were not considered pivotal in the clinical and safety evidence which led to the frontline MA for alectinib in Europe. The company (Roche) submission to NICE for alectinib (TA536) also excluded the J-ALEX and ALESIA studies from the economic modelling, citing *"differences in the patient population and dosing"*.

ALESIA is an east Asian sister trial of ALEX that included 187 Asian patients (recruited from 21 sites in China, South Korea and Thailand). Given its exclusively Asian population, we consider the ALESIA trial to have very limited generalisability to the UK setting. As mentioned above, this position is consistent with the one adopted

by Roche in the NICE submission for alectinib (TA536).[3] Notably, patients in J-ALEX received alectinib 300 mg twice daily (BID) - a 50% lower dose than the 600 mg BID that was used in the ALEX trial, which is the approved dose in Europe. The trial is therefore not reflective of how alectinib is prescribed in the UK. There were also significant imbalances in the J-ALEX trial between the groups in the number of patients with baseline brain metastases; 29 of 104 patients (28%) in the crizotinib arm had baseline brain metastases vs. 14 of 103 patients (14%) in the alectinib arm .[4] This imbalance arose because, unlike the ALTA-1L and ALEX trials, the J-ALEX trial did not include the presence of baseline brain metastases as a stratification factor. Having a higher proportion of patients with baseline brain metastases in the crizotinib arm likely favoured alectinib as it is the more CNS active agent.[5, 6] Brain metastases is a known negative prognostic factor, particularly for crizotinib due to its poor ability to penetrate the blood-brain barrier (see Section B.2.3.4.1 in the CS).

For all of the above reasons, the J-ALEX and ALESIA trials were not considered representative of the UK population and were therefore excluded from the ITCs.

Regarding the enrolment of patients from the UK in the ALTA-1L and ALEX trials, we note that the proportion of UK patients is much higher in ALTA-1L compared to ALEX (13% vs. 1%).

A9. <u>Priority Question:</u> Please provide details of the statistical software and/or package (including example statistical code) used to perform the following analyses:

a. **Anchored Matched Adjusted Indirect Comparison (MAIC)**
b. **Unanchored MAIC**
c. **Unweighted Bucher comparison**
d. **Rank Preserving Structure Failure Time Model (RPSFTM) for treatment switching.**

<u>Response:</u> All analyses described were conducted using the software package R, version 3.6.1 or later, following a “functional programming” paradigm.

The packages used were;

[redacted]

[redacted]

Functions common to the anchored and unanchored MAIC

The functions used for both the anchored and unanchored MAICs align with the algorithm code presented in the NICE technical support document (TSD) 18.[7]

[redacted]

(a) Anchored MAIC

[redacted]

[redacted]

MAIC weights generated also align with the NICE TSD 18.[7]

[redacted]

[redacted]

[redacted]

(b) Unanchored MAIC code

[redacted]

[redacted]

[redacted]

(c) Unweighted Bucher code

[redacted]

(d) Rank Preserving Structure Failure Time Model Code

[redacted]

[redacted]

[redacted]

A10. Priority Question: It is stated within Technical Support Document (TSD) 18 (pages 4-5) that:

"An unanchored MAIC or STC effectively assumes that absolute outcomes can be predicted from the covariates; that is, it assumes that all effect modifiers and prognostic factors are accounted for. This assumption is very strong, and

largely considered impossible to meet. Failure of this assumption leads to an unknown amount of bias in the unanchored estimate."

It is also recommended within that document (page 56) that:

"…if unanchored forms of population adjustment are to be presented, it is essential that submissions include information on the likely bias attached to the estimates, due to unobserved prognostic factors and effect modifiers distributed differently in the trials."

Please provide information on the likely range of bias attached to the unanchored MAIC estimates.

Response: The NICE DSU TSD 18 does not provide guidance as to how to quantify and adjust for bias stemming from differences in unobserved prognostic factors and effect modifiers when using MAIC methodology.[7] Therefore, it is unclear how best to address this question.

However, for PFS endpoints (BIRC-assessed and INV-assessed), the output from the unanchored MAICs can be validated using the anchored MAIC. The anchored MAIC does not need to account for differences in prognostic factors, unlike the unanchored methodology. Therefore, the anchored MAIC estimate can provide a reference estimate without the bias due to unobserved prognostic factors, although it does still require balanced treatment effect modifiers. Hence, it cannot be considered free of all bias. The hazard ratio for BIRC-assessed PFS was 0.974 (95% CI: 0.686 – 1.383) from the unanchored MAIC, which aligned with the anchored MAIC output: 0.969 (95% CI: 0.607 – 1.545). Similarly, for INV-assessed PFS, the results aligned: 0.969 (95% CI: 0.680 – 1.381) and 0.965 (95% CI: 0.615 – 1.515) for the unanchored MAIC and the anchored MAIC, respectively. Therefore, the bias stemming from unobserved prognostic factors can be considered minimal (differences of 0.004-0.005 in the HR). Note: the marginal difference in the point estimate moves in favour of alectinib for the unanchored methodology vs. anchored methods.

The outputs from the anchored MAICs and the unanchored MAICs differ slightly. However, this is thought to reflect the bias introduced by treatment switching and

subsequent therapies, rather than additional differences in unobserved prognostic factors or treatment effect modifiers.

A11. <u>Priority Question:</u> Please clarify the 'target population' (see TSD 18 Section 2.3.5 and Section 2.5) for whom the anchored and unanchored MAICs provide treatment effect estimates of brigatinib versus alectinib.

<u>Response:</u> Formally within a MAIC framework, the target population would be the population described in the ALEX clinical trial (i.e. the individual patient level data from ALTA-1L is weighted to match the ALEX trial).

Although not required for a MAIC analysis, we consider that the shared effect modifier assumption is relevant for brigatinib and alectinib. Therefore, the estimated relative treatment effects can be projected into any population.

The shared effect modifier assumption is detailed in NICE TSD 18 and requires that (1) the effect modifiers of all treatments are the same and (2) the change in treatment effect caused by each effect modifier is the same for all treatments.[7] If these requirements are met, then active-active treatment comparisons (e.g. brigatinib vs. alectinib) may be transported into any targeted population as any effect modifiers cancel out. Clinical feedback sought at the advisory board described in the main submission dossier indicates that baseline CNS metastases is the only effect modifier for both brigatinib and alectinib – as supported by the statistical analyses (see Appendix D.1.4.2 of the submission dossier). Clinicians also considered that the similar intracranial efficacy associated with brigatinib and alectinib satisfies the second condition. Additionally, because brigatinib and alectinib are treatments in the same drug class, it is expected that the treatment effect would respond similarly to changes in effect modifiers – the NICE TSD 18 states that treatments in the same class (i.e. sharing biological properties or mode of action) are likely to satisfy the shared effect modifier assumption. For this reason, we believe that the results of the MAICs can be translated into any target population.

A12. <u>Priority Question</u>: As stated within TSD 16 (page 20), RPSFTM methods can be applied based on one of two assumptions, namely:

1. **assuming an "on treatment" counterfactual survival model where treatment effect is only received while a patient is "on" treatment and treatment effect disappears as soon as treatment is discontinued.**

2. **assuming a "treatment group" model where there is a continued or lagged treatment effect following the discontinuation of treatment**.

Please clarify which assumption was used to adjust the OS data from the crizotinib arm of the ALTA-1L trial and justify the choice of assumption.

<u>Response:</u> The second assumption of a "treatment group" was used to adjust the OS data from the crizotinib arm of the ALTA-1L trial. This assumption allowed for all patients to be treated similarly within the analysis. For example, for patients who did not switch to the other ALTA-1L arm but did switch to another treatment or discontinued treatment, the OS time period was not censored at the time in which the frontline treatment was discontinued (as per the first assumption). Instead, follow-up was continued for these patients until either death or loss to follow-up. Therefore, the second assumption allowed the length of the survival data to be maximised which was considered important given the maturity of the data.

A13. The CS (pages 104-105) includes the following text:

"Note: the analyses presented also adjusted for treatment switching from the brigatinib arm to the crizotinib arm (n=11). However, due to the small number of patients who made this switch and the fact that the impact on survival is negligible, the adjusted brigatinib data were not considered within the economic model."

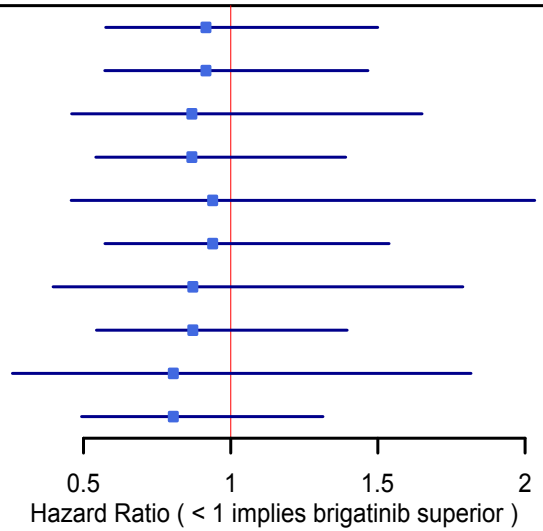
a. Please clarify which (if any) of the results presented in Figure 42 of the CS have been adjusted to take into account the 11 patients who switched from the brigatinib arm to the crizotinib arm of the ALTA-1L trial.

<u>Response:</u> Figure 42 from the original submission dossier is presented in

Figure 1 below – only the “Concomitantmeds Added” switch pool includes the adjustment for the 11 patients switching from brigatinib to crizotinib as these were not termed official switchers under the trial protocol (which defined these as patients switching from crizotinib to brigatinib). The “Concomitantmeds Added” switch pool also includes the 73 patients switching from crizotinib to brigatinib (61 official and 12 additional).

Figure 1: Brigatinib vs. Crizotinib OS HR Forest Plot: Alternative Treatment Switch Adjustment Schemes Bootstrapped (Normal CIs) & Standard (non-bootstrapped) (Figure 42 of original submission dossier)

CI Method	Switch Pool	Re-censoring Applied	HR (95% CIs)
Bootstrap	None	Not Applicable	0.916 (0.576,1.5)
Standard	None	Not Applicable	0.916 (0.572,1.466)
Bootstrap	Official Only	No	0.868 (0.459,1.65)
Standard	Official Only	No	0.868 (0.542,1.39)
Bootstrap	Official Only	Yes	0.939 (0.458,2.033)
Standard	Official Only	Yes	0.939 (0.573,1.538)
Bootstrap	ConcomitantMeds Added	No	0.871 (0.396,1.789)
Standard	ConcomitantMeds Added	No	0.871 (0.544,1.396)
Bootstrap	ConcomitantMeds Added	Yes	0.805 (0.258,1.816)
Standard	ConcomitantMeds Added	Yes	0.805 (0.493,1.313)



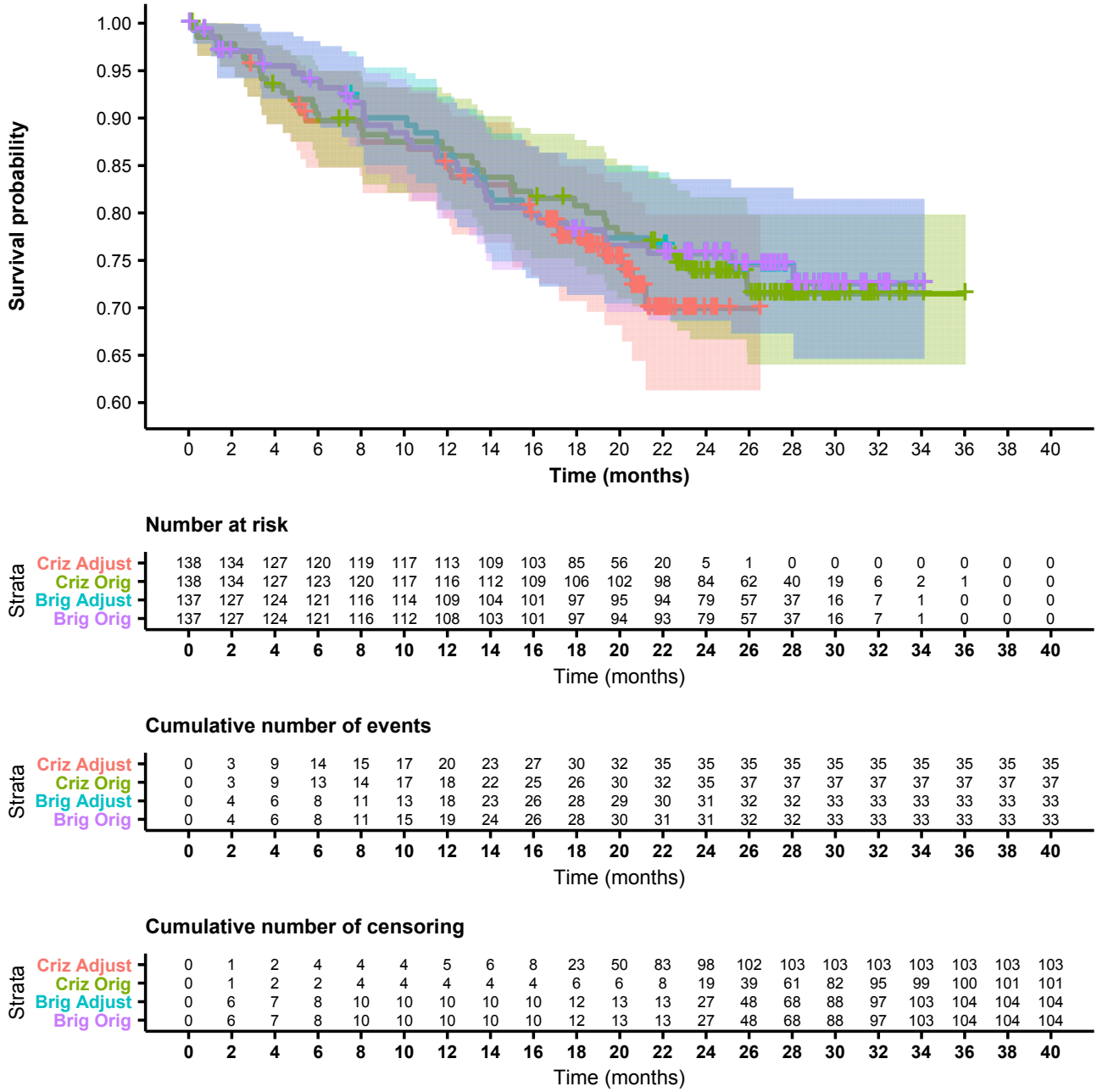
Abbreviations: CI, confidence intervals; HR, hazard ratio; OS, overall survival

b. Please provide any results that demonstrate that the impact on survival was negligible following the adjustment for the 11 patients who switched from the brigatinib arm to the crizotinib arm of the ALTA-1L trial.

Response: Figure 16 and Figure 17 from Appendix L from the CS are presented below as

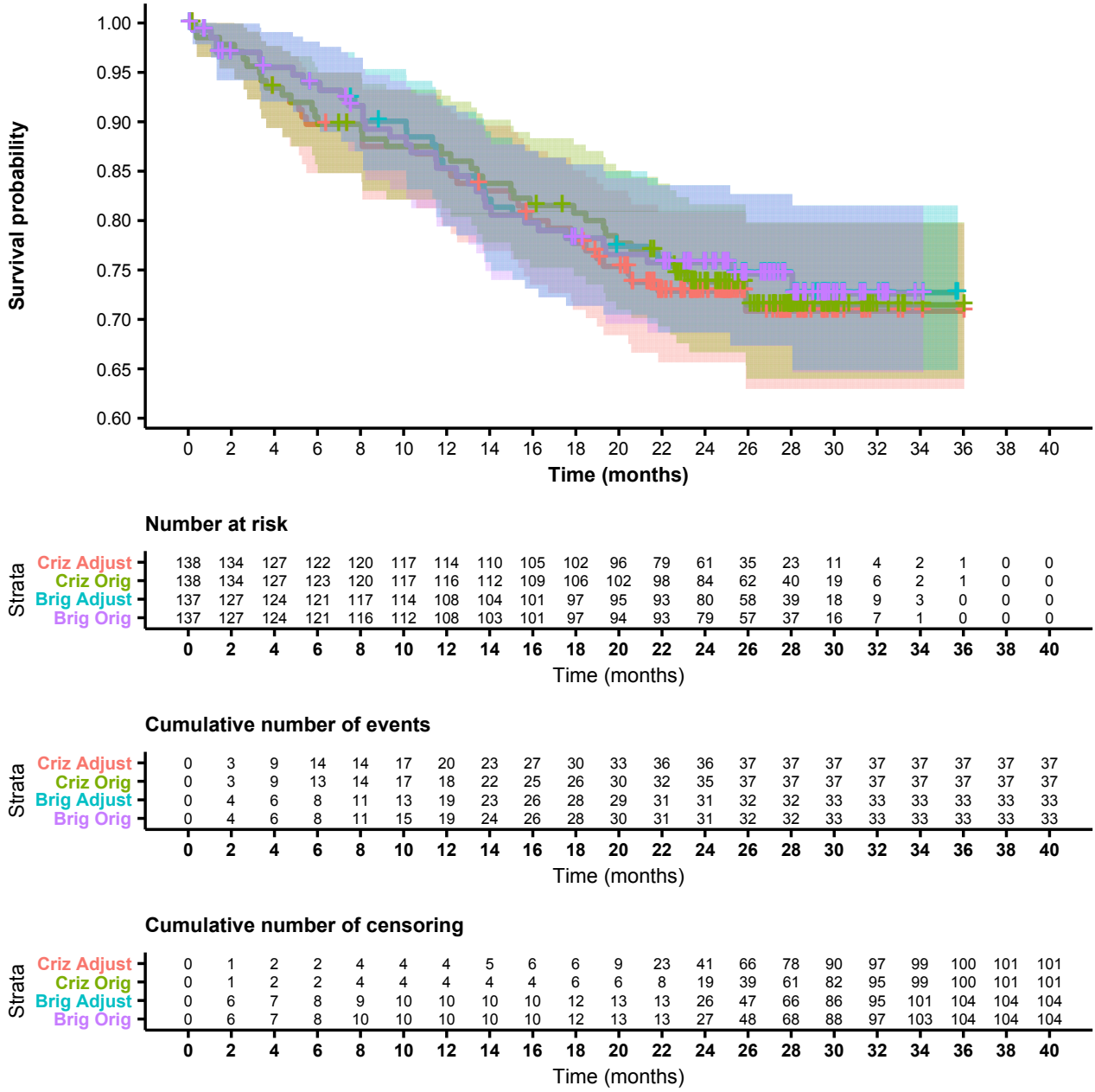
Figure **2** and Figure 3, respectively. These figures demonstrate that the original and adjusted Kaplan-Meier plots for brigatinib lay almost exactly on top of each other – this is also reflected in the near identical cumulative number of events. Therefore, it can be concluded that accounting for patients switching from brigatinib to crizotinib has a negligible impact on survival outcomes.

Figure 2: Kaplan-Meiers: Original OS vs. RPSFT Method using Switch Pool = ConcomitantMeds Added: Re-censoring = Yes (Figure 16 of Appendix L)



Abbreviations: OS, overall survival; RPSFTM, rank preserving survival failure time model

Figure 3: Kaplan-Meiers: Original OS vs. RPSFT Method using Switch Pool = ConcomitantMeds Added: Re-censoring = No (Figure 17 of Appendix L)



Abbreviations: OS, overall survival; RPSFTM, rank preserving survival failure time model

A14. It is stated in the CS (Appendix D, Section D.1.4.3) that: "*Two separate matchings were considered: (1) the baseline CNS metastases in the brigatinib arm of ALTA-1L was matched to the alectinib arm of ALEX and (2) the baseline CNS metastases in the crizotinib arm of ALTA-1L was matched to the crizotinib arm of the ALEX trial."*

Please clarify which of these two matching approaches was used in the anchored MAIC analyses presented within the CS**.**

Response: The wording in Appendix D, Section D.1.4.3 may be better phrased as "two separate matchings were implemented"; in line with published recommendations: "In settings where the aggregate data show substantial imbalances between treatment arms despite randomisation, it may be appropriate to match baseline characteristics for the active treatment arms separately from the placebo arms."[9] Due to differences between the proportion of baseline CNS metastases in the alectinib and crizotinib treatment arms in the ALEX clinical trial (42% and 38%, respectively), a known prognostic factor, two separate matchings were implemented as per these recommendations.

The two separate MAIC weight estimates were then combined into one resultant Cox regression that generated the ALTA-1L weighted brigatinib vs. crizotinib estimates. Following this, standard MAIC methodology was pursued.

A15. Priority Question: Please carry out non-inferiority testing for the comparison of survival estimates (overall survival and progression-free survival) for brigatinib versus alectinib.

Response: We consider that a test of non-inferiority is inappropriate to conduct between brigatinib and alectinib in this setting. Firstly, the ALTA-1L clinical trial was not designed to conduct a non-inferiority indirect assessment between the brigatinib arm and the alectinib arm in the ALEX study. This is reflected by the wide confidence intervals in the ITCs. Therefore, we consider that the null hypothesis underlying the non-inferiority testing will be difficult to reject without large non-inferior margins. This is not necessarily a reflection on the treatment effects, but a consequence of the relatively small sample sizes included in the trials and ITCs.[10]

Secondly, as stated in the original CS, there are important differences between the ALTA-1L and ALEX clinical trials which would not be accounted for in a non-inferiority test. The two key differences: proportion of baseline brain metastases and treatment switching permitted in the ALTA-1L clinical trial, bias against brigatinib when unadjusted.

Finally, assessments of non-inferiority require a pre-specified margin – this margin must be specified based on clinical and statistical reasoning. There is no guidance on selecting this margin within the NICE TSD documents. The pre-specified margin would also need to consider the additional uncertainty necessitated by the indirect nature of the comparison (i.e. would need to be wider than if brigatinib was compared to alectinib directly).

We conclude that the risk of falsely concluding inferiority due to a) ALTA-1L not being designed for this type of test, b) the key differences between the trials, and c) the additional uncertainty due to the necessary ITCs cannot be quantified. Therefore, we consider that the clinical rationale supporting similar efficacy should be considered alongside the results of the ITCs when interpreting the non-inferiority of brigatinib with alectinib.

With respect to the assumption of clinical equivalence between brigatinib and alectinib, it is also worth considering, as recommended by the ERG, the biological/pharmacological plausibility that supports such an assumption. Brigatinib and alectinib are both second generation tyrosine kinase inhibitors (TKIs) that have the same mechanism of action which involves the inhibition of anaplastic lymphoma kinase (ALK).[11] Rearrangements in the ALK gene in ALK-positive NSCLC occur through chromosomal translocation events, which result in the generation of ALK fusion genes.[12] This causes constitutive activation of ALK, which results in an increase in cell proliferation and cell survival through several key signalling pathways, including but not limited to: the JAK-STAT, PI3K-AKT, mTOR, MAPK and the PLCγ cascades.[12, 13] Both alectinib and brigatinib, through their inhibition of ALK, prevent this downstream signalling and ultimately result in an inhibition of cancer cell survival and tumorigenesis.

Brigatinib and alectinib have both demonstrated activity pre-clinically (and in some cases clinically), against a number of ALK mutations, including ALK L1196M; although there are slight differences in their sensitivities to some of the mutations, as is to be expected with different molecules.[11, 14, 15] Both of these TKIs have demonstrated an increased potency in inhibiting ALK compared to crizotinib,[11] which has translated clinically, as both have shown improved efficacy vs. crizotinib in their respective head-to-head trials in the frontline setting.[16-18] Both agents also have good activity against ALK mutations that confer resistance to crizotinib. Brigatinib and alectinib were both designed to penetrate the blood-brain barrier effectively and have demonstrated an improvement compared to crizotinib in this respect, an agent which is known have to poor CNS penetration.[19]

The clinical experts consulted at a Takeda advisory board in January 2020 agreed with a clinical equivalence approach between brigatinib and alectinib. Those who had experience of using both agents in the frontline setting considered that, based on the outcomes from their respective frontline trials (ALTA1L and ALEX) and their own experience, these medicines demonstrate similar overall efficacy. Consistent with NICE's requirements for a cost-comparison, all clinical expert advisors supported the position that brigatinib provides similar or greater health benefits than alectinib in the frontline setting for ALK-positive advanced NSCLC.

The results of the indirect treatment comparisons indicate non-inferiority of brigatinib compared with alectinib for PFS; the point estimates from both the anchored MAIC and the unanchored MAIC are in favour of brigatinib for BIRC-assessed and INV-assessed outcomes: 0.969 (95% CI: 0.607-1.545) vs. 0.974 (95% CI: 0.686-1.383) for BIRC-assessed and 0.965 (95% CI: 0.615-1.515) vs. 0.969 (95% CI: 0.680-1.381) for INV-assessed, respectively. The wide confidence intervals and the proximity of the hazard ratios to 1.0 indicate the similar treatment effect between brigatinib and alectinib.

Section B: Clarification on cost effectiveness data

None.

Section C: Textual clarification and additional points

Systematic literature review methods

C1. Regarding the SLR please explain how many independent reviewers were involved in data extraction and how many were involved in quality assessment.

Response: Two independent researchers performed the quality assessment and data extraction (double data-extraction) whilst a third researcher collated the data from both researchers and identified discrepancies. The third researcher resolved any differences by consulting full text papers and discussing with the researchers who extracted data.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

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

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	ALK Positive UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	We are a registered charity established by patients and their families and friends in 2018. Our purposes are to provide support and advocacy and to improve the overall survival and quality of life of ALK-positive lung cancer patients across the United Kingdom. We do not offer medical advice but we have an active Facebook Group for patients, family and carers where experiences can be shared (see link below). We hold regular meetings in the UK and also share information on Twitter and LinkedIn We currently have 289 members from across the four regions of the UK.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	ALK Positive UK has received funding towards the costs of a two-day patient conference we intended holding in September. We will now hold this event in 2021 and have notified Takeda of this change in circumstances due to Covid19. We are holding the monies, £11,500 in our account. The event will host 100 ALK-positive patients from across the UK where many ALK-positive experts will speak. The agenda for September had 6 speakers confirmed. ALK Positive UK has also received the same amount from Roche as each company agreed to fund the event at 50%.

If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We carried out a comprehensive survey earlier this year through SurveyMonkey, 80 members completed this and we also asked members currently receiving Brigatinib, through the compassionate use programme to send in their experiences to date via our website or on-line fb page.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	It is impossible to forget you have the disease as not only do you have regular monitoring but any ache, pain, cough or feeling tired raises the possibility of progression. The mental health aspects of a diagnosis of ALK-positive LC should not be under-estimated as many patients suffer depression as a result of being diagnosed. Many patients are unable to continue working due to their symptoms, so the many hospital appts can have a significant financial burden on their whole families. Experiencing side effects on treatment means further hospital investigation which incurs further costs – petrol, hospital car-parking, child-minding costs for those with young families, loss of earnings for those who are able to continue to work.

	Life changes beyond all recognition once a diagnosis has been received, not knowing how long you have to live and what quality that life will be is a dark cloud that is permanently overhead for all patients (and carers). All current treatments come with side effects, many of which are significant and impact on quality of life. The side effects can be similar to the symptoms of progression, so these add another level of anxiety into daily life. Side effects can vary from patient to patient and are a varied as weight gain, hair thinning or curling, muscle aches, frequent cramps in limbs, extreme fatigue (feeling like wading through treacle), extreme constipation requiring medical intervention and extreme sun-sensitivity even in winter (requiring factor 50 sunscreen at all times and all limbs to be covered when outside). All current treatments will ultimately fail as the cancer develops resistance to them and many patients progress a lot earlier than the clinical trials report. This means that progression through the treatment options can be swift with many patients having been prescribed 3 over a period of 18mths. Many patients have young families, who also have their lives turned upside down – going to school each day worrying if their parent will be there when they get home, watching their parents suffer with the side effects of treatment and constantly being scared they will lose their parent. Family members can become carers overnight, with all the emotional aspects of watching a loved one suffer whilst having to adapt to being a carer and the demands that has on their time. Anything that results in a hospital visit or admission is an enormous burden for carers who are required to change plans and drop all arrangements when needed. Many patients and carers are scared to go on holiday in case something happens while they are away.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Patients and carers feel that the current targeted treatments are an enormous improvement on the traditional cancer treatment of chemotherapy. Patients can live ‘relatively normally’ without the need for weekly hospital visits and the side effects are generally much easier to tolerate than chemotherapy. Patients don’t lose their hair so feel more confident when out in public as they aren’t constantly stared at. Most patients look well for the majority of their cancer journey which helps keep life normal for their families Patients learn coping mechanisms for the side effects, for example sun-sensitivity is a significant issue for many patients taking targeted therapies. ‘Sun sensitivity’ feels like boiling water has been poured on the skin and can occur very quickly once exposed to the sun so the majority of patients cover up in the sun,

	wear factor 50 sunscreen and stay in the shade to avoid this. Many patients find their initial symptoms improve vastly upon starting treatment, which means they can return to work and continue to contribute to the UK economy. Many patients work for several years until the latter stages when they experience significant progression. Many take on new challenges to raise vital funds for further research as they clearly understand the value and need of such on-going research.
8. Is there an unmet need for patients with this condition?	Yes – choice is very much an unmet need for patients with this condition.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	One tablet once a day minimises the negative impact on quality of life. Patients with a better quality of life visit their Drs less often which impacts capacity and costs in the NHS. Patients receiving targeted therapies with fewer side effects* take fewer other medicines which is a cost benefit for the NHS. ● Small tablets so easy to take ● No sun sensitivity ● Improved GI effects vs Alectinib so better quality of life and reduced number of other medicines required to take. This also benefits the NHS. ● Excellent brain coverage so reduces brain metastasis without the need for expensive radiotherapy (whole brain or SRS) thus reducing the need for other NHS services Results from the ALK Positive UK survey found the following % of patients experienced significant side effects on the targeted therapies – Ceritinib 69% Alectinib 62% Crizotinib 50% Lorlatinib 40% Brigatinib 32%

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	None
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	No
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	No

Other issues	
13. Are there any other issues that you would like the committee to consider?	Quality of life impact: Most lung cancer patients, including ALK positive are diagnosed late with stage 4 disease. However the profile of ALK patients is somewhat different to the sterotype of a smoker with lung cancer in their 70s or 80s. This subset of patient are struck in the prime of their lives whilst in full time employment, with young families, about to get married, still at University, running half marathons. Due to age-range of people affected with the disease, we believe this has a massive impact mentally on those diagnosed as well as their carers, families and friends. The loss of function, curtailment of activities e.g. driving and other changes in lifestyle to adapt to this illness which affects not only the lungs but also spreads to the brain and bones is also more prominent.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- Previous to their diagnosis, ALK-positive LC patients led healthy lives, kept fit and didn't smoke. Their lifestyle did not contribute to their developing lung cancer.
- There are very few treatments currently available on the NHS in England and Wales for patients starting their 1st line treatment and choice is important to ensure each patient receives the best treatment for them first. Many ALK-positive experts agree patients should be given the most effective treatment first as subsequent treatments are generally less effective due to the cancer mutating.
- The majority of patients led full lives before their diagnosis and wish to continue contributing to the UK economy as well as be alive for as long as possible to be with their families.

- Brigatinib use in the UK is reported as ‘much easier than previous targeted treatments’, which all leads to patients living longer with a good/excellent quality of life.

- ALK-positive patients didn’t do anything to deserve this devastating diagnosis. They are struck down with this disease in the prime of their lives and now have a significantly reduced life span.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

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

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	ROY CASTLE LUNG CANCER FOUNDATION
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Roy Castle Lung Cancer Foundation is a UK wide lung cancer charity. We fund lung cancer research, tobacco control initiatives and work in lung cancer patient care (information, support and advocacy activity). Our funding base is a broad mixture including community, retail, corporate, legacies and charitable trusts. Clearly, our patient group members and contacts are a self-selected group, who have taken the step to seek out information or have accessed specialist support services. As most lung cancer sufferers tend to be older, from lower social class groups and with the five year survival being around 15%, less physically well, we acknowledge that our patients are perhaps not representative of the vast majority of lung cancer patients, who are not so well informed. It is, however, important that the opinions expressed to us, be passed on to NICE, as it considers the place of this product in the management of ALK positive advanced Non Small Cell Lung Cancer (NSCLC).
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	The Foundation has contact with patients/carers through its UK wide network of over 55 monthly Lung Cancer Patient Support Groups, patient/carer panel, online forums and its Lung Cancer Information Helpline.

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	According to the National Lung Cancer Audit, the one year survival for lung cancer is 37%. Thus, this group of lung cancer patients have a particularly poor outlook. with an obvious impact on family and carers. Symptoms such as breathlessness, cough and weight loss are difficult to treat, without active anti-cancer therapy. Furthermore, these are symptoms which can be distressing for loved ones to observe. The ALK gene rearrangement is found in about 3% to 5% of patients with NSCLC. These patients tend to be younger and more likely to be light/non-smokers, as compared to the general lung cancer population. With that in mind, it is our observation that, though a younger, fitter patient group (fewer co-morbidities), ALK positive patients tend to be diagnosed later, as they do not fit the 'typical' lung cancer patient profile.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Crizotinib, Certitinib and Alectinib have all been approved by NICE for untreated ALK positive NSCLC patients. Brigatinib has previously been approved for ALK positive disease, after progression on Crizotinib These drugs work in part by blocking the activity of the ALK protein, ultimately inhibiting the growth of tumour cells. Patients typically develop resistance to these drugs when tumour cells develop new gene alterations, in the ALK gene, which renders the protein insensitive to the inhibitor. It appears that most patients progress under ALK inhibition within a few years, the brain being a common site of relapse. Each ALK inhibitor has a different spectrum of sensitivity to ALK mutations, thus making complex the optimal sequencing of ALK inhibitors
8. Is there an unmet need for patients with this condition?	YES.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Outcomes of treatment are seen as an advantage of this technology. We do not have any additional data, beyond that publically available. We note, however, the results of the Phase 3 ALTA-1L study, which compares Brigantinib with Crizotinib in patients with ALK positive locally advanced or metastatic NSCLC, who had not received prior treatment with an ALK inhibitor. Results from the trial showed that Brigatinib demonstrated superiority over Crizotinib, with significant responses observed in patients with baseline brain metastasis. Brigatinib treated patients also reported a median progression free survival, more than two times longer than those receiving Crizotinib. This therapy is given orally (therefore, ease of administration) and in the anecdotal patient experience available to us, it appears to be generally well tolerated.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Side effects of the treatment. As above, there are several ALK inhibitors already in regular practice in this indication and Brigatinib has been available after progression on first line treatment. As such, experience in use and side effect management is now commonplace. We understand that common side effects associated with Brigatinib include diarrhea, nausea, vomiting, tiredness, abdominal pain, cough, headache and decreased appetite. Brigatinib may also cause more serious side effects, such as high blood pressure, high blood sugar, pancreatitis, hepatotoxicity, lung toxicity and cardiac problems including bradycardia. As above, in the anecdotal patient experience available to us, it appears to be generally well tolerated.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues	
13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- ALK positive NSCLC is known to often spread to the brain. As such, it is important to have treatment options which demonstrate both overall and intracranial effectiveness.
- Despite progress in therapies for ALK positive lung cancer in recent years, there is a need for additional and more effective treatments in this segmented patient group.
-
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Thank you for your time.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

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

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	BTOG on behalf of BTOG/RCP/RCR/ACP/NCRI

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The British Thoracic Oncology Group (BTOG) is the multi-disciplinary group for healthcare professionals involved with thoracic malignancies throughout the UK. The mission of BTOG is to support and educate healthcare professionals, creating a professional community to exchange ideas, information and to foster the development of research. The overall aim is to represent the needs of patients and improve their outcomes. BTOG is a registered charity and funding for the key activities is provided by sponsorship and education grants from industry and registration fees. The NCRI-ACP-RCP-RCR is a combination of the National Cancer Research Institute (NCRI), The Association of Cancer Physicians (ACP), the Royal College of Physicians (RCP) and the Royal College of Radiologists (RCR).

4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	NCRI-ACP-RCP-RCR - none BTOG Funding Manufacturer: Takeda: BTOG 2020 £58,500 Comparator: Pfizer: BTOG 2020 £12,500 Roche: BTOG 2020 £36,000 Novartis BTOG 2020 £6,500
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve	The aim is to improve progression-free survival, including whole body and intracranial progression-free survival, to improve response rates, to maintain quality of life. To monitor overall survival, although overall survival improvement may not be detected due to trial immaturity and crossover design.

mobility, to cure the condition, or prevent progression or disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	The supportive trial (ALTA-1L) was powered to detect an improvement in relative progression-free survival (PFS) of 37.5%, although an improvement of 30% or more would be clinically meaningful. An overall response rate (ORR) improvement over crizotinib is not expected, but a difference in intracranial ORR by 10% or an improvement in relative intracranial PFS by even 20% would be considered important.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes; ALK+ NSCLC is a highly aggressive disease predominantly affecting never smokers, with a younger than usual age, and metastasizes early, often to the brain. Whilst effective next generation ALK inhibitors are NICE approved (alectinib and ceritinib) these drugs are not curative, and especially intracranial progression-free survival remains a challenge.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	NICE has approved crizotinib, ceritinib, and alectinib for the treatment of advanced ALK+ NSCLC. ALK testing of tumours is routinely performed (although results can take time to return and a small number of patients have to start chemotherapy due to clinical urgency). In general, despite the options of crizotinib, ceritinib, and alectinib, alectinib is generally used wherever possible. This is since the ALEX, J-ALEX, and ALESIA trials have all demonstrated a marked improvement in progression-free survival predominantly driven by improving intracranial control and potentially delaying time to intracranial disease, agains the

	comparator crizotinib. Ceritinib has never been directly compared to an ALK inhibitor, but it is certainly more toxic than crizotinib and alectinib. Cross trial data and network meta-analyses have demonstrated superiority to crizotinib but inferior outcomes compared to alectinib. On this basis, alectinib is the usual standard of care in England (and the rest of the UK, and globally). Whilst chemotherapy is also NICE approved this is markedly inferior to crizotinib and not at all used for proven ALK+ NSCLC patients.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Guidelines followed include: NICE guidelines (NG122) and algorithm for systemic treatment options European Society of Medical Oncology (ESMO) Clinical Practice Guidelines American Society of Clinical Oncology (ASCO) Advanced NSCLC Guidelines
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Yes, the pathway is as described in the NICE guidelines and drug algorithm and there is UK clinical consensus that alectinib is currently the preferred 1st line drug of choice.
• What impact would the technology have on the current pathway of care?	Brigatinib would offer an alternative drug choice to alectinib, especially in patients with established or detected CNS metastases where it has marked clinical efficacy, potentially superior to that observed with alectinib. However, in order to maximize outcomes for ALK+ lung cancer patients, patients are usually switched to lorlatinib on progression on alectinib as per the EMA licensed indication. This indication is currently undergoing NICE review (ID1338) and drug is currently provided by Pfizer in an expanded access scheme supported by UK oncology opinion. However, the EMA license does not allow brigatinib patients that relapse to receive lorlatinib (as the lorlatinib licensed does not approve patients relapsing after first line brigatinib, as first line brigatinib was not licensed or available during the enrolment time period of the

	lorlatinib trial), despite there now being clinical evidence of benefit and good scientific rationale for benefit, albeit not in a trial, there remains a perverse incentive not to use brigatinib.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes
• How does healthcare resource use differ between the technology and current care?	The ALTA-1L trial data supports brigatinib as an alternative to first line alectinib with potentially superior intracranial efficacy
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Cancer Centres and Cancer Units
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No significant new investment as ALK testing is already implemented and brigatinib is oral therapy
11. Do you expect the technology to provide clinically	We have no head to head data directly comparing brigatinib with alectinib. However, making cross trial comparisons between the ALTA-1L (brigatinib) and ALEX (alectinib) trials, there seems to be similar overall progression free survival and response rates, although there may be superior intracranial efficacy with brigatinib. Moreover brigatinib has been shown to improve some measures of patient reported outcomes,

meaningful benefits compared with current care?	unlike alectinib. Brigatinib also has data to support its use in patients initially started on chemotherapy and then switched to ALK inhibitor (a realistic clinical scenario where the patient urgently needs to start treatment prior to ALK biomarker results being available), for which there is no similar supportive data for alectinib.
• Do you expect the technology to increase length of life more than current care?	Likely, no in the whole population, but perhaps in those with brain metastases
• Do you expect the technology to increase health-related quality of life more than current care?	Yes
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients with baseline CNS metastases seem to derive a major benefit both in terms of intracranial response rate, intracranial progression-free survival and overall (whole body) progression-free survival. In ALTA-1L the PFS HR for patients with baseline CNS metastases was 0.25, with an intracranial PFS of HR=0.31. This compares favourably to that the PFS in patients with CNS metastases in ALEX (alectinib) of HR=0.40. The trial also allowed patients to start chemotherapy and then switch to brigatinib once ALK status known and this would represent another small but important group in the UK that could derive benefit, given the National Lung Cancer audit identified that only 58% of ALK+ patients in the UK started an ALK inhibitor.
The use of the technology	
13. Will the technology be easier or more difficult to use	There is similar blood work monitoring likely required to alectinib, contingent on brigatinib SPC wording, eg amylase and CPK testing, although these were principally biochemical-only abnormalities in the ALTA-1L trial and did not correlate with pancreatitis or myositis, unlike myositis and transaminitis observed for

for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	alectinib and the SPC recommending regular CPK and ALT monitoring. There is a minor increase in early (within 3days) pulmonary events (eg dyspnoea) for brigatinib which is a brigatinib-specific effect not observed with alectinib. By contrast, brigatinib does not have the transaminits, myositis, weight gain, constipation observed with alectinib. Brigatinib is easier re compliance as it is a single daily pill rather than 8 pills per day for alectinib. Alectinib does, however, require blood pressure evaluation as hypertension is a recognized toxicity.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Treatment will continue until progression or loss of clinical benefit as per the trial and as per standard for ALK+ NSCLC. No additional major investment or education is required.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the	No

quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	No, but it does allow for stating urgent patients on chemotherapy for clinical urgency whilst ALK testing and then treating with a next generation ALK inhibitor which is a major advantage for patients. The National Lung Cancer Audit Spotlight evaluation identified that in real life, only 58% of identified ALK+ patients commended an ALK inhibitor.
• Is the technology a 'step-change' in the management of the condition?	No
• Does the use of the technology address any particular unmet need of the patient population?	Yes, this is a simple once daily oral therapy with few toxicities and the only ALK inhibitor that has shown improved quality of life against crizotinib. It is also highly effective in patients with CNS metastases.
17. How do any side effects or adverse effects of the technology affect the	There is a slight excess of early pulmonary events with brigatinib but these are usually grade 1 events and are rarely significant. There are recorded CPK and amylase rises but these are not clinically important and do not translate to myositis or pancreatitis. There is no weight gain, constipation, or myositis seen with alectinib. Brigatinib significantly improved some patient reported outcomes measures against crizotinib in

<table>
<tr><td>management of the condition and the patient's quality of life?</td><td>the ALTA-1L trial, unlike alectinib in the ALEX trial where not improvement in patient reported outcomes was documented.</td></tr>
<tr><td colspan="2">Sources of evidence</td></tr>
<tr><td>18. Do the clinical trials on the technology reflect current UK clinical practice?</td><td>Yes</td></tr>
<tr><td>• If not, how could the results be extrapolated to the UK setting?</td><td>N/A</td></tr>
<tr><td>• What, in your view, are the most important outcomes, and were they measured in the trials?</td><td>The most important efficacy measures were evaluated and are tabulated below for ALTA-1L vs those reported for ALEX
<table>
<tr><td>Measure</td><td>Brigatinib (ALTA-1L trial)</td><td>Alectinib (ALEX trial)</td></tr>
<tr><td>PFS ITT population (BIRC)</td><td>HR=0.49</td><td>HR=0.50</td></tr>
<tr><td>PFS prior chemotherapy</td><td>HR=0.44</td><td>Not reported</td></tr>
<tr><td>PFS no prior chemotherapy</td><td>HR=0.52</td><td>Not reported</td></tr>
<tr><td>PFS CNS mets at baseline</td><td>HR=0.25</td><td>HR=0.40</td></tr>
<tr><td>Intracranial PFS (BIRC)</td><td>HR=0.31</td><td>Not reported</td></tr>
</table></td></tr>
</table>

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	OS was measured but the trial is too immature to comment on this as a measure. Also, since cross over was built into the ALTA-1L trial, the OS benefit from 1st line brigatinib will be difficult to reliably evaluate.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. How do data on real-world experience compare with the trial data?	N/A
Equality	
21a. Are there any potential equality issues that should be	No

taken into account when considering this treatment?	
22b. Consider whether these issues are different from issues with current care and why.	N/A

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.

- Brigatinib is a highly effective next generation ALK inhibitor
- Brigatinib has similar efficacy data in the ITT population to alectinib, the current standard of care, but with reduced pill burden
- Brigatinib has numerically superior intracranial efficacy to that reported for alectinib, in patients with CNS metastases
- Brigatinib efficacy data supports its use when chemotherapy has had to be initially commenced due to clinical urgency, an large issue for UK practice
- Brigatinib is the only ALK inhibitor shown to improve some quality of life domains over crizotinib

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

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

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Alastair Greystoke**
2. Name of organisation	**Newcastle upon Tyne Hospitals NHS Trust**

3. Job title or position	**Senior Lecturer and Honorary Consultant in Medical Oncology**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Maintain quality of life and prevent disability, improve survival, improve or prevent cancer related symptoms (in particular those related to central nervous system disease)
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	An improvement in survival by 2 months. Delay in neurological symptoms impacting on independence by 3 months. A response rate of over 30% maintained for over 2 months
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, although there is an available 1st line option in alectinib this is sometime not tolerated and this would provide a valuable alternative for select patients and healthcare professionals
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	A number of ALK inhibitors are approved in the untreated ALK +ve NSCLC; these include crizotinib, certinib and alectinib. On progression options include lorlatinib, the ABCP chemo-immunotherapy regimen, chemotherapy alone or best supportive care. In patients previously treated with crizotinib brigatinib can be used Radiotherapy may be used for symptomatic control or for the treatment of resistant brain disease using stereotactic radiotherapy
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	The technology appraisals for Crizotinib TA 406 Ceritinib TA 500 Alectinib TA 536 The quadruple regimen of carboplatin paclitaxel, bevacizumab and atezolizumab (ABCP; TA584) Lorlatinib TA628 The European Society of Medical Oncology guidelines are commonly used https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	No. Whilst the pathway is well defined in patients 1st presenting, the pathway of care on prgoression is poorly defined with variable access to clinical trials and compassionate access to other ALK inhibitors often being restricted to more specialist centres. Experience with using chemotherapy and the quadruple regimen ABCP will vary from centre to centre. Management of oligoprogressive cancer and surveillance and treatment of the Central Nervous System will vary from centre to centre.
• What impact would the technology have on the current pathway of care?	It would provide another option in the 1st line setting

11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes
• How does healthcare resource use differ between the technology and current care?	Minimal changes. It will be used in the same way as present ALK inhibitors primarily in the outpatient setting.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist oncology clinics
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No change in facilities will be required. Minimal training into the different side effect profiles compared to other ALK inhibitors will be needed, but some clinicians will already be using it in the patients who have received prior crizotinib
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	

• Do you expect the technology to increase length of life more than current care?	No. Clinical data suggests comparable efficacy to other 2nd generation ALK inhibitors such as alectinib
• Do you expect the technology to increase health-related quality of life more than current care?	No. I would suggest equivalent to use of other 2nd generation ALK inhibitors such as alectinib.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients who struggle with oral medication (less tablets than alectinib, certinib) Patients intolerant of alectinib Patients with pre-existing moderate to severe constipation
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for	Easier for patients (less tablets); although does require a dose escalation after 1 week. Probably equivalent for clinicians Requires monitoring of Creatinine Kinase and amylase although in general elevations are asymptomatic and require no change in therapy

example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No additional testing will be required. Patients will be monitored clinically and with CT/MRI scans until symptomatic progression when it is likely they will be changed to lorlatinib provided they meet the blueteq criteria at that time
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No

17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	No
• Does the use of the technology address any particular unmet need of the patient population?	No
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	In general well tolerated.

Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Progression free and overall survival; CNS response rate and duration of control; health related quality of life
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No

20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	UK ALK database; results have been presented at BTOG. Most brigatinib use was in the late line setting, not 1st line but will give data as to tolerability and overall survival from time of diagnosis.
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA536 and TA500]?	Long term survival data has been presented for the Profile 1014 (crizotinib) and ALEX (alectinib) studies
22. How do data on real-world experience compare with the trial data?	In general real world data are significantly worse than in clinical trials. This is a result of both the patient group (poorer PS and co-morbidities) and a lower standard of care (access to subsequent lines of therapies, regular brain monitoring, optimal treatment of CNS disease).
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	No

23b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
24. Please provide the estimated percentage usage of alectinib, crizotinib and ceritinib in ALK-positive untreated NSCLC 25. What treatment is currently standard of care for ALK-positive patients who have received treatment with chemotherapy (pemetrexed and cisplatin) prior to ALK status confirmation? 26. What percentage of patients receive treatment with	24)At present I believe 90% of patient newly presenting with ALK NSCLC would receive alectinib with a small percentage receiving crizotinib. There is a substantial legacy with some patients still receing 1st line crizotinib or certinib from before the availability of alectinib 25) Crizotinib followed by sequencing to brigatinib on progression

chemotherapy due to delays in confirming ALK status? 27. In clinical practice, would you expect any difference in outcomes of ALK-inhibitor use between Asian populations and other populations? 28. How would you describe the health related quality of life of patients with CNS progression versus of those without? 29. How would you describe the safety profile of the technology compared to other existing ALK-inhibitors?	26) This will vary markedly from centre to centre, and depend on testing pathways and methodology used. This may worsen with the development of the optimal lung pathway and the implementation of the genomic laboratory hubs but at present may be approximately 30-40% 27) The may be some differences in tolerability and slight improvements in PFS/OS in the Asian population but overall I think these are minor. 28) Patients with CNS progression have a significantly worse quality of life than those with extracranial disease. This is due to symptomatology, treatment with steroids, psychological impact and loss of independence (both mobility and driving) 29) I would say this was a well tolerated agent. The dose escalation strategy seems to have eliminated the issue with pulmonary toxicity and in general the elevations in amylase and creatine kinase are asymptomatic and do not require changes in therapy. It has less gastrointestinal toxicity than ceritinib and alectinib
Key messages	

25. In up to 5 bullet points, please summarise the key messages of your statement.

- Efficacy data similar to Alectinib the primary ALK inhibitor in use at present
- No issues with implementation
- Would provide an alternative 1st line option with different side effects and administration that would be welcomed by patients and clinicians
-
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Thank you for your time.

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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]

Confidential until published

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 128262

Completed 21 July 2020

CONTAINS [redacted]
AND [redacted] DATA

UNIVERSITY OF LIVERPOOL
LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

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Title:	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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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= and QALYs respectively; ITC approach=unadjusted Bucher, "official switchers", with re-censoring) to £1,520,162 (incremental cost and QALY= and 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.

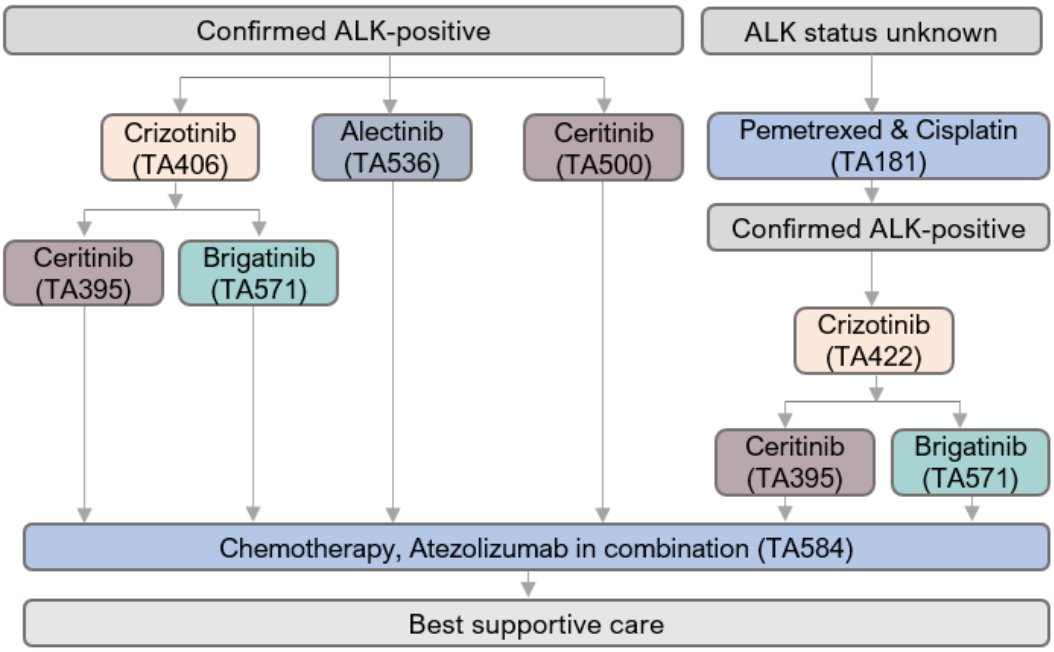

Figure 1 Current treatment pathway for patients with ALK-positive advanced NSCLC

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

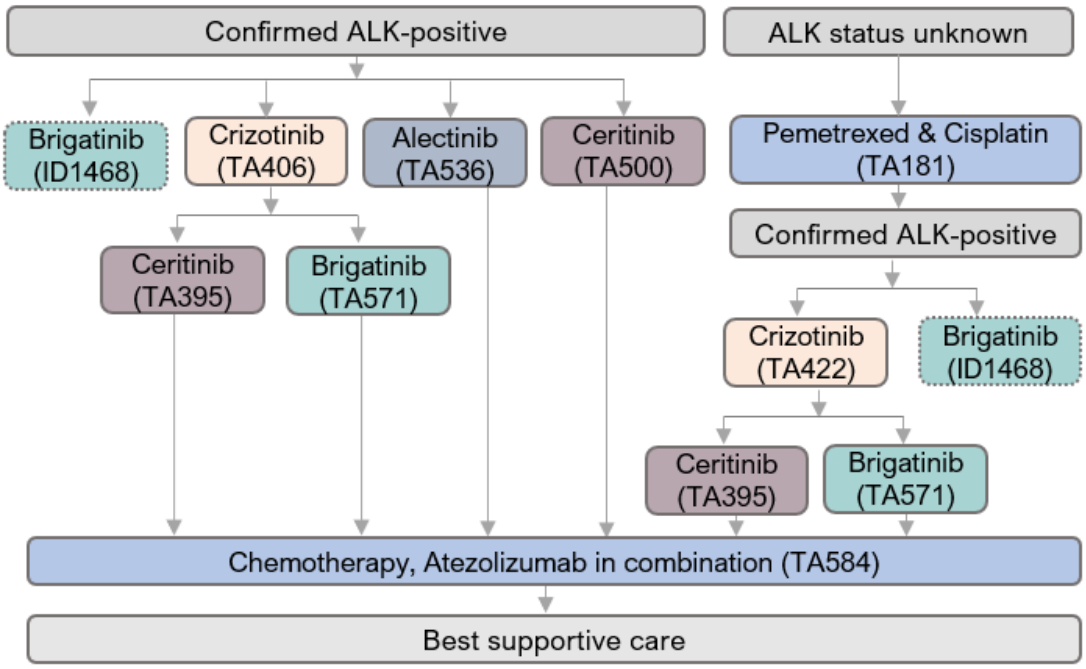

Figure 2 Proposed treatment pathway for patients with ALK-positive advanced NSCLC

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 36 (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.

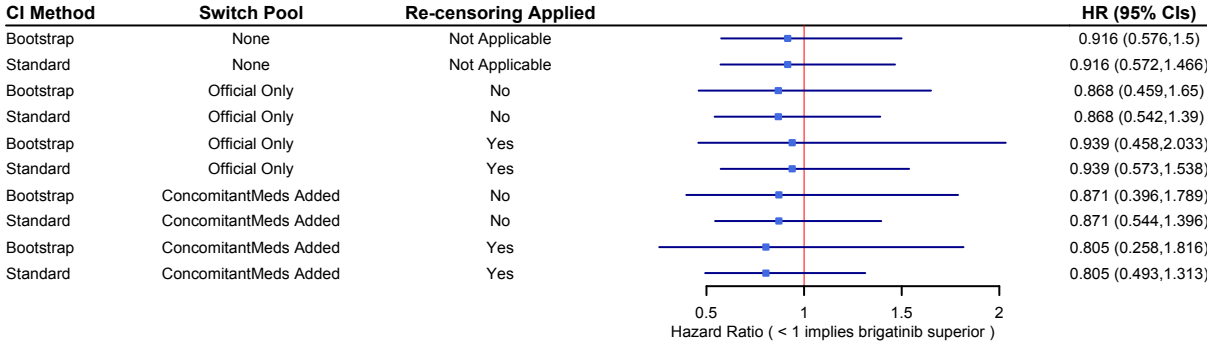

Figure 3 Brigatinib versus crizotinib OS HRs: results of alternative treatment switching adjustment scenarios

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.

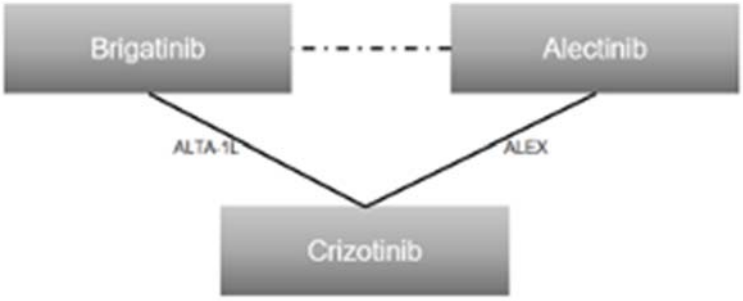

Figure 4 Network diagram of indirect comparison of brigatinib and alectinib

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 38 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).

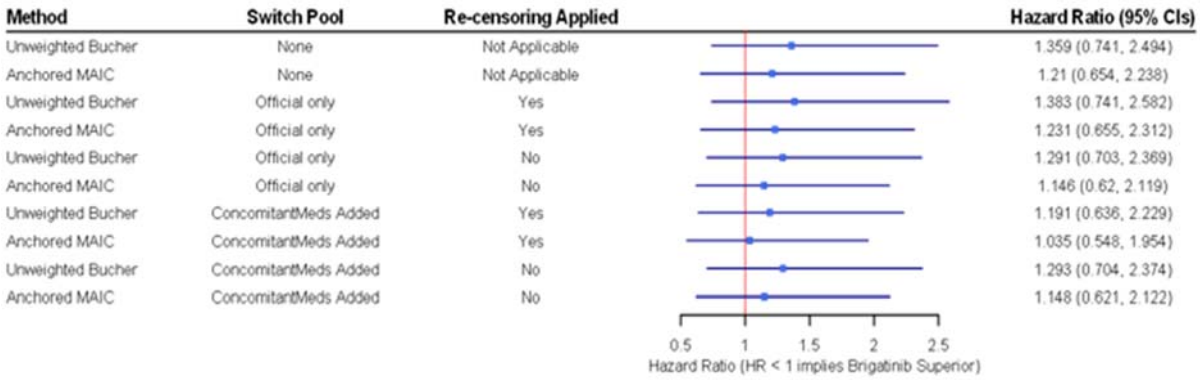

Figure 5 Brigatinib versus alectinib OS HRs: results from the anchored MAICs and unweighted Bucher ITCs with alternative treatment crossover scenarios

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.

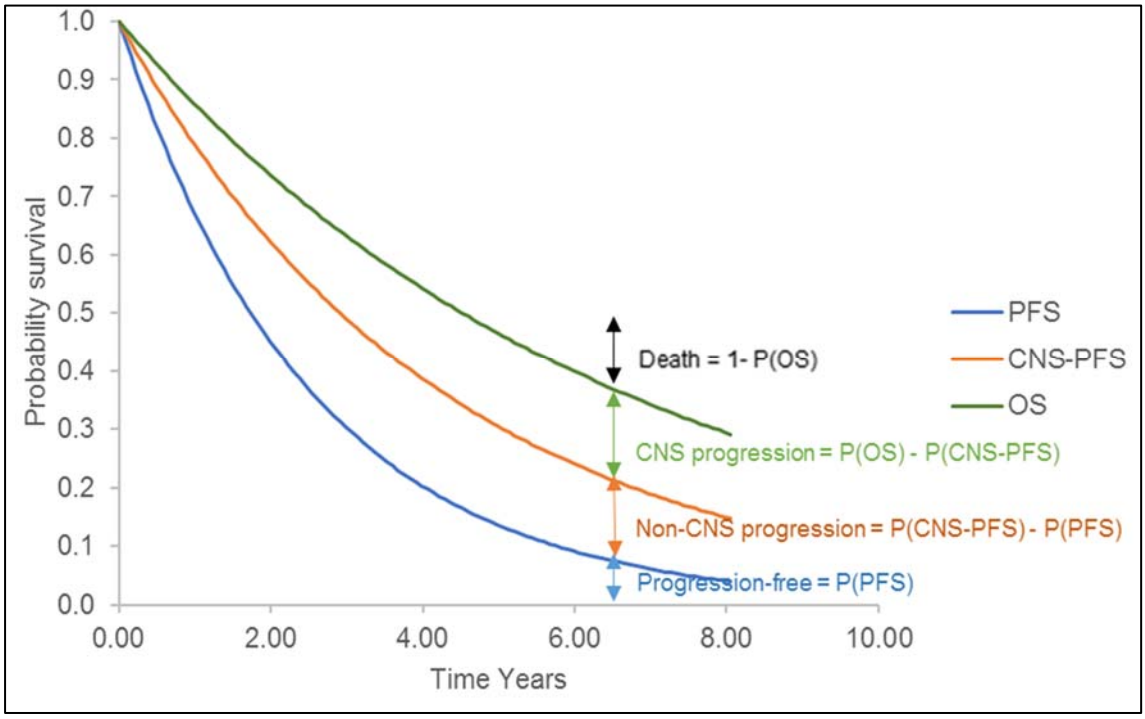

Figure 6 Structure of the company model

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).

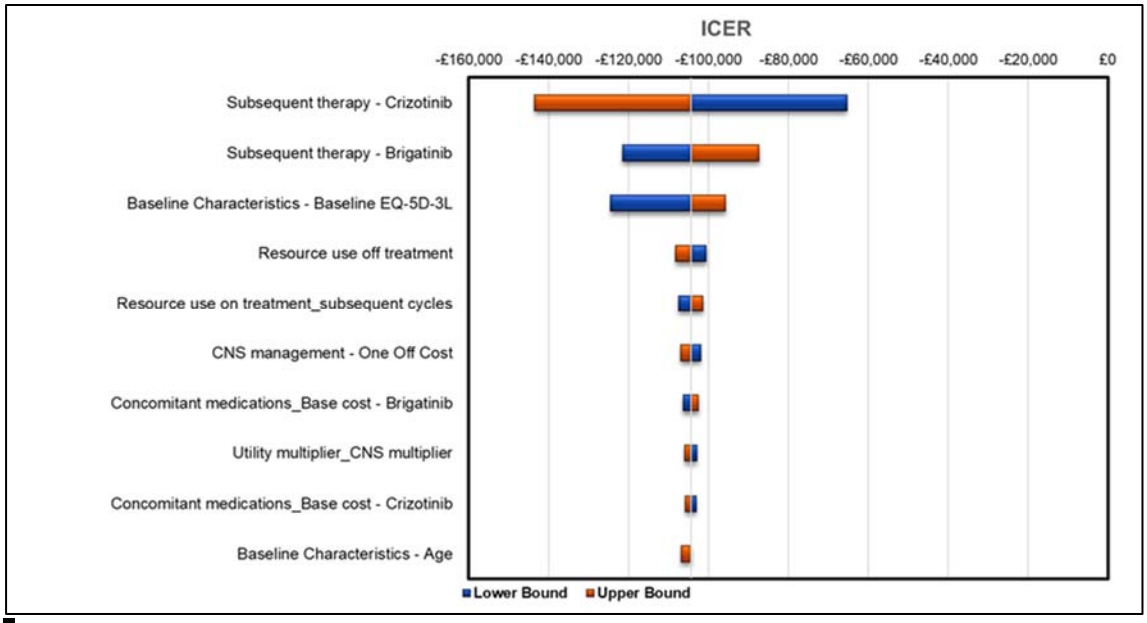

Figure 7 Tornado diagram showing OWSA results for the comparison of treatment with brigatinib versus crizotinib

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

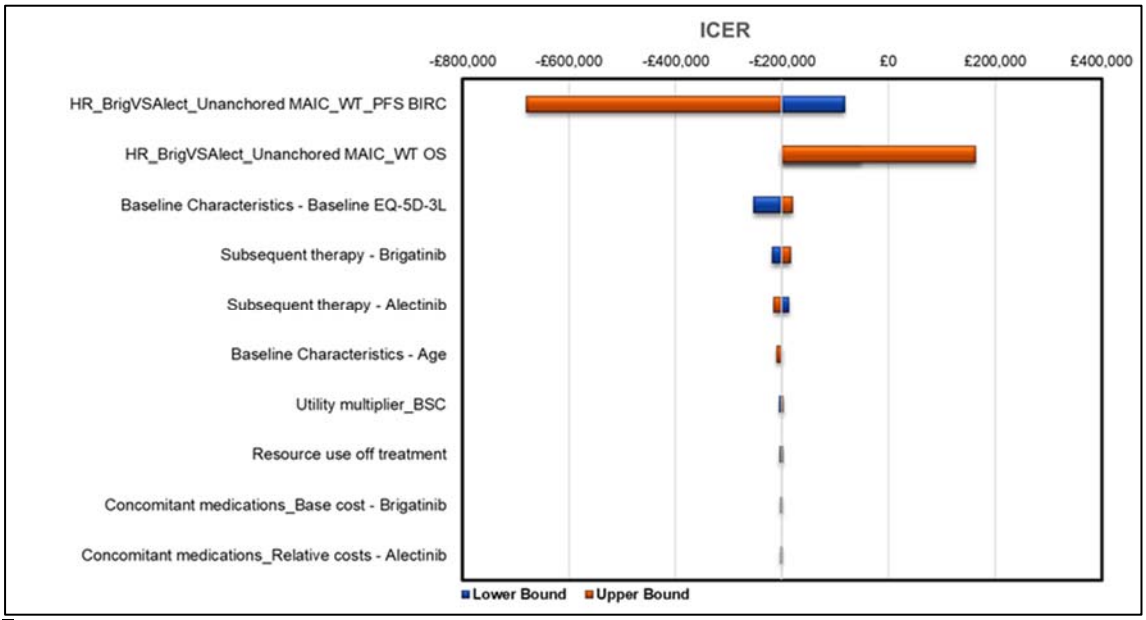

Figure 8 Tornado diagram showing OWSA results for the comparison of treatment with brigatinib versus alectinib

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.

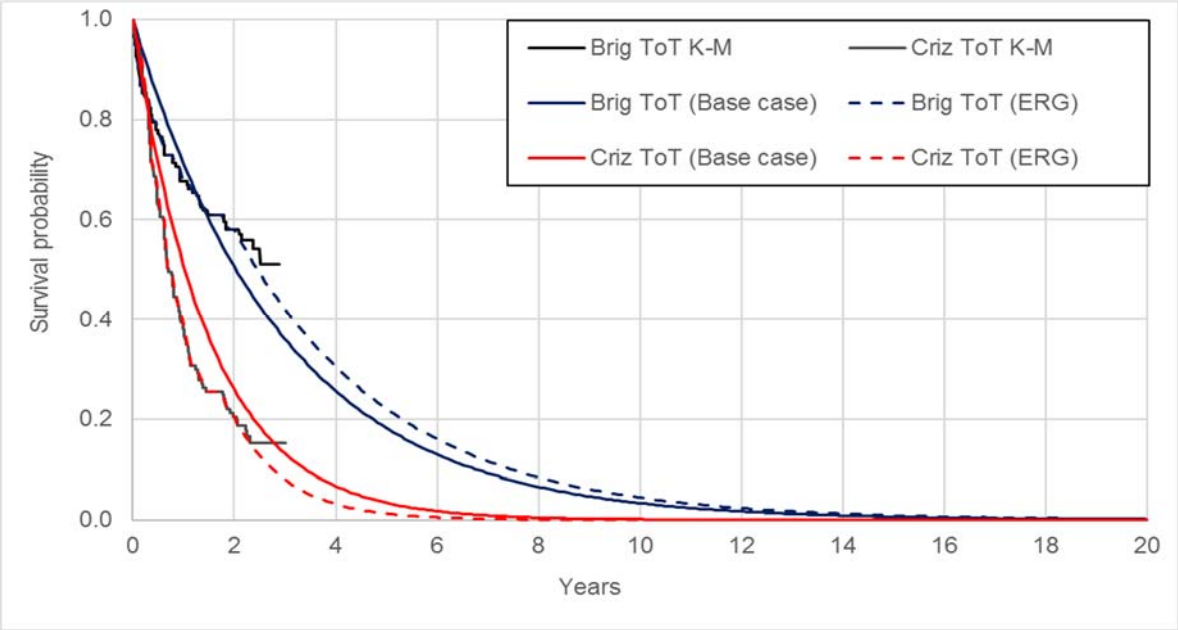

Figure 9 Progression-free survival and time on treatment curves for brigatinib and crizotinib: from company base model and from the ALTA-1L trial with appended exponential function

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.

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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))))

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check

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

You are asked to check the ERG report to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies, you must inform NICE by **5pm on Tuesday 4 August 2020** using the below comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The factual accuracy check form should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Rate of crossover in crizotinib arm – ALTA-1L trial

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 10 – *"Further, OS results were confounded due to the high proportion of patients in the crizotinib arm who received brigatinib on disease progression (82.4% of patients randomised to the crizotinib arm who progressed)."* This proportion only reflects the proportion of crizotinib treated patients who were "official switchers" (i.e. crossed over to brigatinib as per the crossover protocol). An additional 12 patients "unofficially" switched from crizotinib to brigatinib in the ALTA-1L trial. Hence, in total, 98.6% of patients who progressed in the crizotinib arm went on to receive brigatinib on disease progression.	Change this sentence to read: *"Further, OS results were confounded due to the high proportion of patients in the crizotinib arm who received brigatinib on disease progression (officially, 82.4% of patients randomised to the crizotinib arm who progressed; in total, 98.6% of patients who progressed on crizotinib)."*	To accurately reflect the total number of patients in the crizotinib arm who went on to receive brigatinib on disease progression.	Thank you for pointing this out. We wished to describe the proportion of patients in the crizotinib arm who received brigatinib on disease progression, whether officially or via concomitant medications Therefore, we have edited the sentence on page 10 to: *"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)."*

Issue 2 Proportion of patients with baseline brain metastases – ALTA-1L and ALEX trials

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 32 - *"The company highlights (CS, pp37-38) that compared with the ALEX trial, the ALTA-1L trial included a greater proportion of patients with brain*	Change this sentence to read: *"The company highlights (CS, pp37-38) that compared with the ALTA-1L trial, the ALEX trial included a greater proportion of patients with brain metastases at baseline (40% versus*	To accurately reflect the proportion of patients with brain metastases at baseline in both trials.	Thank you for pointing out the typographical error. We have corrected the sentence on page 32:

metastases at baseline (40% versus 30%).” This is incorrect as the trial names are the wrong way around. See Table 10 on page 37 of the CS.	*30%).”*		*“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.”*

Issue 3 Typo – page 37

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 37 - *“The ERG considers that key efficacy results were consistent between IA1 and IA2 and that the awareness of the amendments made to the statistical analysis plan following IA1 should is required when directly comparing numerical results from IA1 and IA2 (see Table 11 of this ERG report for details of amendments made).”* There is a typo in this sentence – correct this by deleting the word “should”.	This sentence should read: *“The ERG considers that key efficacy results were consistent between IA1 and IA2 and that the 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).”*	To correct a typo.	Thank you for pointing out the typographical error. We have corrected the sentence on page 37 to: *“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).”*

Issue 4 Typo – page 40

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 40 – *"The ERG agrees that, for this appraisal, the RPFSTM method is appropriate seems to have been implemented correctly."* There is a typo in this sentence – correct this by adding the word "and".	This sentence should read: *"The ERG agrees that, for this appraisal, the RPFSTM method is appropriate and seems to have been implemented correctly."*	To correct a typo.	Thank you for pointing out the typographical error. We have corrected the sentence on page 37 to: *The ERG agrees that, for this appraisal, the RPFSTM method is appropriate and seems to have been implemented correctly."*

Issue 5 Intracranial outcomes in the ALTA-1L trial

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 42 - *"The ERG considers the magnitude of treatment effect of brigatinib over crizotinib for intracranial outcomes is very uncertain."* We regard this comment as unfair because: 1) It fails to consider - in addition to intracranial ORR - other clinically relevant intracranial endpoints presented in the CS (e.g. intracranial PFS and intracranial DOR all of which show a clear benefit of brigatinib over crizotinib). 2) It fails to take into consideration clinical	We believe this sentence should be deleted. If the ERG is unwilling to do this, then we would suggest that this comment should be put into a broader context by also referencing some of the other evidence regarding intracranial outcomes from the ALTA-1L trial (e.g. BIRC-assessed PFS, BIRC-assessed intracranial duration of response). See Section B.2.6.3.3 of the CS for full details of the intracranial outcomes in the ALTA-1L trial.	To amend what we regard as an unfair comment.	This is the ERG interpretation of the evidence and not a factual error. We've added the word 'ORR' to the text on page 42: *"The ERG considers the magnitude of treatment effect of brigatinib over crizotinib for intracranial ORR outcomes is very uncertain."*

expert views on the intracranial efficacy of brigatinib compared to crizotinib (see page 158, Section.B.3.10.1of the CS). 3) There is a clear difference in confirmed intracranial ORR in patients with measurable baseline brain metastases between the crizotinib and the brigatinib arms – 77.8% vs. 26.1%, p value=0.0014 and an odds ratio of 11.67 in favour of brigatinib (see Table 16 of the CS). Furthermore, in the non-measurable brain metastases group (58.6% with brigatinib vs. 7.7% with crizotinib, p value=0.0001) and the any brain metastases group (66% vs. 16.3%, p value<0.0001), consistent benefit of brigatinib over crizotinib is shown across all the subgroups, despite the patient numbers (which is already accounted for in the statistically significant p-values). It is also important to note that these estimates are all based on confirmed, as opposed to unconfirmed intracranial response rates.			

Issue 6 HRQoL results in the ALTA-1L trial

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 45 – *"The company considers (CS, p160) that ALTA-1L trial HRQoL results demonstrate that treatment with*	Add the following sentence to the end of this paragraph: *"However, the ERG notes that the ALEX trial of alectinib vs. crizotinib was also open-label and*	To provide necessary context for the ERG's comment.	The section relates to HRQoL results from the ALTA-1L trial. Results of the ALEX trial are not relevant to this section.

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." This comment requires to be put into context.	*that no such improvement in HRQoL was seen for alectinib compared with crizotinib in that trial."*		No changes made.

Issue 7 Prognostic factors considered for the unanchored MAIC

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 50 – *"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."* This statement contradicts the ERG's conclusion in Appendix 2 which states: *"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*	We suggest the ERG modifies this statement to accurately reflect the fact that, although the unanchored MAIC relies on a strong assumption, clinical expert opinion sought by both the ERG and the company agrees that all prognostic factors were identified, and these were accordingly accounted for in the unanchored MAIC.	To correct a contradictory statement.	As stated within Appendix 9.2.2, the ERG considers that all important prognostic factors were identified and the method used to identify effect modifiers was appropriate. However, appropriate identification of prognostic factors and effect modifiers is not the same as accounting for all of these prognostic factors and effect modifiers in the analysis of the unanchored MAIC. Therefore, the highlighted

approach used by the company to identify effect modifiers was appropriate." This statement also fails to convey that extensive clinical feedback was sought to both identify and validate an exhaustive list of all clinically relevant prognostic factors and modifiers as described in the CS (see page 158, Section B.3.10 of the CS).			statements are not contradictory. No changes made.

Issue 8 Inclusion of ALESIA trial

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 52 – *"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"* This comment fails to acknowledge the important differences in population between ALTA-1L, ALEX and the ALESIA study. Race (Asian vs. non-Asian) is a known prognostic factor and treatment	We suggest the ERG includes a narrative which acknowledges the population differences between the ALTA-1L, ALESIA and ALEX studies and the impact of race as a prognostic factor.	To provide necessary context for the ERG's comment.	The company has omitted the reference to Appendix 9.3 at the end of the highlighted statement from page 52. Within Appendix 9.3, the ERG makes the following statement regarding the differences between the studies (page 95): "*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*

effect modifier as confirmed by clinical experts hence, including the ALESIA trial increases the uncertainty and would require matching based on race. We note that the ERG itself acknowledges on page 53 of its report that "The ERG highlights that the addition of data from the ALESIA trial increases uncertainty".			*permitted, investigator assessed PFS as the primary outcome).*" The ERG also highlights the limitations of the additional ITCs performed by the ERG in Appendix 9.3 (page 97): "*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…"* No changes made.

Issue 9 Costs and QALYs associated with PD for CNS vs. no CNS

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 59, Table 21 – "*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".* This statement is incorrect, CNS metastases is a known negative prognostic factor which also requires	We believe that this statement should be deleted.	To amend what we regard as an incorrect conclusion.	This is the ERG interpretation of the evidence and not a factual error. No changes made.

additional resource use to manage as validated by clinical experts. See page 160-161 Section B.3.10.1 of the CS. Furthermore, the model structure specifically differentiates PD for CNS vs. no CNS in line with the recommendation from the Committee during the Alectinib NICE appraisal (TA536), so that important differences in costs and QALYs can be adequately captured.			

Issue 10 Incremental QALYs for alectinib

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 68, Table 28 and Table 29 – Incremental QALYs for alectinib stated to be 0.450.	Amend the incremental QALYs for alectinib to 0.449	Inaccurate QALYs.	Thank you for pointing out the rounding error. We have corrected the incremental QALY for alectinib in Table 28 and Table 29.

Issue 11 Proportion of patients who receive chemotherapy as a subsequent therapy in the crizotinib arm

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In the CS, we assumed based on clinical expert input that 20% of	Amend the proportion of patients who go on to have subsequent chemotherapy in the	To correct a minor error in our	Although the ERG acknowledges that the

<table>
<tr>
<td>patients who progress on crizotinib go on to receive chemotherapy, but in the model we erroneously set this at 30%. Please find below the corrected base case results (with brigatinib PAS). This table would replace the existing Table 28 in the ERG report. The impact on the cost effectiveness results is minor.</td>
<td>crizotinib arm.</td>
<td>model.</td>
<td>proportion of patients who receive chemotherapy after progression on crizotinib should have been 20%, the ERG considers that it is equally plausible for this proportion to be 30%.

Table 26 of the ERG report already highlights that the proportion reported in the CS is different to the value used in the economic model.

For clarity, we added the value (20%) that was used in the model into the legend of Table 26.</td>
</tr>
<tr>
<td colspan="3">
<table>
<tr><th>Intervention</th><th>Total Costs</th><th>Total Life Years</th><th>Total QALYs</th><th>Inc Costs</th><th>Inc Life Years</th><th>Inc QALYs</th><th>ICER</th><th>Interpretation</th></tr>
<tr><td>Brigatinib</td><td>[redacted]</td><td>5.868</td><td>[redacted]</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Crizotinib</td><td>[redacted]</td><td>5.610</td><td>[redacted]</td><td>[redacted]</td><td>0.26</td><td>[redacted]</td><td>Brigatinib is dominant</td><td>SE Quadrant</td></tr>
<tr><td>Alectinib</td><td>[redacted]</td><td>5.072</td><td>[redacted]</td><td>[redacted]</td><td>0.80</td><td>[redacted]</td><td>Brigatinib is dominant</td><td>SE Quadrant</td></tr>
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(please cut and paste further tables as necessary)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technical report

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

This document is the technical report for this appraisal. It has been prepared by the NICE technical team.

The technical report and stakeholder's responses to it are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

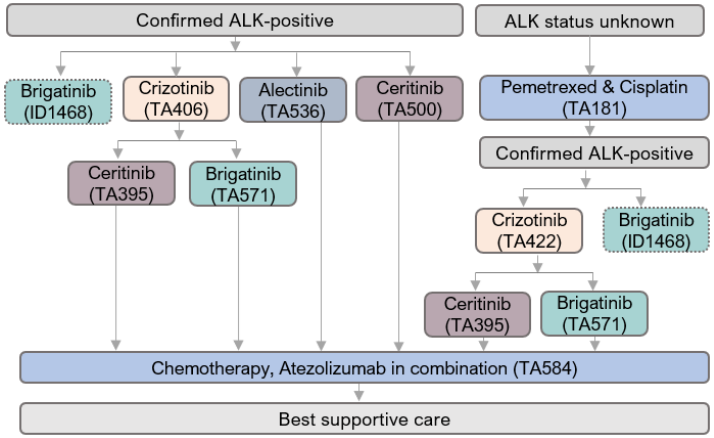
This report is based on:

- the evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

The technical report should be read with the full supporting documents for this appraisal.

1 Key issues summary

Issue	Summary	Technical Team Preliminary Judgement
1. Comparators	• The final scope listed alectinib, ceritinib and crizotinib as comparators, however the company submitted evidence for only alectinib and crizotinib • Evidence for ceritinib was not provided by the company since it said that market share data indicates that only between 0 – 2% of patients in the NHS receive ceritinib. This was confirmed by clinical advice and accepted by the ERG • Crizotinib is currently the only ALK-inhibitor recommended for use in patients with ALK-positive NSCLC who have received chemotherapy (TA422; see treatment pathway below). During a previous appraisal for the use of brigatinib (TA571), NHS England confirmed that ALK-status testing is now routine clinical practice, so ALK status is known before starting treatment. The committee therefore agreed to focus its discussion on people whose ALK status is known before starting treatment	• The technical team agrees that the comparator of interest is alectinib. Use of ceritinib is limited in current clinical practice and as discussed by NHS England in TA571, ALK status is generally known prior to treatment, limiting use of crizotinib

	 • The ERG considers that only alectinib is standard of care in the NHS.	
2. *Indirect treatment comparison (ITC)*	<u>Trials included within ITC:</u> • There is no direct evidence comparing brigatinib with alectinib so the company submitted ITCs including 2 trials: o The ALTA-1L trial (brigatinib versus crizotinib) o The ALEX trial (alectinib versus crizotinib). • The company excluded the J-ALEX and ALESIA trials because: o The patient populations were Asian and were not considered representative of UK clinical practice o The trials were not considered by the EMA during the approval process for alectinib or included in the company submission to NICE for alectinib (TA536). • The ERG agreed with the company that the J-ALEX trial was not appropriate because the alectinib dose is not consistent with UK clinical	• An anchored MAIC analysis that includes the ALESIA trial may be informative • Stakeholders are invited to comment on the generalisability of data from Asian populations to clinical practice in the NHS

	practice. However, the ERG considers it inappropriate to exclude ALESIA solely on the basis that the trial included an Asian study population: o In ALEX, 46% of patients were from Asian countries whereas the company considered 1% to be relevant for the UK population o The European Public Assessment Report (EPAR) for brigatinib states that it is possible to extrapolate efficacy in the Asian population to the European mainly white population, as brigatinib is a specific targeted treatment for ALK+ NSCLC. <u>ITC methods:</u> • The company conducted anchored MAICs, unanchored MAICs and unweighted Bucher ITCs • The company's base case utilised unanchored MAIC results. This was the only ITC that showed brigatinib overall survival (OS) to be numerically superior to alectinib (not statistically significant) o The company explained that this method enabled estimation of the relative efficacy of brigatinib and alectinib as if they were from two single arm trials (i.e. removing the crizotinib link which was influenced by treatment cross-over and differences in proportions of patients with baseline brain metastases) • Reliable unanchored MAIC results rely on an assumption that all prognostic factors/treatment effect modifiers are all accounted for. The ERG did not consider this assumption to be demonstrated within the company submission and does not	

	consider the unanchored MAIC estimates suitable for decision-making • The ERG considers the best available OS data to be from the anchored MAIC. However it does not have access to individual patient level data and prognostic factors to enable replication of the company's analysis, with inclusion of the ALESIA trial. Therefore, the ERG has conducted unweighted Bucher ITC scenario analyses including the ALESIA trial (Appendix 9.3 in ERG report). These analyses: o are similar to the company unweighted Bucher ITCs including only the ALTA-1L and ALEX trials o show no statistically significant evidence, that at the 5% significance level, treatment with brigatinib is superior alectinib o report HRs that favour alectinib more strongly compared with the company's analysis o are limited because different data sources were used, and it was not possible to adjust for cross-over or differences across the trial populations.	
3. Overall survival (OS)	<u>ALTA-1L OS data limitations:</u> • Immaturity of data (median OS had not been reached at the time of the second interim analysis). • Confounding due to 98.6% of patients in the crizotinib arm receiving brigatinib on disease progression (i.e. cross-over) • To adjust for the cross-over, the company applied Rank Preserving Structure Failure Time Model (RPSFTM) methods. The ERG considered these methods to be appropriate, however state that the	• There is uncertainty regarding the OS results and cost-effectiveness for brigatinib, however in all ERG scenarios for the comparison of brigatinib versus alectinib, brigatinib dominates • It may be informative to see a later data cut from the ALTA-1L trial if this is available

	available OS data did not allow for a robust analysis of the impact of crossover. <u>Modelling of OS (brigatinib vs. crizotinib):</u> • The company base case used different exponential functions to extrapolate OS Kaplan-Meier (K-M) data for brigatinib and crizotinib • The ERG argues that as no statistically significant OS difference was found between treatments, differences should not have been modelled. The ERG therefore generated results using the same (brigatinib) OS estimates for both treatment arms: o The ERG has stressed that they do not consider the OS between the two treatments to be the same. This scenario has been used to illustrate impact on cost effectiveness of not modelling an OS advantage for brigatinib over crizotinib (due to insufficient evidence). <u>Modelling of OS (brigatinib vs. alectinib):</u> • The company chose to use results from the unanchored MAIC within the model. However (as discussed in detail in Issue 2), the ERG does not consider this to be a robust analysis. <u>Cost-effectiveness estimates:</u> • In all ERG scenarios for the comparison of brigatinib versus alectinib, brigatinib dominates. However, the ERG has not generated a preferred incremental cost-effectiveness ratio (ICER) per QALY gained on the basis that it is not possible to generate robust OS estimates and consequently, it is not possible to generate robust cost-effectiveness results.	

4. Cost-comparison/minimisation versus alectinib	• The company submitted both a cost-effectiveness analysis and a cost-comparison/minimisation versus alectinib. The cost-comparison/minimisation approach was considered appropriate by the company on the basis that: o Cost-effectiveness analyses are difficult to interpret due to immaturity and uncertainty associated with OS outcomes (see Issue 3) o Equivalence between brigatinib and alectinib is supported by wide overlapping confidence intervals o Expert judgement from two advisory boards indicate that the real-world experience of brigatinib and alectinib are similar. • The NICE Methods guide state "A cost comparison case can be made if a health 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 same indication." However, the ERG does not consider the cost-comparison to be suitable in this appraisal on the basis that: o Clinical advice stating similarity is not the same as providing statistical evidence that that there is no difference between two treatments (or that brigatinib is non-inferior to alectinib) o A lack of demonstration of equivalence or non-inferiority introduces the risk that an inferior treatment to standard of care could be preferred on price-alone o Conclusions about non-inferiority and superiority are conclusions about the relative effectiveness of treatments and so	• • The technical team considers there to be a need for further clinical expert opinion on the equivalence between brigatinib and alectinib before a decision on the acceptability of a cost-comparison can be made

	require the same level of confidence in the evidence as cost-effectiveness analyses • The issues above were discussed during the clarification stage where the ERG asked the company to carry out a non-inferiority test versus alectinib. The company did not test for non-inferiority on the basis that: o Neither ALTA-1L nor the ALEX trial was designed to conduct non-inferiority assessment and both trials have relatively small sample sizes o There are differences between ALTA-1L and ALEX trial population that cannot be accounted for in a non-inferiority test o There is no Decision Support Unit guidance on setting a non-inferiority margin and that the margin would likely be wide.	

2 Other issues

Issue	Summary	Technical Team Preliminary Judgement
5. Duration of treatment	• The Summary of Product Characteristics (SPC) states that treatment with brigatinib should "continue as long as clinical benefit is observed". However, the company modelled time on treatment (ToT) based on PFS from the ALTA-1L trial and explained that this was aligned with the alectinib appraisal (TA536) and supported by clinical expert feedback from an advisory board. In addition, the company has stated that this approach avoids making an additional assumption for ToT relating to alectinib (due to a lack of data)	• The technical team agrees with the ERG preferred ToT as this is considered to better reflect duration of treatment seen within the ALTA-1L trial. This is consistent with the approach taken in other appraisals including TA571

	• The ERG preferred ToT to be based on available ToT K-M data from the ALTA-1L trial. Figure 43 in the company submission shows that ToT from the ALTA-1L trial was longer than PFS for brigatinib and shorter than PFS for crizotinib. This leads to the potential of underestimating the cost of brigatinib and overestimating the cost of crizotinib. • Based on this, the ERG modelled ToT for brigatinib and crizotinib 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. Brigatinib remained the dominant technology when these changes were included (i.e. when comparing treatments, brigatinib remained the option that is both more effective and less costly than the alternatives) • In a previous brigatinib appraisal (TA571), the committee preferred to use ToT data rather than PFS data for duration of treatment. Clinical experts explained that treatment is continued after disease progression because it might control cancer at sites other than the lungs. They estimated that, in clinical practice, progressed disease could be treated for a further 2 to 3 months. However, the committee was aware that ToT data were available from trials and concluded that data from the available evidence was preferred.	
6. Partitioning progressed disease by CNS progression	Use of partitioning: • The company model includes a progressed disease (PD) health state partitioned into a PD-no-CNS health state and a PD-CNS health state to reflect the assumption that costs and HRQoL differ	• The technical team understands that there may be other specific types of extrapulmonary progressions that could incur very specific costs. However the technical team believes these are likely to have a small impact

	between patients with and without CNS progression • Whilst the ERG agree that it is clinically plausible for patients with CNS progression to have a lower HRQoL and to incur more costs than those without, the point out that the company has not explored other specific types of extrapulmonary progression (e.g. bone metastasis) that may also incur very specific costs and QALYs • The ERG considers that if PFS is partitioned, then OS should also be partitioned • Overall, the ERG considers there is insufficient evidence to partition the PD health state. <u>Utility values within the PD-CNS health state:</u> • Utility values to represent the experience of patients in the PD-CNS state is based on data from a cross-sectional survey of patients with metastatic NSCLC in France and Germany (Roughley et al. (2014)). This is aligned with the data used in the alectinib NICE appraisal (TA536) • The ERG considers this data to be limited by: o The small number of patients with brain metastasis o A lack of reporting of other factors which may be responsible for the observed differences in HRQoL (for example, treatment-related AEs, comorbidities, and age) o Limited information which precludes further investigation of the reliability of the CNS multiplier used by the company. • The ERG states considers there to be insufficient evidence to apply robust utility weights to PD-CNS health state.	on the cost-effectiveness results of brigatinib • The technical team notes that the Roughley et al. (2014) abstract has limitations, however, it considers that these will have a small impact on the cost-effectiveness of brigatinib and it is suitable for use in this instance

7. Excluding PFS and intracranial PFS in treatment waning	• The company scenario analyses assume mortality rates after 7-, 10- and 20-years. The company explained that: o Treatment waning was explored in line with the alectinib appraisal (TA536) o Capping at 3- and 5-years were considered inappropriate given that 37% and 19% of patients remain on treatment with brigatinib at these time points. • The ERG considered the OS treatment waning scenarios to be flawed as: o PFS and intracranial PFS treatment effects were not waned o There is considerable uncertainty around the best way to estimate duration of treatment effect, that cannot be resolved using published data o There is uncertainty around the appropriate approach to implementing treatment waning within a partitioned survival model. • Although the company has stated that treatment waning was explored in line with the alectinib appraisal (TA532), the company did not include treatment waning for PFS (which was included within the TA532 appraisal). The company did not provide a reasoning for not including treatment waning for PFS and intracranial PFS • 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 technical team agrees with the ERG's approach of considering PFS and intracranial PFS within treatment waning
8. End-of-life criteria	• The company submission explains that brigatinib does not meet either the short life expectancy or	• The technical team agrees that brigatinib does not meet end-of-life criteria

	the extension to life criteria. The ERG agrees with this assessment.	

3 Questions for engagement

Issue 1: Comparators

1. Which ALK-inhibitors are typically used in routine NHS practice for patients with confirmed ALK-positive untreated NSCLC? Please provide details of which are most commonly used, e.g. Treatment 1: 60% of patients, Treatment 2: 10% of patients, and so on.

2. Which ALK-inhibitors are typically used in routine NHS practice for patients with confirmed ALK-positive NSCLC who have previously received treatment with chemotherapy (before confirmation of ALK status)? Please provide details of which are most commonly used, e.g. Treatment 1: 60% of patients, Treatment 2: 10% of patients, and so on.

Issue 2: Indirect Treatment Comparison

3. Is the population of the ALESIA trial (Asian population) generalisable to clinical practice in the NHS in England?

    a. Does race (Asian versus non-Asian) impact prognosis in patients with ALK+ NSCLC?

    b. Is race (Asian versus non-Asian) a treatment effect modifier? If yes, please provide details

Issue 3: Overall survival

4. What percentage of people with ALK-positive advanced NSCLC seen in the NHS would likely to be alive at 1-year, 2-years, 5-years, 10-years if treated with brigatinib? How would this compare to the OS expected for alectinib?

Issue 4: Cost-comparison/minimisation versus alectinib

5. Please describe similarities and differences seen with brigatinib and alectinib within clinical practice.

Issue 5: Duration of treatment

6. How long do people typically spend on ALK-inhibitors such as brigatinib, alectinib and crizotinib? Is duration of treatment likely to be the same for patients receiving alectinib and patients receiving brigatinib?

7. What percentage of patients stop treatment before disease progression? For what reasons is treatment stopped in these patients?

8. What percentage of patients continue treatment after progression of disease? For what reason would patients continue treatment after progression of disease

Issue 6: Partitioning progressed disease by CNS progression

9. Are there any other forms of extrapulmonary progression (e.g. bone metastasis) that may incur very specific costs and QALYs? If yes, please specify.

10. The company used data from an abstract by Roughley et al. (2014) to compare differences in health-related quality of life between patients with and without CNS-progression. 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). Does it appear to be clinically feasible for this difference in health-related quality of life to be due to CNS-progression?

    a. If not, what other factors could be contributing to a difference in health-related quality of life?

Issue 7: Excluding PFS and intracranial PFS within treatment waning

11. Do you consider it acceptable for treatment waning to include PFS and intracranial PFS?

12. What duration do you think is suitable for modelling treatment-waning?

NICE National Institute for Health and Care Excellence

Technical engagement response form

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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About you

Your name	Eugene Benson
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	Takeda UK Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Questions for engagement

<table>
<tr><th colspan="2">Issue 1: Comparators</th></tr>
<tr><td>Which ALK-inhibitors are typically used in routine NHS practice for patients with confirmed ALK-positive untreated NSCLC? Please provide details of which are most commonly used, e.g. Treatment 1: 60% of patients, Treatment 2: 10% of patients, and so on.</td><td>Alectinib is the main ALK inhibitor that is routinely used in NHS practice for untreated patients with confirmed ALK-positive NSCLC. Crizotinib and ceritinib are also available for use in untreated patients with ALK-positive NSCLC. However, both are less commonly used in the NHS in this setting due to the availability of alectinib which is considered by clinicians to be superior in efficacy and safety. This is reflected in the recent market research data (July 2020) presented below on the use of ALK inhibitors in the UK:

<table><tr><td>Treatment 1</td><td>Alectinib</td><td>85%</td><td rowspan="3">Source: Takeda UK Ltd presentation of Medimix LiveTrackerTM data of July 2020</td></tr><tr><td>Treatment 2</td><td>Crizotinib</td><td>7%</td></tr><tr><td>Treatment 3</td><td>Ceritinib</td><td>1%</td></tr></table>
Please note that the estimates above do not add up to 100% because chemotherapy is excluded as per question 1.</td></tr>
<tr><td><ol start="2">
Which ALK-inhibitors are typically used in routine NHS practice for patients with confirmed ALK-positive NSCLC who have previously received treatment with chemotherapy (before confirmation of ALK status)? Please provide details of which are most commonly used, e.g. Treatment 1: 60% of patients, Treatment 2: 10% of patients, and so on.</td><td>For patients with confirmed ALK-positive advanced NSCLC who have previously been treated with chemotherapy, the only available subsequent ALK inhibitor recommended by NICE for use in the NHS is crizotinib. There is no existing evidence and no funding in place for treatment with alectinib or ceritinib in ALK-positive patients who initially received chemotherapy.</td></tr>
</table>

Issue 2: Indirect Treatment Comparison	
3. *Is the population of the ALESIA trial (Asian population) generalisable to clinical practice in the NHS in England?* a) *Does race (Asian versus non-Asian) impact prognosis in patients with ALK+ NSCLC?* b) *Is race (Asian versus non-Asian) a treatment effect modifier? If yes, please provide details*	No, the population of the ALESIA study is not generalisable to clinical practice in England. The individuals recruited into the ALESIA study were exclusively east Asian specifically from China, South Korea and Thailand only. The most recent census by the Office of National Statistics showed that less than 2% of the UK population is likely to be from China, South Korea and Thailand. Therefore, the population of patients in the ALESIA study is not at all representative of the UK demographic. a) We believe this is really a question for clinical experts to answer. However, in addition to just focusing on race, we would suggest that NICE also seeks clinical expert input on the potential impact of the healthcare system itself (e.g. there may be significant regional differences in health systems and pathways of care, and these may impact patient outcomes). Such differences would again argue against the inclusion of the ALESIA trial within the ITCs. b) See our response to Question 3a).
Issue 3: Overall survival	
4. *What percentage of people with ALK-positive advanced NSCLC seen in the NHS would likely to be alive at 1-year, 2-years, 5-years, 10-years if treated with brigatinib? How would this compare to the OS expected for alectinib?*	We are unable to comment on the first question and we see this as one for clinical experts to address. Regarding the second question, as per our submission (and assuming all other things are equal) we would expect OS outcomes to be the same for patients treated with brigatinib or alectinib.
Issue 4: Cost-comparison/minimisation versus alectinib	
5. *Please describe similarities and differences seen with brigatinib and alectinib within clinical practice.*	**Similarities** • Brigatinib and alectinib are both oral, second-generation tyrosine kinase inhibitors with similar mechanisms of action which involves the inhibition of anaplastic lymphoma kinase (ALK).

	• Both have demonstrated an increased potency in inhibiting ALK compared to crizotinib. This has translated clinically, as both have shown improved efficacy vs. crizotinib in their respective head-to-head trials in the frontline setting. • Brigatinib and alectinib were both designed to penetrate the blood-brain barrier effectively and have demonstrated improved intracranial efficacy compared to crizotinib. • Both have good activity against ALK mutations that confer resistance to crizotinib. **<u>Differences</u>** • Brigatinib and alectinib are both administered orally. However, brigatinib has a more convenient dosing regimen of one tablet taken once-daily with or without food, whereas alectinib requires four capsules to be taken twice-daily with food. • Brigatinib has demonstrated efficacy in patients regardless of whether they have been previously treated with chemotherapy or not; alectinib has no evidence supporting its efficacy in patients who were initially treated with chemotherapy. • Brigatinib is the only ALK inhibitor in the frontline setting to have demonstrated clinically relevant and statistically significant quality of life improvements compared to crizotinib (in the ALTA-1L trial). Please see the company response to ERG clarification question 15 for more detailed information.
Issue 5: Duration of treatment	
6. *How long do people typically spend on ALK-inhibitors such as brigatinib, alectinib and crizotinib? Is duration of treatment likely to be the same for patients receiving alectinib and patients receiving brigatinib?*	We believe clinical experts are best placed to answer the first question. Our understanding is that the decision to continue treatment beyond progression (or not) is affected by the availability (or not) of efficacious subsequent therapies. If there are limited options available for a patient after progression, a clinician may opt to continue treatment beyond progression provided that the patient is still receiving some clinical benefit. Given that this is an

	area of some uncertainty, our health economic model explores a number of scenarios, including: treat until progression or treat 1, 2 or 3 cycles beyond progression. Regarding the second question, we would expect this to be the same for either brigatinib or alectinib in the frontline setting.
7. *What percentage of patients stop treatment before disease progression? For what reasons is treatment stopped in these patients?*	The majority of patients in the ALTA-1L and ALEX clinical trials continued treatment until they experienced progressive disease, failed to gain any clinical benefit or had intolerable toxicity. This is considered to be reflective of clinical practice. In the most recent ALTA-1L analyses, 13% of patients treated with brigatinib discontinued treatment before disease progression due to adverse events (compared with 9% of patients in the crizotinib arm). This is comparable with the alectinib arm in the ALEX study (also from the latest safety data), where 15% of patients treated with alectinib discontinued treatment due to adverse events, compared with 15% of patients treated with crizotinib. As we understand it, the major reasons for stopping treatment before disease progression would be adverse events or patient choice.
8. *What percentage of patients continue treatment after progression of disease? For what reason would patients continue treatment after progression of disease*	We believe clinical experts are best placed to answer these questions. Please also see our answer to question 6.
Issue 6: Partitioning progressed disease by CNS progression	
9. Are there any other forms of extrapulmonary progression (e.g. bone metastasis) that may incur very specific costs and QALYs? If yes, please specify.	With the exception of progression in the CNS, we are not aware of any other forms of extrapulmonary progression that incur very specific costs and QALYs. Clinician input has highlighted that the most significant of site-specific costs and health-related quality of life (HRQoL) impacts in advanced ALK-positive NSCLC are in patients with brain or CNS

	metastases. The CNS is a known and key sanctuary site for progression in advanced ALK-positive NSCLC. In the presence of CNS metastases, patients may experience greater symptom burden in the form of confusion, drowsiness, weakness in the limbs and severe headaches which can negatively impact their HRQoL. Additionally, everyday activities (such as driving) can be affected by CNS metastases. In relation to costs, CNS metastases are commonly associated with severe morbidity and increased economic burden resulting from frequent hospital visits and inpatient stays, increased medical treatment, imaging and radiotherapy. Because of these very specific impacts, CNS progression has been modelled separately within the cost-effectiveness model. This approach aligns with the methodology used in the alectinib NICE submission (TA536) – the key comparator to brigatinib. A practical consideration adds to this argument as studies of ALK-inhibitors have only reported CNS progression endpoints alongside PFS and OS data – this emphasises the relevance of intracranial endpoints to clinicians, patients and the overall healthcare system.
10. The company used data from an abstract by Roughley et al. (2014) to compare differences in health-related quality of life between patients with and without CNS-progression. 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). Does it appear to be clinically feasible for this difference in health-related quality of life to be due to CNS-progression? *a) If not, what other factors could be contributing to a difference in health-related quality of life?*	Yes, we believe this is clinically feasible given the significant increase in symptom burden due to CNS metastases (see our answer to Question 9 above). The utility decrement published by Roughley et al. (2014) provides the best available data for the impact of CNS metastases in this patient population. This is the same source which was used in the alectinib NICE submission (TA536). In line with the NICE Decision Support Unit Technical Support Documents, we have applied this using a multiplicative method to reflect the relative change in HRQoL (a 75.4% decrease in utility value). Based on the feedback we have received as part of this appraisal, we consider that a 75.4% decrease in utility is in line with patients' experience. Regarding Question 10 a), we are not aware of any other factors that could be contributing to this difference in health-related quality of life.

Issue 7: Excluding PFS and intracranial PFS within treatment waning	
11. *Do you consider it acceptable for treatment waning to include PFS and intracranial PFS?*	We do not think it is relevant to include treatment waning for PFS and intracranial PFS outcomes. On average, patients receive treatment until progression – based on the ALTA-1L clinical data and the feedback from the real-world setting. It is counter-intuitive to discontinue the treatment effect associated with brigatinib whilst patients are on treatment. It is important to note that the model discontinues the treatment effect completely in these scenarios and does not wane it over time – this is the same for OS endpoints. Therefore, scenarios looking at treatment waning for PFS and intracranial PFS remove the brigatinib treatment effect such that the probability of progression is in line with patients treated with crizotinib. This is considered clinically implausible whilst patients are still receiving brigatinib.
12. *What duration do you think is suitable for modelling treatment-waning?*	We would like to hear the feedback from the clinical experts in relation to this question. The duration of treatment effect beyond drug discontinuation is unknown for all ALK inhibitors. However, we consider that whilst patients are receiving treatment, the treatment effect would be expected to be maintained. Therefore, we consider that the application of treatment waning at 3- and 5-years is unlikely and conservative as approximately 37% and 19% of patients remain on treatment with brigatinib, respectively. As previously stated, the model discontinues the treatment effect completely in these scenarios and does not wane it over time. This simplification has been made due to the difficulty in reflecting this complex phenomenon in the model structure. Nevertheless, we consider that these scenarios show an unrealistic lower bound for the duration of the treatment effect. The scenarios presented in the company submission explored treatment waning at 7, 10 and 20 years: • By 7 years, <10% of patients remain on treatment. • By 10 years, <4% of patients remain on treatment.

	• By 20 years, approximately all patients have discontinued treatment. Please see Section B.3.8.3 and Table 63 in the company submission for a more detailed outline of the scenario analyses regarding treatment waning. It is important to note that this phenomenon affects the brigatinib vs. crizotinib comparison only. As the OS profiles for brigatinib and alectinib are considered to be the same, treatment waning does not impact the relative difference nor the cost-effectiveness results for the brigatinib vs. alectinib comparison.

NICE National Institute for Health and Care Excellence

Technical engagement response form

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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Deadline for comments **5.00pm on 1 October 2020**

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About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**ALK Positive UK**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Comparators	
1. *Which ALK-inhibitors are typically used in routine NHS practice for patients with confirmed ALK-positive untreated NSCLC? Please provide details of which are most commonly used, e.g. Treatment 1: 60% of patients, Treatment 2: 10% of patients, and so on.*	**Current practice, as evidenced by our members, suggests the majority of newly diagnosed ALK-positive patients are prescribed Alectinib first line – up to 95%. Of the 150+ ALK-positive patients in our group only a handful were started on chemotherapy before their ALK status had been confirmed.**
2. *Which ALK-inhibitors are typically used in routine NHS practice for patients with confirmed ALK-positive NSCLC who have previously received treatment with chemotherapy (before confirmation of ALK status)? Please provide details of which are most commonly used, e.g. Treatment 1: 60% of patients, Treatment 2: 10% of patients, and so on.*	**The experience of our members has shown that Crizotinib is prescribed in all cases where ALK-positive patients were started on chemotherapy treatment at first line.**
Issue 2: Indirect Treatment Comparison	
3. *Is the population of the ALESIA trial (Asian population) generalisable to clinical practice in the NHS in England?* *a) Does race (Asian versus non-Asian) impact prognosis in patients with ALK+ NSCLC?* *b) Is race (Asian versus non-Asian) a treatment effect modifier? If yes, please provide details*	**Whilst not medically qualified, my opinion would be there are distinct differences between Asian and non-Asian patients with ALK-positive NSCLC. This opinion is formed from the clinical papers I have read.**

Issue 3: Overall survival	
4. *What percentage of people with ALK-positive advanced NSCLC seen in the NHS would likely to be alive at 1-year, 2-years, 5-years, 10-years if treated with brigatinib? How would this compare to the OS expected for alectinib?*	**Not qualified to respond**
Issue 4: Cost-comparison/minimisation versus alectinib	
5. *Please describe similarities and differences seen with brigatinib and alectinib within clinical practice.*	I can't comment on clinical efficacy, however I would like to highlight the difference in side effects experienced by our members. When surveyed 32% of patients receiving Brigatinib (through the Takeda compassionate access programme) reported significant side effects vs 62% of patients receiving Alectinib.
Issue 5: Duration of treatment	
6. *How long do people typically spend on ALK-inhibitors such as brigatinib, alectinib and crizotinib? Is duration of treatment likely to be the same for patients receiving alectinib and patients receiving brigatinib?*	Not qualified to respond
7. *What percentage of patients stop treatment before disease progression? For what reasons is treatment stopped in these patients?*	Not qualified to respond
8. *What percentage of patients continue treatment after progression of disease? For what reason would patients continue treatment after progression of disease*	Not qualified to respond

Issue 6: Partitioning progressed disease by CNS progression	
9. *Are there any other forms of extrapulmonary progression (e.g. bone metastasis) that may incur very specific costs and QALYs? If yes, please specify.*	
10. *The company used data from an abstract by Roughley et al. (2014) to compare differences in health-related quality of life between patients with and without CNS-progression. 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). Does it appear to be clinically feasible for this difference in health-related quality of life to be due to CNS-progression?* a) *If not, what other factors could be contributing to a difference in health-related quality of life?*	The presence of CNS-progression has a significant impart on patients' quality of life. Many patients experience life changing effects – difficulty in walking, memory, increase in headaches with brain metastases. Patients have to surrender their driving licence once CNS-progression is diagnosed. Travel insurance can be much more difficult to acquire as well. Once CNS-progression has been confirmed, patients will be required to have brain MRI's (to review how the brain mets are responding to treatment) every 3 months rather than every 6 months for those patients without CNS-progression. This results in more visits to the hospital with more parking fees/bus fares/taxi fares. This increase in hospital visits may mean more childcare costs or loss of earnings if patients are working.
Issue 7: Excluding PFS and intracranial PFS within treatment waning	
11. *Do you consider it acceptable for treatment waning to include PFS and intracranial PFS?*	In my non-clinical capacity, I would say yes.
12. *What duration do you think is suitable for modelling treatment-waning?*	Not qualified to respond

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About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Roche UK**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	

Questions for engagement

Issue 1: Comparators	
1. *Which ALK-inhibitors are typically used in routine NHS practice for patients with confirmed ALK-positive untreated NSCLC? Please provide details of which are most commonly used, e.g. Treatment 1: 60% of patients, Treatment 2: 10% of patients, and so on.*	Alectinib is the current standard of care in the NHS practice for patients with confirmed ALK-positive untreated NSCLC.
2. *Which ALK-inhibitors are typically used in routine NHS practice for patients with confirmed ALK-positive NSCLC who have previously received treatment with chemotherapy (before confirmation of ALK status)? Please provide details of which are most commonly used, e.g. Treatment 1: 60% of patients, Treatment 2: 10% of patients, and so on.*	No comment
Issue 2: Indirect Treatment Comparison	
3. *Is the population of the ALESIA trial (Asian population) generalisable to clinical practice in the NHS in England?* *a) Does race (Asian versus non-Asian) impact prognosis in patients with ALK+ NSCLC?* *b) Is race (Asian versus non-Asian) a treatment effect modifier? If yes, please provide details*	No comment

Issue 3: Overall survival	
4. What percentage of people with ALK-positive advanced NSCLC seen in the NHS would likely to be alive at 1-year, 2-years, 5-years, 10-years if treated with brigatinib? How would this compare to the OS expected for alectinib?	When trying to predict alectinib vs brigatinib long term data through extrapolation, please seek out the evidence provided in the Mok et al trial for the alectinib 5yr OS. "Updated overall survival and final progression-free survival data for patients with treatment-naïve advanced ALK-positive non-small-cell lung cancer in the ALEX study. Mok et al. Annals of Onc 2020". “Mature PFS data showed significantly prolonged investigator-assessed PFS with alectinib [hazard ratio (HR) 0.43, 95% confidence interval (CI) 0.32-0.58; median PFS 34.8 versus 10.9 months crizotinib]. **Median OS was not reached with alectinib versus 57.4 months with crizotinib (stratified HR 0.67, 95% CI 0.46-0.98). The 5-year OS rate was 62.5% (95% CI 54.3-70.8) with alectinib and 45.5% (95% CI 33.6-57.4) with crizotinib, with 34.9% and 8.6% of patients still on study treatment, respectively.** The OS benefit of alectinib was seen in patients with central nervous system metastases at baseline [HR 0.58 (95% CI 0.34-1.00)] and those without [HR 0.76 (95% CI 0.45 -1.26)]. Median treatment duration was longer with alectinib (28.1 versus 10.8 months), and no new safety signals were observed.” “Mature PFS data from ALEX confirmed significant improvement in PFS for alectinib over crizotinib in ALK positive NSCLC. OS data remain immature, with a higher 5-year OS rate with alectinib versus crizotinib. This is the first global randomized study to show clinically meaningful improvement in OS for a next-generation tyrosine kinase inhibitor versus crizotinib in treatment-naive ALK-positive NSCLC.”
Issue 4: Cost-comparison/minimisation versus alectinib	
5. Please describe similarities and differences seen with brigatinib and alectinib within clinical practice.	No comment

Issue 5: Duration of treatment	
6. *How long do people typically spend on ALK-inhibitors such as brigatinib, alectinib and crizotinib? Is duration of treatment likely to be the same for patients receiving alectinib and patients receiving brigatinib?*	In the latest published data, the median treatment duration with alectinib was 28.1 months and no new safety signals were observed. (Ref: "Updated overall survival and final progression-free survival data for patients with treatment-naïve advanced ALK-positive non-small-cell lung cancer in the ALEX study. Mok et al. Annals of Onc 2020".)
7. *What percentage of patients stop treatment before disease progression? For what reasons is treatment stopped in these patients?*	Ref: ALEX Trial (NEJM 2017): Adverse events leading to discontinuation of treatment was 11% in the alectinib arm.
8. *What percentage of patients continue treatment after progression of disease? For what reason would patients continue treatment after progression of disease*	No comment
Issue 6: Partitioning progressed disease by CNS progression	
9. Are there any other forms of extrapulmonary progression (e.g. bone metastasis) that may incur very specific costs and QALYs? If yes, please specify.	No comment
10. The company used data from an abstract by Roughley et al. (2014) to compare differences in health-related quality of life between patients with and without CNS-progression. 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). Does it	No comment

appear to be clinically feasible for this difference in health-related quality of life to be due to CNS-progression? *a) If not, what other factors could be contributing to a difference in health-related quality of life?*	
Issue 7: Excluding PFS and intracranial PFS within treatment waning	
11. *Do you consider it acceptable for treatment waning to include PFS and intracranial PFS?*	No comment
12. *What duration do you think is suitable for modelling treatment-waning?*	No comment
Issue 8: Inaccuracies for correction	
13. Were there any discrepancies in the Technical Report?	Yes. Correction required on page 4 bullet point 1 in the Technical Report: In the ALEX trial the population of asian patients treated with alecensa was 45% NOT 46% (46% was crizotinib).