‘Brigatinib for treating ALK-positive non-small-cell lung cancer after crizotinib [ID1328]

A Single Technology Appraisal

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Ed Griffin	Provided overall project management and led the economic evaluation team. Oversight and author of sections within the critique of cost-effectiveness; wrote the Decision problem and End-of-life chapters; co-authored the Background chapter; collated the report.
Max Barnish	Provided project management of the clinical evidence team; led the critique of the clinical evidence; critiqued the methods of review(s) and wrote the corresponding sections of the report; critiqued the meta-analysis of Indirect Treatment Comparisons; contributed to the writing and editing of the report, including summary and background.
David Packman	Led the critique of the economic model; fully checked/corrected the model and added ERG-specific controls to create the ERG base case; and wrote the corresponding sections of the report.
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Sophie Dodman	Provided research assistance to the economic team; critiqued the economic literature search; drafted economic sections within critique of the economic evaluation. Provided quality assurance assistance to the clinical review team.
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Martin Hoyle	Project director with overall oversight and contribution to economic critique. Contributed to the editing of the report.

Please note that: Text highlighted in yellow and underlined is '[redacted]. Text highlighted in aqua and underlined is '[redacted]'. Text highlighted green and underlined is '[redacted]'.

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Abbreviations

AE	Adverse event
AIC	Akaike information criteria
ALK	Anaplastic lymphoma kinase
ALK+	Anaplastic lymphoma kinase positive
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
CS	Company submission
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
EoL	End of Life
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30
EOPE	Early onset pulmonary events
EQ-5D	EuroQol 5-dimensions
ERG	Evidence review group
ESS	Effective sample size
FE	Fixed effect

HR	Hazard ratio
HRQL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IDCR	Intracranial disease control rate
IGF-1R	Insulin-like growth factor 1 receptor
INV	Investigator
IQR	Inter-quartile range
IPD	Individual patient data
IRC	Independent review committee
ITC	Indirect treatment comparison
ITT	Intention-to-treat
K-M	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
NA	Not available
NCI	National Cancer Institute (US)
NHS	National health service
NICE	National Institute for Health and Care Excellence
NR	Nor reached *or* Not reported
NSCLC	Non-small cell lung cancer
OR	Odds ratio
ORR	Objective response rate/ Overall response rate
OS	Overall survival
PD	Progressive disease
PenTAG	Peninsula Technology Assessment Group
PF	Prognostic factor
PFS	Progression-free survival
PK	Pharmacokinetics
PR	Partial response
PRISMA	Preferred reporting items for systematic review and meta-analysis
PRO	Patient reported outcomes
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
SAE	Serious adverse event
SCLC	Small cell lung cancer
SD	Stable disease
SLR	Systematic literature review
SMC	Scottish medicines consortium
SmPC	Summary of product characteristics
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

1 Summary

1.1 Critique of the decision problem in the company submission

Brigatinib would sit alongside ceritinib in the targeted treatment options for previously treated, advanced or metastatic, ALK+ NSCLC, and be available to those who have previously been treated with crizotinib.

In the company's submission the modelled population, treatment strategies, and outcomes align with the technology's full currently proposed marketing authorisation for this indication, and the evaluation specifications set out in the project scope. The ERG are satisfied that the submission correctly addressed the decision problem.

1.2 Summary of clinical effectiveness evidence submitted by the company

Two clinical studies for brigatinib (ALTA and Study 101) and two clinical studies for ceritinib (ASCEND-2 and ASCEND-5) provided the clinical effectiveness evidence base for this appraisal. All four studies were single-arm for the purposes of this appraisal. ALTA (n=110 for the relevant arm) included one UK centre, while Study 101 (n=25 for the relevant subgroup) included no UK centres. A systematic literature review (SLR) was conducted to identify evidence and this was informed by four major scholarly bibliographic databases plus supplementary sources. Study selection was conducted using a three-stage process in Covidence software. Risk of bias assessment was conducted for both brigatinib studies using the broad domains of the Cochrane Risk of Bias tool, adapted for the single-arm nature of the studies. ALTA was rated as at low risk of bias on all domains, while Study 101 was rated as at low risk of bias for 5 domains and at unclear risk of bias for 3 domains. ASCEND-2 was critiqued as a single-arm study and risk of bias was generally low (although unclear for performance bias on safety outcomes and detection bias, and high for 'other bias'), while ASCEND-5 was critiqued as an RCT and risk of bias was generally low (although unclear for performance and detection bias on safety outcomes, and for 'other bias').

In the absence of direct head-to-head trials of brigatinib and ceritinib, indirect treatment comparison (ITC) analysis was used to compare the clinical effectiveness evidence for brigatinib and ceritinib. All eligible studies were single-arm studies for the purposes of this appraisal, and therefore all ITC analysis was unanchored. ITC analysis was originally provided using the February 2017 data cut for the ALTA trial for brigatinib, although at the Clarification stage an Addendum was provided updating the analysis to the September 2017 data cut. The outcome measures for ITC analysis were overall survival (OS), progression-

free survival (PFS), and objective response rate (ORR). Naïve ITC and matching-adjusted indirect comparison (MAIC) analyses were performed separately against ASCEND-2 and against ASCEND-5. Bayesian meta-analyses were performed to synthesise the outputs of the ITC analyses against the two comparator studies. For OS, using pooled ALTA/Study 101 data, the meta-analysed hazard ratio (HR) in favour of brigatinib was 2.14 (95% credible interval 1.51-3.06) for the fixed effects MAIC, 2.14 (1.29-3.54) for the random effects MAIC, 2.11 (1.56-2.86) for the fixed effects naïve ITC, and 2.10 (1.32-3.34) for the random effects naïve ITC. For both PFS and ORR, the provided meta-analyses only included ALTA data for brigatinib. For PFS, the meta-analysed HR in favour of brigatinib was 3.39 (2.39-4.82) for the fixed effects MAIC (using the full covariate set), 3.50 (2.06-6.26) for the random effects full MAIC, 3.01 (2.34-3.89) for the fixed effects naïve ITC, and 3.02 (1.90-4.78) for the random effects naïve ITC. For ORR, the meta-analysed odds ratio (OR) in favour of brigatinib was 0.48 (0.30-0.76) for the fixed effects full MAIC, 0.47 (0.26-0.85) for the random effects full MAIC, 0.49 (0.34-0.71) for the fixed effects naïve ITC, and 0.49 (0.29-0.82) for the random effects naïve ITC.

Therefore, the clinical effectiveness evidence presented by the company in the submission showed brigatinib to offer a significant advantage in terms of clinical effectiveness for brigatinib over ceritinib. In terms of safety and tolerability, there was an advantage for brigatinib in terms of common adverse events compared to ceritinib, although there was a slight increase in terms of serious adverse events for brigatinib.

1.3 Summary of the ERG's critique of the clinical effectiveness evidence submitted

The ERG considered the SLR to be broadly appropriate, although no specific searches for adverse events were reported and the SLR inclusion criteria were somewhat broader than the NICE scope, although all included studies met the NICE scope. The ERG noted that all included studies were single arm for the purposes of this appraisal, which raises questions about the robustness of the evidence base. There was a lack of clarity about data extraction methods in the SLR. The ERG considered that it would have been more appropriate to assess ASCEND-5 for risk of bias as a single-arm study not an RCT. The ERG performed this, and found the results of these two approaches to be consistent. The ERG largely agreed with the company with regard to risk of bias. It is important to note that the patients from Study 101 eligible for this appraisal represent a small sub-sample (n=25) of those from the total study. Kaplan-Meier curves were presented additionally for brigatinib patients with brain metastases. Compared to the intention to treat (ITT) population, brigatinib patients with brain metastases have a steeper drop in clinical outcomes over time.

Unanchored ITC analyses were performed. While NICE DSU TSD 18 recognises the limitations of unanchored ITCs, it does consider them to be appropriate in cases where there is no direct head-to-head evidence and no common comparator. Nevertheless, the general limitations and uncertainties associated with ITC analysis should be considered. Naïve ITC and population-adjusted MAIC analyses were both reported. The ERG considered this to be appropriate in light of the relative strengths and limitations of both approaches in the current context. The concept of performing multiple ITC analyses and then performing a meta-analysis of these is supported by NICE DSU TSD 18. The ERG note the considerable consistency of the meta-analysis results irrespective of the analytical choices made. The similarity of the results of the naïve ITC analyses and the MAIC analyses suggests that the population-matching process did not influence the results substantially. The evidence provided in the company submission (CS) consistently shows a significant advantage for brigatinib over ceritinib in terms of clinical effectiveness.

However, there were certain issues that the ERG noted with regard to the analytical methodology. Firstly, when ITC analyses against ASCEND-2 and ASCEND-5 were meta-analysed, there was no correction applied for correlated data since data from the brigatinib studies contribute twice to the analysis. NICE DSU TSD 2 recommends this correction be used, and that the absence of this correction may render the confidence intervals in the CS unrealistically precise. Secondly, for analyses using pooled ALTA and Study 101 for brigatinib, NICE DSU TSD 18 recommends that the data should have been meta-analysed rather than solely pooled. However, the ERG do note that there is considerable consistency between the results of analyses using pooled ALTA/Study 101 data and those using only ALTA data, where both are available. Thirdly, the ERG note that the prior chosen in the Bayesian meta-analysis was relatively generic, when a prior specifically for pharmacological data was also available in the source used by the company.

1.4 Summary of cost-effectiveness evidence submitted by the company

The company conducted a literature search to support its review of cost effectiveness. The same protocol was also used for the review of quality of life and the review of costs, with no changes. The company stated that the included economic studies were subsequently quality appraised, but these results were not reported. Of the 17 studies identified, none evaluated brigatinib.

Their *de novo* economic evaluation was in accordance to the specified population, using an ‘area under the curve’ partitioned survival semi-Markov model, with three health states: pre-progression, progressed and death. Clinical effectiveness was based on the four clinical

trials include in the clinical review (ALTA and Study 101 trials of brigatinib, and ASCEND-2 and ASCEND-5 trials of ceritinib). The Gompertz distribution was used to extrapolate both progression-free survival and overall survival outcomes for the baseline strategy (brigatinib), to which the indirect treatment comparison hazard ratios were applied to inform PFS and OS for ceritinib. Estimates for time on treatment in the company base case was based on treatment until progression, with the progression-free survival HR used to estimate time on treatment for the comparator, ceritinib. Both strategies assumed 1.5 months continuation on treatment post-progression.

The company adhered to the NICE reference case: the time horizon was effectively lifetime; HRQoL was measured in the brigatinib trial ALTA. For pre-progression utility estimates; mapping was used to convert EORTC-QLQ-C30 scores to EQ-5D scores; post-progression estimates were identified through literature searching; UK tariff values were used; evidence for unit costs came from standard sources; resource consumption was, where possible, identified through literature searching; and future costs and benefits were discounted at the recommended rate.

Mean utility values for health states were the same irrespective of treatment strategy except that decrements were differentially applied according the type and frequency of trial reported severe adverse events. Utility in the pre-progression (sourced from the ALTA trial) was subsequently adjusted using regression of trial baseline characteristics to fit the characteristics of the model's starting cohort. The mean values before AE adjustments were 0.774 for pre-progression, and 0.594 for post-progression.

The primary (deterministic) result set for brigatinib versus ceritinib (Sept 2017 ALTA data cut) found that a strategy of brigatinib was both more effective (1.58 LYs; 1.12 QALYs) and more costly (£61,097). The ICER = £54,311 per QALY gained. Additional QALYs were gained in both pre- and post- progression health states. Additional costs were almost entirely borne pre-progression (91.5%), since they were mostly the additional cost of purchasing brigatinib.

The company conducted (as is required) a univariate sensitivity analysis of deterministic parameters, and a probabilistic sensitivity analysis (PSA ICER = £51,882 per QALY gained). The PSA estimate did not depart significantly from the deterministic estimate.

The univariate analysis found the deterministic ICER sensitive to small changes in the OS hazard ratio and the OS and PFS distribution parameters, and to a lesser extent, some factors effecting estimates of utility (number of metastatic sites, age, and presence of brain metastases).

The company provided results for a range of scenarios for alternative approaches: use of the included data sources for ITC (relative effect); statistical distributions for outcome extrapolation; approaches to estimate time on treatment; lengths of treatment benefit; cost assumptions around wastage and administration. Results indicated that the ICER was sensitive to selection of trial data, selection of distribution for progression-free survival and overall survival extrapolation, as well as the method for estimates of time on treatment. The ICER was less sensitive to alternative cost assumptions, since ALK+ targeted treatment price (not explored in the main report) is the overwhelming factor.

1.5 Summary of the ERG's critique of the cost-effectiveness evidence submitted

The company's search objective, strategy and inclusion and exclusion criteria aligned with the parameters of the scope of this appraisal. The systematic review of cost-effectiveness studies followed general systematic review guidelines and appeared to be well-conducted. No economic studies were identified which evaluate the cost-effectiveness of brigatinib; but there exists sizable evidence to inform appropriate methods; and one fully published HTA is directly applicable to the ceritinib strategy. This was NICE TA395, an STA of ceritinib versus best supportive care in the same population and treatment line, so should be viewed as an informative source for consistency.

The structure of the company model was consistent with that used in numerous previous submissions for cancer, including ALK+ lung cancer. The use of a partition survival model, rather than a full Markov cohort model, is appropriate. It means that the clinical endpoints are estimated and extrapolated using time-variant parametric distributions, rather than fixed transition probabilities.

Outcomes used as inputs in the model were drawn from participants of the included trials; they match the population described in the NICE Scope. In order to estimate the PFS HR between brigatinib and ceritinib, the company chose to include a small subset of phase I/II participants, Study 101, in preference to ASCEND-5, a larger higher quality trial. A trade-off is necessitated by the combination of the unavailability of independent review board PFS results for Study 101, and the unavailability of investigator PFS results in ASCEND-5. So the ERG preference is for the independent result reporting and general higher quality of the ASCEND-5 trial. This is reflected in the ERG base case selections.

Perspective, time horizon and discounting are appropriate and consistent with NICE reference case. However, the accuracy of extrapolation of OS to the time horizon is very uncertain. Observation periods of trials are short, and the ability of clinicians to accurately forecast survival with a new treatment at second-line of advanced disease at 20 or even ten

years is tenuous. The company's selection Gompertz for PFS extrapolation is not justified. It may be acceptable when paired with the conservative selection of Gompertz for OS, but it has a secondary impact by producing the lowest estimate of OS for ceritinib of all the distributions, an important criterion for End of Life designation (comparator OS should be under 24 months). The best statistically fitting distribution is the Gamma, which we use for the ERG base case.

Consistent with NICE preferences, changes in HRQL were obtained from a relevant patient population. Utility values were calculated from preference data representative of the UK population and based on choice experiments. It is unclear what mapping algorithm was used to convert EORTC-QLQ-C30 to EQ-5D. The choice of algorithm was not justified and no sensitivity analyses explored the impact of alternative mapping functions. The ERG is satisfied with the company's selection of the two-category response definition (not-progressed; progressed) for the weighting of response rates in the estimation of progression-free utility. The approach is consistent with that used for the evaluation of ceritinib TA395 (Warwick ERG report, Section 5.2.7, p69). The regression of baseline trial characteristics in ALTA to derive adjusted baseline estimates for health state utilities, the methods to adjust utility for aging and treatment related risk of serious adverse events were reasonable. The health state utility value for pre-progression (0.744) was consistent with those reported in Chouaid *et al*, however this is a general NSCLC population, which differs from the younger healthier ALK+ population. Similarly, using Chouaid *et al.* to source the progression increment (0.17), and therefore the post-progression utility (0.594), may be a source of inaccuracy because literature estimates are lower (Chouaid *et al*. = 0.46; Nafees *et al.* = 0.473).

The unit costing of resources used appropriate and standard sources; resource type and consumption was verified by ERG expert clinical opinion as representative of clinical practice. However, assumptions underlying the mean per patient drug acquisition cost for each of the strategies did not utilise all the available information and may underestimate the ICER. Firstly, we believe that time on treatment should have been modelled independently of PFS given evidence ToT data from ALTA was available, and that discontinuation may not occur at radiological progression should some clinical benefit still be achievable. Instead, ToT should be extrapolated from the Kaplan-Meier ToT plot for a brigatinib baseline, and ceritinib derived using the PFS HR (in the absence of a ToT HR). This single change substantially increases the ICER for brigatinib versus ceritinib. Secondly, the company assumed full financial recovery of unused drug, meaning that tablets not used due to short-term dose reductions or treatment holidays are not wasted. Since longer term below target dosing is probably recoverable, the ERG preference is for a compromise whereby half the in-

trial mean dose adjustment is applied and costed in the model. Finally, the company do not include the pharmacy cost to the NHS of delivering these oral self-administration drugs to the patients' home, which the ERG are advised is widespread practice. The ERG base case includes a fixed unit cost per item per cycle (£42.50).

The ERG's primary (deterministic) result set for brigatinib versus ceritinib (Sept 2017 ALTA data cut) found that a strategy of brigatinib was both more effective (1.58 LYs; 1.16 QALYs) and more costly (£104,493). The ICER = £90,032 per QALY gained. In deterministic univariate sensitivity analysis, and probabilistic sensitivity analysis, the ERG found the ICER sensitive to the same parameters as the company model. A set of alternative scenario analyses focussing on the key areas of uncertainty in the ERG base case have been presented in Section 5.4. The areas of greatest uncertainty arise from the methods used to estimate beyond follow-up the risk of progression, death, and time of treatment.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

The company provides clinical effectiveness evidence from two brigatinib studies and two ceritinib studies resulting from a SLR that the ERG considered to be broadly appropriate and in line with the NICE scope for this appraisal.

The ERG considers the risk of bias assessment conducted by the company for both the brigatinib and ceritinib studies to be broadly appropriate.

The ERG considers the ITC analysis to be broadly appropriate and to be largely conducted in line with relevant NICE DSU TSD recommendations.

The ERG note the considerable consistency in the results of the meta-analyses of ITC analyses irrespective of the analytical strategy selected.

The company modelled a detailed simulation of patient outcomes and resource use.

Parameter uncertainty was explored and a broad set of alternative parameters and approaches were modelled and reported.

Model build, coding, and implementation was high quality and generally reliable.

1.6.2 Weaknesses and areas of uncertainty

All included studies were single-arm studies for the purposes of this appraisal, which raises questions about the robustness of the clinical effectiveness evidence base.

No correction for correlated data was applied when ITC analyses against ASCEND-2 and ASCEND-5 were meta-analysed. Such a correction is included in NICE DSU TSD recommendations.

For analyses involving both ALTA and Study 101, NICE DSU TSD recommendations would prefer that the studies had been meta-analysed, rather than simply pooled. However, the ERG note the considerable consistency between these analyses and the analyses that solely used ALTA as an evidence source for brigatinib, where both are available

A generic prior distribution was chosen in the Bayesian meta-analysis, when a prior distribution specifically for pharmacological data was also available.

The modelling of long-term PFS used brigatinib Study 101 in preference to the larger higher quality ceritinib trial ASCEND-5.

The trials underlying the model have short follow-up periods, which makes the extrapolation periods relatively long. Extrapolation under these conditions attracts significant uncertainty to the ICER, particularly the extrapolation of OS.

The mean OS of patients in the model's ceritinib strategy may have been underestimated due to the selection of the Gompertz statistical distribution for long-term estimation. This is relevant to considerations about End of Life designation.

The company made assumptions about treatment costing (time on treatment, wastage, and cost of home delivery) which we believe have underestimated the ICER.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

Following a full critique of the company economic evaluation, review of available data and NICE committee preferences in this disease area, the ERG adopted a new base case for the company model, with revisions in the following areas:

1. The data sources used for the simulation of PFS should include the ASCEND-5 trial in preference to Study 101. Since neither IRC nor INV reported data is available for all four included trials the inclusion the choice of which trials to include must incorporate considerations of trial size, quality, and availability of the preferred IRC reported outcomes. Using existing readily available analyses within the company model, we included ASCEND-5 by using the meta-analysis of the MAIC of ALTA versus ASCEND-2 (using INV results), and the MAIC of ALTA versus ASCEND-5 (using IRC results).

2. We prefer to extrapolate PFS to the full time horizon using the gamma, rather than Gompertz, distribution. This provides the best statistical fit to the observed data. The ERG rejects the company's justification for Gompertz, which is that the distribution should match the one chosen for OS (this would be a valid justification for retaining the same distribution between strategies for a single outcome). No implausible scenario whereby there become more patients progression-free than alive is created.

3. The estimate of time spent on treatment for both therapies can be improved. It is preferable to extrapolate observed ToT from ALTA, rather than assuming that brigatinib is discontinued 1.53 months after progression. Evidence from both ALTA and ASCEND-2, as well as clinical advice received by the ERG, supports a relaxed link between treatment discontinuation and progression. The post-progression period on treatment in ALTA was 1.53 months and in ASCEND-2, 3.1 months. Since it was not possible to calculate a hazard ratio for time of treatment, it is necessary to use the PFS HR as a best approximation to estimate time on ceritinib treatment. The ERG base case uses ToT extrapolation (gamma distribution) with a PFS HR (an existing alternative scenario presented by the company).

4. The company assume no wastage in their base case, i.e. the NHS saves all costs associated with reduced dose intensity observed in-trial (88.9% for brigatinib and 83.59% for ceritinib). The company justify the assumption of no wastage with the precedent of NICE TA395, however no wastage was not the final position of the committee. The committee settled on the pragmatic assumption that the NHS will pay for some unused tablets; that relative dose intensity adjustment should be lower than 100% but higher than the trial based estimate used by the company. Here we consider two ALK inhibitors with differing tolerability, so to maintain this characteristic we apply half the difference between observed and expected dose (Equal to [redacted]% for brigatinib, and 91.80% for ceritinib). Note that the observed relative RDI reported in the ALTA CSR was preferred to estimate reported in the CS.

5. The company assume there is no administration cost for brigatinib and ceritinib in their base case. In a scenario analysis they explore the impact of applying HRG currency code SB11Z; Deliver exclusively oral chemotherapy (unit cost = £170.75). The ERG consulted with a senior NHS pharmacist: typically pharmacy costs are outsourced for oral chemotherapy. For the NHS Peninsula Purchasing Alliance this cost (a home delivery charge) is £42.50 per item, monthly in this case. The ERG base case adopts this estimate.

Implementation of all five preferred approaches increased the ICER from the company base case estimate (£54,311 per QALY gained) to the ERG's base case estimate of £90,032 per QALY gained. An increase of 65.8%. Note that lack of randomised data; the small trials; and the long extrapolation of survival, all make these ICER estimates highly uncertain.

The ICERs here do not include the ceritinib or tentative brigatinib Patient Access Scheme arrangements. Results including these can be found in Appendices 1 and 2.

1.8 Innovation and end-of-life status

The company make a case for innovation by virtue of meaningful extension to life with improvement in progression-free life, relieving disease burden in a population whose general characteristics are of a type for which the benefits may not be fully captured in the QALY. (1) This population may slightly contrast with the older smoking population of the non-ALK+ lung cancer population but this argument is vague. However, the company makes the case for evaluation of brigatinib as an End of Life treatment.

Life expectancy criterion

We have found that, under the company's base case, the first EoL criterion is not strictly satisfied because the modelled mean life expectancy on the comparator treatment is slightly greater than 24 months (24.34 months, CS addendum, Appendix J update, p39, Table 17 – undiscounted life-years). This is not changed by the ERG base case. The range of median life-expectancies from the included ASCEND trials is below 24 months.

Extension of life criterion

The company modelled mean overall survival on ceritinib of 24.34 months (compare with median estimates of 14.9 months and 18.1 months in ASCEND-2 and ASCEND-5 respectively); and mean overall survival of brigatinib of 46.83 months, so the estimate of mean life extension is 22.49 months.

2 Background

2.1 Critique of company's description of the underlying health problem

The CS presents the health condition and treatment pathway on pages 14-16.

Lung cancer can be divided into two main histological categories: non-small-cell lung cancer (NSCLC) and small cell lung cancer. NSCLC has been estimated to account for 88% of all lung cancer cases.(2) Anaplastic lymphoma kinase (ALK) fusion genes are chromosomal alterations that are involved in tumour growth. They occur almost exclusively in tumours with non-squamous adenocarcinoma histology, which is confirmed in around 36% of NSCLC patients.(2) Approximately 5% of people with stage III or IV non-squamous NSCLC have ALK fusion genes, representing about 1,170 people in England and Wales.(3) NSCLC is most commonly diagnosed at an advanced stage (61% stage IIIB/IV).(2, 4) ALK+ NSCLC is associated with younger age than the overall NSCLC population(5, 6) and within a population with a profile of low-suspicion, since there may be no history of smoking.(7)

The population in this appraisal accords closely with the NICE TA395 appraisal for ceritinib for previously treated anaplastic lymphoma kinase positive non-small-cell lung cancer.(8) Relatively few people qualify for treatment with ALK+ targeted therapies, since they represent a subset of the NSCLC population. Indeed, even fewer qualify for these therapies at second-line, which is the treatment position for brigatinib under the proposed indication for market authorisation (expected from the EMA in September/October 2018).The company estimate that the likely eligible prevalent population for brigatinib treatment in England numbers 46. These are adults with ALK+ NSCLC with a good performance status (0 or 1), who have advanced disease and have been previously treated with crizotinib (any line). However, it is noted that this number is likely to fall in future with the increased availability and use of alternatives to crizotinib.

NICE guideline CG121 (Lung cancer diagnosis and management, 2011) recommends that ALK status testing should be performed for all people with non-squamous NSCLC at diagnosis, which may be up to 78% of patients with NSCLC as 22% will have squamous histology.(2, 9) Positive status on ALK testing is a prerequisite for crizotinib prescription, therefore repeat ALK testing prior to treatment with brigatinib should not be required in this population.(10) Platinum-based doublet chemotherapy was traditionally the mainstay of treatment and remains a treatment option, typically to be used in latter lines, along with the newer option of immunotherapy. Prior to the introduction of targeted ALK therapy, namely crizotinib, people with ALK+ NSCLC had double the risk of progression or recurrence of disease within five years compared those with ALK- disease.(11)

ALK+ targeted therapies have considerably improved response rates and survival considerably compared to traditional systemic non-targeted chemo-therapeutic approaches.(12, 13) At second-line after progression on crizotinib, ceritinib offers a median overall survival of 14.9 months according to the ASCEND-2 study and 18.1 months according to the ASCEND-5 study (Table 19), and a median progression-free survival of 5.7 months and 5.4 months according to these studies respectively (Table 20). Ceritinib is also approved for use as a first-line treatment, although this is outside the scope of this appraisal.

The company describe brain metastases as affecting up to 70% of patients with ALK+ NSCLC who have been previously treated with crizotinib.(14) Intracranial progression is reported to be due to acquired resistance to crizotinib, sub-optimal target inhibition (15) and inadequate penetration of crizotinib into the central nervous system (CNS).(16)

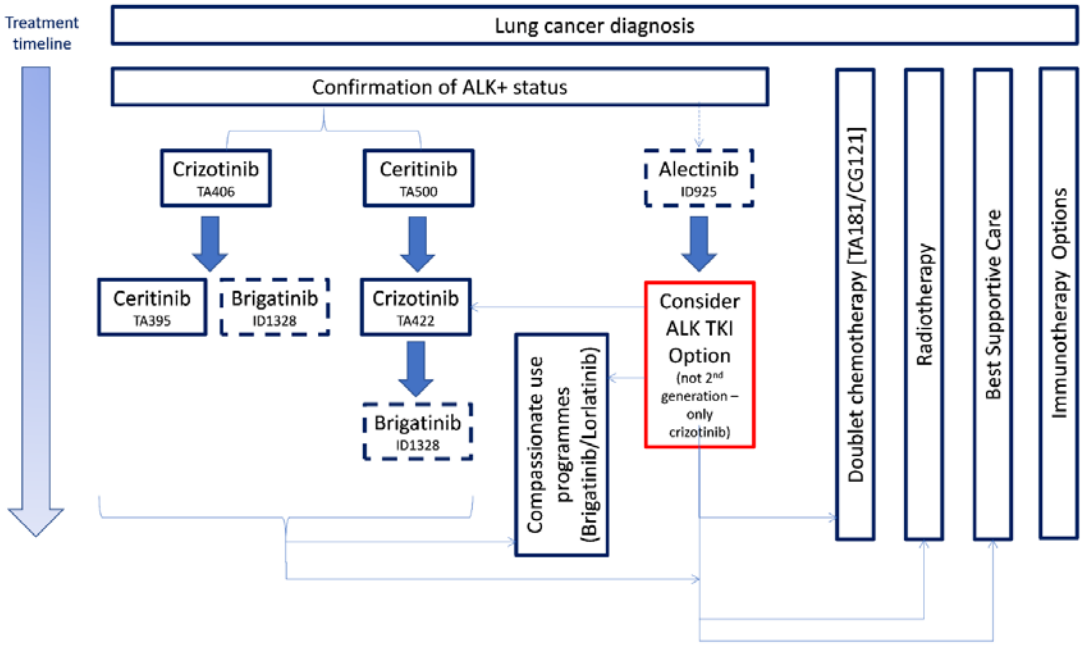
ERG opinion:

- The ERG with the help of advice from clinical experts in lung oncology considered the company's description of the underlying health problem to be accurate and relevant to the decision problem under consideration.

2.2 Critique of company's overview of current service provision

The company sets out the current treatment pathway as follows:

Figure 1. Treatment flow for ALK+ NSCLC patients



Source: CS, p.16, Figure 1 (Takeda Ltd)

The ERG and its clinical advisors consider the treatment pathway above to be reasonably representative of standard NHS treatment for ALK+ NSCLC currently in England and Wales. While ceritinib is approved for first-line use according to NICE TA500, clinical advisors to the ERG reported that it was rarely used in this position in the treatment pathway, partly due to concerns over adverse events and tolerability. In addition, there is little evidence to support the use of crizotinib after ceritinib, although it remains a potential treatment option. The clinical advisors to the ERG noted that additional treatment options, such as brigatinib, alectinib and lorlatinib, were sometimes available through compassionate use programmes and other initiatives, although they did not yet form part of standard routine care.

Changes to service provision

If approved by NICE for routine NHS use after crizotinib in England and Wales, brigatinib would offer a compelling alternative to ceritinib as second-line treatment for ALK+ NSCLC. The company state that brigatinib would be indicated for a small number of patients, currently estimated at 46. Clinical opinion sought by Takeda suggests that current use of crizotinib is over 95% in eligible patients, however Takeda (CS, p.16) and expert advisors to the ERG suggest this proportion to be lower and is expected to decline in future due to the introduction and wider adoption of alternative first-line treatments. Therefore, the number of patients for whom brigatinib would be indicated under the current appraisal is likely to fall over time. No service provision beyond the current levels of assessment and monitoring for ceritinib would be necessitated by the introduction of brigatinib into the current treatment pathway before or instead of ceritinib.

ERG opinion:

The CS accurately describes the treatment landscape around the proposed position of brigatinib; and fairly describes the extent of any changes that may be required to service provision (none substantial).

3 Critique of company's definition of decision problem

3.1 Population

The population in the decision problem was presented within the clinical evidence of the CS; it matched that modelled in the economic evaluation and the population described in the final scope (17). The population also aligns with the technology's full currently proposed marketing authorisation for this indication. The population of relevance is adults with ALK+ advanced NSCLC who have previously been treated with crizotinib.

3.2 Intervention

The intervention in the scope and decision problem is brigatinib (Alunbrig®), an oral CNS active pan-ALK inhibitor.(18) The summary of product characteristics (SmPC) and European public assessment report (EPAR) were provided in Appendix C. Note that brigatinib does not currently have EU marketing authorisation. In the CS the company state that it submitted an application in February 2018 and give a target of September/October 2018 for receiving full approval from the European Medicine Agency (EMA) Committee for Medicinal Products for Human Use (CHMP). Brigatinib is licensed in the U.S. On April 28, 2017, the U.S. Food and Drug Administration granted accelerated approval to brigatinib for the treatment of patients with metastatic anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. Approval was based on evidence from the ALTA trial; NCT02094573. As a condition of the accelerated approval, the company is required to verify the clinical benefit of brigatinib in a confirmatory trial.(19)
The company provided a description of the technology and the mechanism of action of brigatinib (CS Section B1.2, page 12, Table 2). Brigatinib is a phosphine oxide-containing, potent, orally active, tyrosine kinase inhibitor (TKI),(20) developed for the treatment of anaplastic lymphoma kinase rearranged (ALK+), non-small cell lung cancer (NSCLC), a genetically defined subgroup. Brigatinib was designed for activity against a broad range of ALK resistance mutations and has demonstrated a broad spectrum of preclinical activity against all seventeen of the secondary known crizotinib-resistant ALK mutants.(15) In this setting, after crizotinib therapy, it is likely that an ALK status would already be known at the time of consideration of brigatinib therapy.

Clinical evidence regarding brigatinib is from the ALTA study which is a phase II, open-label, non-comparator trial,(21) and from Study 101, a phase I/II, single arm, open-label, multi-cohort trial, in which a small subgroup of patients are eligible for the proposed indication.(1)

Brigatinib in the UK are film coated tablets (30mg, 90mg and 180mg dose options), they should be initiated and supervised by a physician but can be they are to be self-administered orally by the patient. The recommended starting dose of Alunbrig™ is 90 mg once daily for the first 7 days, then 180 mg once daily.(22) Tablets are available in 28-tablet (28-day) packs, for which the company give an intended list price of £4,900.(18)

3.3 Comparators

Brigatinib is compared to a single comparator, the current routine option for second-line targeted therapy after crizotinib. The comparator described in the CS decision problem is ceritinib, and this matches that specified in the NICE scope.

Ceritinib is a targeted therapy, a highly selective second-generation ALK inhibitor. It is indicated for the treatment of ALK+ metastatic NSCLC in those who have progressed on, or are intolerant to, treatment with crizotinib.(23) Ceritinib received conditional marketing authorisation for use after crizotinib from the European Medicines Agency (EMA) in May 2015(24); and from the FDA in April 2014.(25) In June 2016 ceritinib was recommended by NICE for use in the relevant population.(26) In January 2018, ceritinib was subsequently recommended for patients with untreated ALK+ NSCLC.(27)

3.4 Outcomes

The outcomes reported in the decision problem, described in the CS, and used in the economic evaluation, match those specified in the NICE scope. These are overall survival (OS), progression-free survival (PFS), response rates, adverse effects of treatment, and health-related quality of life (HRQoL).

3.5 Other relevant factors

The CS makes a case for innovation with the dual argument of meaningful extension to life as well as improvement in progression-free life. This is particularly impactful for this young, generally non-smoking population who typically present later than other lung cancer patients(5); with high rates of brain metastases(28); and progress within 1 year of initiation of treatment with crizotinib.(29) This patient population is viewed as moving quickly from high performance status to highly morbid. Brigatinib offers systemic and intracranial PFS response with the alleviation of intracranial symptoms, and the opportunity to continue working and family life; representing a relief from disease burden of a type the company suggests is not fully captured in the QALY.

Further, company suggests there is reluctance amongst clinicians to use ceritinib in these pre-treated patients with advanced disease stage due to its toxicity profile, since they consider the risk-benefit profile to be too unfavorable for their patients.(30)

4 Clinical effectiveness

4.1 Critique of the methods of review(s)

The company submission (CS) included a systematic literature review (SLR) to provide data relating to the clinical effectiveness and safety of brigatinib and to inform the indirect treatment comparisons (ITCs) of brigatinib versus ceritinib.

4.1.1 Searches

The company presented a literature search protocol to support its review of clinical effectiveness. This systematic review was conducted in two stages with two different search questions. Both protocols included systematic searches of key biomedical databases using a literature search strategy, searching of conference websites and clinical trials websites. The literature searches were last updated in November 2017.

The bibliographic database searching for part one of the systematic review used a search strategy that took the following form:

1. (controlled index terms for non small cell lung cancer) OR
2. (free-text terms for nsclc and for anaplastic lymphoma kinase) AND
3. (free-text terms for palliative therapy or brigatinib or crizotinib or ceritinib or alectinib) NOT
4. (a range of search terms to exclude case studies, letters and editorials) AND
5. (limited to 2006 onwards and humans).

The bibliographic database searching for part two of the systematic review used a search strategy that took the following form:

1. (controlled index terms for non small cell lung cancer) OR
2. (free-text terms for nsclc and for anaplastic lymphoma kinase) AND
3. (free-text terms for pemetrexed or docetaxel) AND
4. (free text terms for crizotinib) NOT
5. (a range of search terms to exclude case studies, letters and editorials) AND
6. (limited to 2006 onwards and humans).

The search strategy for each search stage was applied in the following bibliographic databases: Medline-in-Process and Medline (OvidSP), PubMed, Embase (platform not stated) and The Cochrane Library.

A range of other sources were also searched for each search stage, including: Science Citation Index and Conference Proceedings Citation Index (Web of Science), International

Clinical Trials Registry Platform, Clinicaltrials.gov and EU Clinical Trials Register. A good selection of conference websites was also searched.

The literature searching for clinical effectiveness studies for both stages is well conducted and reported. However there are some concerns:

- No information was given about the platform used for the Embase searches, therefore it was not possible to fully test the searches that were carried out.
- No MeSH (Medical Subject Heading) terms were searched for the majority of the search terms in the protocol. This is not best practice and there is a risk that some relevant papers could be missed if MeSH terms are not searched.

The company did not undertake separate literature searches to identify studies reporting adverse events. It is possible that the exclusion of case studies as publication type in the clinical effectiveness literature searches means that papers reporting adverse events may have been missed.

4.1.2 Inclusion criteria

The inclusion criteria for the company's SLR of clinical effectiveness (stage 1) are summarised in Table 1. These criteria were applied to searches undertaken on 2nd August 2017 and updated on 14th November 2017.

Table 1 Eligibility criteria for the SLR (Stage I)

Criterion	Inclusion criteria	Exclusion criteria
Population	Studies of patients: • Aged ≥ 18 years old • With non-small cell lung cancer (NSCLC) and altered anaplastic lymphoma kinase gene (ALK+): • Who have been previously treated with crizotinib	Studies of patients: • <18 years of age • Who have NSCLC but are not ALK+ • With small cell lung cancer (SCLC) • Who have not been treated with crizotinib • Who are treatment naïve
Interventions	Any of the following treatments post-crizotinib: • brigatinib • crizotinib • ceritinib • alectinib • best supportive care Interventions can be: • any treatment duration and follow-up period • monotherapies or in combination with any other intervention.	
Comparators	Studies that include a comparator of any type or with no comparator	

Criterion	Inclusion criteria	Exclusion criteria
Outcomes	Efficacy outcomes including: • Objective response rate (ORR) • Progression free survival (PFS) • Overall survival (OS) • Time to response • Duration of response (DOR) • Health related quality of life (HRQL) Safety outcomes: • Safety assessments e.g. examinations, vital signs and ECGs; • Adverse events (treatment emergent adverse events (TEAEs), treatment related adverse events (TRAEs), Serious adverse events (SAEs)) • Treatment interruption or discontinuation due to AEs • Frequency and severity of overall toxicity • Tolerability	• Reports with no eligible outcomes • Outcomes that are not reported independently for eligible patients e.g. where outcomes for NSCLC patients with and without ALK+ are grouped together.
Study designs	• RCTs; • Non-randomised clinical trials; • Open-label extension trials; • Retrospective and prospective cohort studies (for context only) ; • Abstracts, conference presentations and where adequate data are provided.; • Study protocols; • Systematic reviews (for hand-searching only).	• Phase I studies; • In vitro and animal studies; • Non-systematic reviews; • Opinion pieces; • Editorials; • Press releases; • Case series studies; • Case studies.
Limits	• Journal articles, reports, abstracts, posters and summaries • Papers published from 2006 (inclusive) to July 2017 • Conference abstracts published within the last three years (January 2013- July 2017, inclusive)	• Papers published before 2006 • Conference abstracts published before 2013
Abbreviations: AE, adverse event; ALK, anaplastic lymphoma kinase; DOR, duration of response; ECG, electrocardiogram; HRQL, health-related quality of life; NSCLC, non-small-cell lung cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RCT, randomised controlled trial; SCLC, small-cell lung cancer; SLR, systematic literature review; TEAE, treatment emergent adverse events; TRAE, treatment related adverse events		

Source: CS Appendix, pp.27-28, Table 6 (Takeda Ltd)

A second stage of searching was undertaken on 16th November 2017 and screened for potential inclusion using the criteria in Table 2.

Table 2 Eligibility criteria for the SLR (Stage II)

Criterion	Inclusion criteria	Exclusion criteria
Population	Studies of patients: • Aged ≥ 18 years old • With non-small cell lung cancer (NSCLC) and altered anaplastic lymphoma kinase gene (ALK+):	Studies of patients: • <18 years of age • Who have NSCLC but are not ALK+ • With small cell lung cancer (SCLC)

Criterion	Inclusion criteria	Exclusion criteria
	• Who have been previously treated with crizotinib	• Who have not been treated with crizotinib • Who are treatment naïve
Interventions	Any of the following treatments post-crizotinib: • Pemetrexed (Alimta ®) • Docetaxel (Taxotere ®) Interventions can be: • Any treatment duration and follow-up period • Monotherapies or in combination with any other intervention.	
Comparators	Studies that include a comparator of any type or with no comparator	
Outcomes	Efficacy outcomes including: • Objective response rate (ORR) • Progression free survival (PFS) • Overall survival (OS) • Time to response • Duration of response (DOR) • Health related quality of life (HRQL) Safety outcomes: • Safety assessments e.g. examinations, vital signs and ECGs; • Adverse events (treatment emergent adverse events (TEAEs), treatment related adverse events (TRAEs), Serious adverse events (SAEs)) • Treatment interruption or discontinuation due to AEs • Frequency and severity of overall toxicity • Tolerability	• Reports with no eligible outcomes • Outcomes that are not reported independently for eligible patients e.g. where outcomes for NSCLC patients with and without ALK+ are grouped together.
Study designs	• Randomised controlled trials (RCTs); • Non-randomised clinical trials; • Open-label extension trials; • Retrospective and prospective observational studies (for context only) ; • Abstracts, conference presentations and where adequate data are provided.; • Study protocols; • Systematic reviews (for hand-searching only).	• Phase I studies; • In vitro and animal studies; • Non-systematic reviews; • Opinion pieces; • Editorials; • Press releases; • Case series studies; • Case studies.
Limits	• Journal articles, reports, abstracts, posters and summaries • Papers published from 2006 (inclusive) to July 2017 • Conference abstracts published within the last three years (January 2013- July 2017, inclusive)	• Papers published before 2006 • Conference abstracts published before 2013
Abbreviations: AE, adverse event; ALK, anaplastic lymphoma kinase; DOR, duration of response; ECG, electrocardiogram; HRQL, health-related quality of life; NSCLC, non-small-cell lung cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RCT, randomised controlled trial; SCLC, small-cell lung cancer; SLR, systematic literature review; TEAE, treatment emergent adverse events; TRAE, treatment related adverse events		

Source: CS Appendix, p29-30, Table 7 (Takeda Ltd)

The inclusion criteria were broadly appropriate and consistent with the decision problem specified in the final NICE scope, taking the criteria across the two stages to represent a whole. The CS does not however provide a clear rationale for separating the process into these two stages, which the ERG does not consider to be standard practice. The first stage was a search targeted at ALK inhibitors, while the second stage was a search targeted at chemotherapy. The likely impact of this is small, if the two stages were themselves conducted and combined appropriately. However, chemotherapy does not fit within the NICE scope for this appraisal, so stage two of the searches does not actually contribute to identifying relevant evidence for this appraisal.

The inclusion criteria for the company SLR encompass all relevant technologies, but also includes additional interventions that are beyond the scope of the NICE appraisal. The SLR restricts the population to adults in line with the inclusion criteria for the pivotal brigatinib studies. We also note that only studies from 2006 onwards were included. Start date limitations can be problematic in the context of systematic reviews. However, in this instance, a start date of 2006 appears justifiable in line with the drug development timescales. All relevant outcomes from the NICE scope are included, although additional outcomes are also included. The ERG has no substantial concerns about the stated inclusion criteria.

4.1.3 Critique of data extraction

A three-stage screening process was conducted separately for stages I and II of the search. Covidence software was used, which has been shown to have both substantial strengths and limitations as a SLR facilitation tool.(31) However, it is a popular tool, and its choice appears justifiable.

The three stages of study selection are detailed below (*Source: CS Appendix, p30*):

1. “At the first stage the search results were uploaded to EndNote software and were scanned by a single experienced reviewer who removed obviously irrelevant records (e.g. animal studies, editorials, case-reports).

2. The titles and abstracts of remaining records were then assessed based on the eligibility criteria. Two independent reviewers undertook this process using Covidence online software. Disagreements between reviewers regarding the inclusion or exclusion of a record were discussed with a third reviewer. If there was uncertainty about the relevance of a record based on the abstract alone, it was included in the full text screening stage. The number of rejected records at the title and abstract screening Stage are shown in the PRISMA diagrams.

3. The full text of potentially relevant studies was obtained. Two independent reviewers using Covidence online software assessed the full documents in detail for eligibility. Disagreements were resolved by discussion with a third reviewer. Non-English studies that were potentially relevant were translated at this stage and screened in the same way as English studies."

The latter two stages were conducted by two independent reviewers, with any discrepancies reconciled by a third independent reviewer. The ERG consider this to be good methodological practice. The initial screening stage, however, was conducted by only one reviewer, which is a departure from good practice. However, the ERG considers that the likely impact of this is low since it relates solely to the exclusion of 'obviously irrelevant records', which marginal and subjective decisions are unlikely to occur.

Data extraction methods for included studies in the clinical effectiveness SLR are not provided in the CS. Therefore, the ERG could not critique the company's data extraction methodology specifically for the clinical effectiveness SLR. However, it is stated that two independent reviewers were used for the data extraction in the cost-effectiveness SLR (CS Appendix, p.90). Provided that this approach was also used for the clinical effectiveness SLR, the ERG would be satisfied with its appropriateness.

Quality assessment methods

The company conducted a quality appraisal of the two brigatinib studies (ALTA and Study 101). For the purposes of this STA, and thus for quality assessment purposes, the two brigatinib studies were considered to be single-arm trials, even though the ALTA trial is an RCT of two different brigatinib dosing regimens. The ERG agree that it is correct to consider both trials to be single-arm studies for the purposes of this STA and that study quality should be evaluated based on a single-arm design. It is important to note that single arm studies are open to considerable bias compared with RCT designs, for example. Indeed the company states that:

"…the non-RCTs had a high risk of 'other bias' in that they did not include a control arm or comparator. Without the inclusion of a control arm, it is not possible to conclude with certainty that outcomes observed are directly caused by study interventions." (CS Appendix, p80)

The company address this risk of bias by performing MAIC analyses. A critique of the MAIC analyses is available in sections 4.3 and 4.4.

The company assessed risk of bias in the two brigatinib studies using the broad domains of the Cochrane Risk of Bias tool. The Cochrane Risk of Bias tool is designed to assess RCTs. Adaptions were made (see Table 7 and Table 8), therefore, to account for the fact that both trials were single-arm studies for the purposes of this STA. The company used the CRD guidance given for quasi-experimental study designs to make these adaptions. It should be noted that the CRD guidance does not give specific detailed instructions for adapting the tool, rather general guidance about appraising risk of bias in different study designs (including quasi-experimental designs) is provided.(32) The CRD guidance does note that many of the key aspects of risk of bias that are evaluated in RCTs can also be evaluated in quasi-experimental designs,(32) and the company have done this by assessing blinding (of participants and study personnel and outcome assessors), adequacy of follow-up, attrition bias (including the appropriateness of the analysis) and reporting bias. The company has also included an evaluation of participant selection, including representativeness of the recruited sample.

The ERG is satisfied that all key areas of potential bias have been considered in the quality assessment. Although the Cochrane Risk of Bias tool is the usual tool used in the assessment of RCTs, and the ERG feel that it has been appropriately adapted, an alternative approach to the one used by the company would have been to use a quality appraisal tool more suited to single-arm study designs (e.g. the CASP tool for cohort studies).(33) However, the ERG notes that all key aspects of risk of bias included in this alternative tool are covered in the assessment made by the company.

Evidence synthesis

The CS reports that “no meta-analysis was performed because the brigatinib evidence was provided by the availability of individual patient data (IPD) from the two single-arm studies: ALTA and Study 101 as described further in Section B.2.9.” (CS p51). However, a meta-analysis was indeed used to synthesise data from matched-adjusted indirect comparison (MAIC) analyses, which are critiqued below in Section 4.4. The overall evidence synthesis approach comprised indirect treatment comparisons (ITCs) – using both naïve and MAIC approaches – for pooled brigatinib data from ALTA and Study 101 compared separately against ceritinib data from ASCEND-2 and ASCEND-5. Then, separately for the naïve and MAIC approaches, the ITC results against ASCEND-2 were meta-analysed with the ITC results against ASCEND-5, to provide an overall estimate of clinical effectiveness.

4.1.4 Critique of key studies

4.1.4.1 Summary of excluded studies

Two hundred and seventy two publications were excluded at the full-text screening from stage I of the searches, which as discussed above the ERG considered to be the searching stage relevant to the appraisal. A full list of excluded studies with the reasons for exclusion is provided in Appendix 3, Table 56 and Table 57.

The reasons for excluding studies at full-text screening were largely consistent with the inclusion criteria for the company SLR. However, in a few instances, it appears that the criteria may not have been followed strictly. Seven publications were excluded at the full-text screen of stage I searches for having fewer than 10 patients. A minimum number of patients per study is not mentioned in the inclusion criteria for the company SLR, although very low numbers of participants are unlikely to produce generalizable results, so this decision does not appear unreasonable to the ERG.

'Relevant SLR handsearched' is listed as the reason for the exclusion of eight publications from the stage I searches. This refers to a situation in which a primary study is excluded because it has already been identified through a systematic review. This does not appear in the inclusion criteria, although is highly unlikely to result in any inappropriate exclusions, since the relevant papers are likely to have been identified through the relevant SLR that was handsearched. Additionally, 'pooled data not from systematic review/meta-analysis' is cited as the reason for the exclusion of 21 publications from the stage I searches. This does not feature in the inclusion criteria, although the ERG did not consider any relevant data to have been missed.

The ERG specifically note that the ASCEND-8 trial for ceritinib is not included or discussed in the CS. The ERG became aware of this study through scoping searches conducted by the ERG for internal checking purposes. An electronic search of the CS and its Appendices found no mention of this study or its exclusion, including in the lists of studies excluded at full-text screening (CS Appendix, p37-55, Tables 10-11), in which a manual search was also conducted. The primary journal publication for ASCEND-8(34) was published online in July 2017 and in print in September 2017, therefore pre-dating the final search date of November 2017 in the CS (CS Appendix, p30-31). No other full-text publication could be identified for ASCEND-8.

Assessing ASCEND-8, the ERG noted that the results for patients who had previously taken crizotinib (comprising 48% of the sample) were not publically reported separately from those who had not, rendering ASCEND-8 ineligible for this appraisal. No relevant conference abstracts were identified that presented this additional information. The ERG considered that

publication bias in the ASCEND-8 trial in the form of the non-publication of subgroup results for patients who had previously taken crizotinib, is likely to have played a major role in its exclusion from this appraisal. ASCEND-8 was a dosing study, and has resulted in a change to dosing instructions and a lowering of the recommended dose. This may result in improved tolerability for ceritinib. The study reported predominantly on pharmacokinetic characteristics and adverse events. Based on the information available to the submitting company, the ERG is satisfied that there is a low risk of inappropriate exclusion of relevant studies.

4.1.4.2 Summary description of included studies

The clinical effectiveness evidence for brigatinib within the CS was based on two 'single-arm non-comparator trials' (CS p17) of brigatinib that the company considered to be relevant to the decision problem.

1. ALTA

ALTA (NCT02094573) is described (CS p17) as an "open-label, multi-national, non-comparator phase II study" of brigatinib. It is reported across one journal article, (21) one conference abstract,(35) and four company documents.(36-39) Summary information about the ALTA trial is provided in Table 3 below.

Table 3 Clinical effectiveness evidence for brigatinib from the ALTA trial

Study	ALTA (AP26113-13-201; NCT02094573)				
Study design	An open-label, multi-national, non-comparator phase II study				
Population	Adult patients with locally advanced or metastatic ALK+ NSCLC, previously treated with crizotinib				
Intervention(s)	• Brigatinib 90mg once daily (Arm A) • Brigatinib 180mg once daily (with a 7-day lead-in at 90mg once daily) (Arm B)				
Comparator(s)	None.				
Indicate if trial supports application for marketing authorisation	Yes	✓	Indicate if trial used in the economic model	Yes	✓
	No			No	
Rationale for use in the model	ALTA is a pivotal trial of brigatinib that formed the efficacy data for the marketing authorisation submission to EMA and represents the primary evidence base for efficacy and safety in this submission.				
Reported outcomes specified in the decision problem	• Response rates (investigator-assessed ORR per RECIST v1.1 was the primary endpoint) • Overall survival • Progression-free survival • Adverse effects of treatment • Health-related quality of life				

All other reported outcomes	• CNS responses (ORR and PFS in patients with baseline brain metastases) • Duration of response (DOR)
Main trial publications and company evidence sources *	Kim D-W, *et al.* Brigatinib in Patients with Crizotinib-Refractory Anaplastic Lymphoma Kinase–Positive Non–Small-Cell Lung Cancer: A Randomised, Multicentre Phase II Trial. Journal of Clinical Oncology. 2017;35:1-9.(21) Ahn M, *et al*. Brigatinib in crizotinib-refractory ALK+ NSCLC: updated efficacy and safety results from ALTA, a randomised phase 2 trial. International Association for the Study of Lung Cancer (IASLC), 18th World Conference on Lung Cancer (WCLC), Yokohama, Japan. 15-18 October, 2017.(35) ARIAD Pharmaceuticals Inc. Clinical Study Report AP26113-13-201 (IRC data extraction to 31 May 2016): A Randomised Phase 2 Study of AP26113 in Patients with ALK-positive, Non-small Cell Lung Cancer (NSCLC) Previously Treated with Crizotinib. 11 July 2016.(36) ARIAD Pharmaceuticals Inc. AP26113-13-201 Clinical Study Report: Section14 (Feb 2017). 2017.(37) Takeda Pharmaceuticals Ltd. Brigatinib (ALUNBRIG™) Study AP26113-13-201 Clinical Data Update (21 February 2017 Data Extraction). 1st August 2017.(39) ARIAD Pharmaceuticals Ltd. Brigatinib (ALUNBRIG™) Study AP26113-13-201: Clinical Study Report Addendum I (29 September 2017 Data Extraction). 11 January 2018.(38)
* Kim *et al*. 2017 is the main trial publication, reporting data from the May 2016 data extraction point. This is updated with the Ahn *et al.* 2017 abstract giving data from the February 2017 data extraction. Company documents are used to support these publications and also to provide data from a more recent data extraction date of September 2017, which has not yet been published in the public domain.	

Source: CS, p17-18 (Takeda Ltd)

ALTA comprises two intervention arms, and only Arm B corresponds to the recommended dose in the context of this NICE appraisal. Descriptive data from both arms are provided, when Arm A is in fact ineligible. However, only data from Arm B are used in the ITCs and as clinical inputs to the economic model. Therefore, this issue does not affect the conclusions of the CS. The population, Arm B dosing schedule, and key outcome measures are all relevant to the NICE scope for this appraisal. Therefore, the inclusion of ALTA as an evidence source for brigatinib in this appraisal appears appropriate in the view of the ERG.

2. Study 101

Study 101 (NCT01449461) is described (CS p19) as an “open-label, phase I/II” study of brigatinib. It is reported across one journal article,(1) one conference abstract,(40) and two company documents.(41, 42) It is noted (CS p19) that the main study journal article does not report on the subgroup of 25 patients relevant to the NICE decision problem. Therefore, the conference abstract and company documents are the key information sources for Study 101 in the context of this appraisal, meaning that the key sources are not peer-reviewed full-text

articles, which may reduce the robustness of this information. Summary information about Study 101 is provided in the table below (Table 4).

Table 4 Clinical effectiveness evidence for brigatinib from Study 101

Study	Study 101 (AP26113-11-101; NCT01449461)				
Study design	Open-label, phase I/II				
Population	Relevant sub-group: Adult patients with locally advanced or metastatic ALK+ NSCLC, previously treated with crizotinib				
Intervention(s)	Brigatinib 90mg once daily escalated to 180mg once daily				
Comparator(s)	None.				
Indicate if trial supports application for marketing authorisation	Yes	✓	Indicate if trial used in the economic model	Yes	✓
	No			No	
Rationale for use in the model	Study 101 included patients with various malignancies with different dosing regimens of brigatinib and with varied treatment history profiles. However, there is a sub-group of ALK+ NSCLC patients (n=25) who were treated with the recommended dose of brigatinib, and previously treated with crizotinib. Study 101 also contributed efficacy data for the marketing authorisation submission to EMA. Therefore, this subgroup of Study 101 patients meets the scope of this submission and shall be considered herein.*				
Reported outcomes specified in the decision problem	Response rates (investigator-assessed ORR per RECIST v1.1 was the primary endpoint) Overall survival Progression-free survival Adverse effects of treatment				
All other reported outcomes	CNS responses Duration of response (DOR)				
Main trial publications and company evidence sources *	Gettinger SN, et al. Activity and safety of brigatinib in ALK -rearranged non-small-cell lung cancer and other malignancies: a single-arm, open-label, phase 1/2 trial. The Lancet Oncology. 2016;17(12):1683-96.(1) Bazhenova L, et al. Brigatinib (BRG) in patients (pts) with ALK+ non-small cell lung cancer (NSCLC): Updates from a phase 1/2 trial. American Society of Clinical Oncology; 2-6 June 2017; Chicago, IL.2017.(40) ARIAD Pharmaceuticals Inc. Clinical Study Report AP26113-11-101 (31 May 2016 Data Cut): A Phase 1/2 Study of the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-Tumour Activity of the Oral ALK/EGFR Inhibitor AP26113. 21 December 2016.(41) ARIAD Pharmaceuticals Inc. AP26113-11-101 Clinical Study Report: Section14 (May 2016). 2016.(42)				
* For Study 101, Gettinger et al. 2016 is the main trial publication. However, this paper does not report on the subgroup of 25 patients relevant to this decision problem independently, hence the Bazenhova (2017) abstract and company documents are cited as references going forward.					

Source: CS, p19 (Takeda Ltd)

Study 101 is a broader study that encompasses a wider range of dosing regimens and a broader patient population than are eligible for this appraisal under the NICE scope. (1) However, the CS includes in its analyses only a subgroup of 25 patients from the Study 101 sample that correspond to the NICE scope in terms of inclusion criteria, and received brigatinib at the recommended dose as submitted to NICE. The outcome measures of the study fall within the NICE scope. Therefore, the inclusion of Study 101 appears appropriate as an evidence source for brigatinib in this appraisal.

4.1.4.3 Baseline characteristics

Table 5 below presents an overview of the baseline characteristics for patients in ALTA and Study 101. Both arms of ALTA are shown here, while data for Study 101 are restricted to the eligible subgroup (n=25) for this appraisal. ALTA arm B is the arm relevant to this appraisal.

Table 5 Baseline characteristics for brigatinib-treated patients in ALTA and Study 101

Trial name	**ALTA Arm A**	**ALTA Arm B**	**Study 101 Relevant subgroup only**
No. of patients	112	110	25
Intervention	Brigatinib 90mg QD	Brigatinib 180mg QD (with 7-day lead-in 90mg QD)	Brigatinib 90 → 180mg QD
Population	Locally advanced or metastatic ALK+ NSCLC investigator determined disease progression while receiving crizotinib	Locally advanced or metastatic ALK+ NSCLC investigator determined disease progression while receiving crizotinib	Subgroup of patients with locally advanced or metastatic ALK+ NSCLC that progressed while on crizotinib
Age Median Range 65+	 50.5 18-82 NR	 56.5 20-81 30 (27.3)	 57.0 32-73 5 (20)
Gender (%) Male Female	 50 (44.6) 62 (55.4)	 46 (41.8) 64 (58.2)	 14 (56.0) 11 (44.0)
Race (%) Asian White Other Unknown	 39 (34.8) 72 (64.3) 1 (0.9) 0 (0)	 30 (27.3) 76 (69.1) 2 (1.8) 2 (1.8)	 3 (12.0) 20 (80.0) 2 (8.0) 0 (0)

Trial name	**ALTA Arm A**	**ALTA Arm B**	**Study 101 Relevant subgroup only**
ECOG PS (%)			
0	34 (30.4)	45 (40.9)	10 (40.0)
1	71 (63.4)	56 (50.9)	15 (60.0)
0 or 1	105 (93.8)	101 (91.8)	25 (100)
2	7 (6.3)	9 (8.2)	0 (0)
3+	0 (0)	0 (0)	0 (0)
Missing	0 (0)	0 (0)	0 (0)
Smoking status (%)			
Never	71 (63.4)	63 (57.3)	NR
Former	40 (35.7)	43 (39.1)	
Current	0 (0)	4 (3.6)	
Unknown	1 (0.9)	0 (0)	
Histology (%)			
Adenocarcinoma	107 (95.5))	108 (98.0)	24 (96.0)
Adenosquamous	1 (0.9)	0 (0)	0
Large-cell carcinoma	1 (0.9)	1 (0.9)	0
Squamous cell carcinoma	2 (1.8)	1 (0.9)	0
Other	1 (0.9)	0 (0)	1 (4.0)
Prior therapy (%)			
Crizotinib	112 (100)	110 (100)	25 (100)
Platinum-based chemo	NR	80 (72.7)	NR
Any chemo	83 (74.1)	81 (73.6)	17 (68.0
Prior radiotherapy to the brain (%)	50 (44.6)	46 (41.8)	7 (28.0)
Disease Stage at study entry			
IIIA	0 (0)	1 (0.9)	NR
IIIB	3 (2.7)	1 (0.9)	
IV	109 (97.3)	108 (98.2)	
Other	0 (0)	0 (0)	
Brain metastases N (%)	80 (71.4)	74 (67.3)	18 (72.0)
Abbreviations: Abbreviations: ALK+, anaplastic lymphoma kinase positive; NSCLC, non-small cell lung cancer; NR, not reported; ECOG PS, Eastern Co-operative Oncology Group Performance Score.			

Source: CS, p30-31 (Takeda Ltd)

The ERG notes that data for the ALTA trial were extracted using several different data cuts. In the original company submission the ITC analysis and the economic model were informed by data from the February 2017 data cut rather than the most recent data cut from September 2017 (CS p21), although certain other results were presented either for both data cuts or solely for the more recent data. Following the Clarification meeting, an Addendum

was provided with the ITC analyses and the economic model updated to incorporate the September 2017 data cut for ALTA.

4.1.4.4 Statistical analysis

Table 6 below provides an overview of the statistical analysis approach within the two included studies for brigatinib, as originally presented in the CS.

Table 6 Overview of the statistical approach in ALTA and Study 101

Trial number (acronym)	**ALTA**	**Study 101**
Study objectives	To prospectively assess brigatinib efficacy and safety at 90 mg QD and 180 mg QD (with lead-in) in patients with crizotinib-refractory advanced ALK+ NSCLC	To describe the preliminary anti-tumor activity of brigatinib in NSCLC with ALK gene rearrangement or mutated EGFR, and other cancers with abnormal targets
Statistical analysis and data cut offs	Efficacy was evaluated in the ITT population. Patients who received any brigatinib were included in the safety population. CIs calculations: exact binomial method; 97.5% CIs for confirmed ORR/95% CIs for other end points. Time-to-event efficacy analyses (duration of response, PFS, and OS): K-M methods to estimate median values and two-sided 95% CIs. Investigator-assessed efficacy data cut-off: February 29, 2016. IRC-assessed whole-body had last scan dates of May 16, 2016, and April 14, 2016, 90mg and 190mg arms, respectively. The trial was not designed for statistical comparisons between arms, but post-hoc HRs were estimated for PFS to support dose selection.	Objective response was calculated with exact binomial 95% confidence intervals. Time-to-event efficacy analyses (duration of response, PFS, and OS): K-M methods to estimate median values and two-sided 95% CIs.
Power calculations	Power calculation: A sample size of >= 109 patients in each arm provided approximately 90% power to rule out an ORR of 20% when the true ORR is >= 35% with a two-sided alpha level of 0.025	The sample size was determined based on clinical rather than statistical considerations
Data management, patient withdrawals	3/112 patients did not receive 90mg brigatinib; 2 patients due to SAEs prior to the first dose of study drug and 1 patient withdrew consent to participate prior to the first dose of	All patients who received at least 1 dose of brigatinib comprised the main population for efficacy and safety analyses. All patients enrolled in the study received at least one dose of

Trial number (acronym)	ALTA	Study 101
	study drug. All randomised patients in Arm B received brigatinib 180mg. For the primary outcome of ORR – patients were considered not evaluable if an assessment was missing or not adequate. All randomised patients were included in analyses of the primary outcome. Patients with no measurable disease at baseline or no adequate post-baseline radiographic response assessment were included as non-responders.	brigatinib, therefore the main population was identical to ITT population and the safety population. Withdrawal was not reported independently for the relevant subgroup of post-crizotinib patients in the phase 2 dose arms.
Abbreviations: AEs, adverse events; ALK, anaplastic lymphoma kinase positive; CIs, confidence intervals; EGFR, epidermal growth factor receptor; ITT, intention-to-treat; IRC, independent review committee assessed; K-M, Kaplan-Meier; ORR, objective response rate; PFS, progression free survival; SAEs, serious adverse events.		

Source: CS, p31, Table 9 (Takeda Ltd)

The ERG consider this statistical analysis approach as outlined in the CS to be broadly appropriate. The analysis for ALTA was conducted on the ITT population, while Study 101 was a single-arm study, so the ITT principle is not applicable. A power calculation is reported for ALTA which achieves approximately 90% statistical power (although it should be noted that this was designed to compare Arms A and B, while only Arm B is used for ITC analyses and the economic model in the CS). For Study 101 the sample size was determined based on "clinical rather than statistical considerations" (CS p31). Following the NICE Clarification meeting, a Report addendum was provided with the ITC analyses and the economic model updated to incorporate the September 2017 data cut for ALTA. The initial report included this updated data, but did not incorporate it into the ITC analyses and the economic model. The ERG critique incorporates data from the Addendum as appropriate.

4.1.5 Risk of bias assessment

This section provides a critique of the risk of bias assessment for the two brigatinib studies. Quality appraisal of the two ceritinib studies was also conducted by the company, and this will be evaluated as part of the critique of the ITC analyses (section 4.3.5).

4.1.5.1 Quality assessment of ALTA

The company produced a tabulated quality assessment of ALTA (assessed as a single-arm study). Table 7 provides this assessment alongside ERG comments.

Table 7: Risk of Bias in ALTA, evaluated as a single-arm study

Trial name: **ALTA**	Item	Company rating	ERG comments
Selection bias	Representative sample selected from a relevant population	Low – representative sample, from multi centres, enrolled at similar Stage of disease and functional level stated. Patients had similar prior treatment	The ERG agrees that participant characteristics appear to be largely consistent with clinical practice The ERG notes that it is unclear whether all eligible patients were recruited.
	Explicit inclusion/exclusion criteria	Low – patients selected according to inclusion/exclusion specified in protocol	The ERG agrees that inclusion/exclusion criteria appear to be appropriate, and that participants were selected using these criteria.
	If comparisons of sub-series are being made, was there sufficient description of the series and the distribution of prognostic factors?	Low – patients were randomly assigned to dosing arms and were similar in terms of prognostic factors	The ERG agrees that participants in the two dosing arms are similar in terms of key prognostic factors.
Performance bias	Blinding of participants and personnel	Efficacy outcomes Low – patients and personnel not blinded to treatment but were unlikely to influence objective efficacy outcomes Safety outcomes – Unclear – patients and personnel more likely to influence safety and PRO outcomes	The ERG notes that even objective outcomes may be influenced by lack of blinding. However, this is unlikely to have a large influence on these outcomes. The ERG agrees that safety and PRO outcomes are likely to be influenced by lack of blinding to a larger extent than objective outcomes but that the extent of this remains unclear.
Detection bias	Blinding of outcome assessment	Primary outcome (investigator-assessed ORR) – Unclear – investigator assessed with no blinding, but based on confirmed response >4 weeks after initial response Secondary outcomes – Unclear – IRC assessed blinded to dosage assignment, but not to treatment. However,	The ERG agrees that it is unclear as to what extent the lack of blinding of assessors would have influenced study results.

Trial name: **ALTA**	Item	Company rating	ERG comments
		based on confirmed response >4 weeks after initial response	
	Long enough follow up for important events to occur	Unclear – no calculation of the number of events required	The ERG agrees that this is unclear due a lack of a calculation of number of events required.
Attrition bias	Incomplete outcome data	Low– withdrawal reasons reported. Analyses were conducted in ITT sample and Kaplan Meier analysis for analyses.	The ERG agrees that incomplete data were appropriately handled
Reporting bias	Selective reporting	Low – protocol checked, no evidence of selective reporting	The ERG found no evidence of selective reporting.
Other bias	Bias due to problems not covered elsewhere	High – no comparator or control group.	The ERG agrees that there is high risk of bias where no comparator is included.

Source: Adapted from CS Appendix D (Takeda Ltd)

As previously mentioned, the company states that the largest risk of bias in the ALTA trial is related to the fact that no comparators are included. The ERG agrees with this, and the method for addressing this; namely the performance of MAIC analyses. This is critiqued in sections 4.3 and 4.4. With regard to other sources of bias, risk is generally low and sometimes unclear (see Table 7).

With regard to the risk of selection bias (in the context of a single-arm study), the ERG note that it is unclear whether all eligible participants were approached and recruited to the ALTA trial. However, the participants were selected according to appropriate inclusion/exclusion criteria and appeared to be largely representative of clinical practice. Indeed, in each study arm, key prognostic factors (e.g. brain metastases, prior radiotherapy to the brain, squamous histology, disease stage, age, ECOG performance status, prior treatment) were similar and representative of clinical practice. For the purposes of this STA it is still important that each arm is independently representative of the clinical population because only one of the study arms was used in the MAIC analyses (Arm B [n=110], but not Arm A [n=112]). The ERG's view is that this is acceptable and does not constitute missing data because only Arm B evaluates brigatinib at a dose of 180mg QD (with 7-day lead-in 90mg QD).

With regard to blinding, the participants, study personnel, and outcome assessors, were not blinded to treatment. The ERG agrees with the company that this is likely to have most

impact on patient reported and safety outcomes, although impact on other outcomes cannot be completely ruled out. The study was also assessed by the company to be of low risk of attrition and reporting bias. The ERG agree with this view; in both arms of the study all participants are included in analyses for the primary endpoint, and all treated participants are included in safety analyses. The ERG has checked the study results against the endpoints described in the study protocol (protocol is provided as an Appendix to the Kim *et al* paper) and results are available for all primary and secondary endpoints.(21)

4.1.5.2 Quality assessment of Study 101

The company produced a tabulated quality assessment of the single-arm Study 101. The quality assessment is based on known information about the subgroup relevant to this STA. Table 8 provides this assessment alongside ERG comments.

Table 8: Risk of Bias in Study 101

Trial name: Study 101	Item	Company rating	ERG comments
Selection bias	Representative sample selected from a relevant population	High – sample eligible to this SLR was very small and no power calculation used to ascertain sufficient sample size.	The ERG agrees with the company's concerns. The ERG also notes that it is unclear whether all eligible patients were recruited. The ERG does note that the population appears to be largely representative of the clinical population, however, data for disease stage at baseline and smoking status are not reported for this subgroup.
	Explicit inclusion/exclusion criteria	Low – inclusion including of those post-crizotinib patients were clearly specified.	The ERG agrees with this rating: inclusion/exclusion criteria appear to be appropriate, and participants in this subgroup were selected using these criteria.
	If comparisons of sub-series are being made, was there sufficient description of the series and the distribution of prognostic factors?	NA	NA

Trial name: Study 101	Item	Company rating	ERG comments
Performance bias	Blinding of participants and personnel	Investigator assessed ORR Unclear – patients and personnel not blinded to treatment – personnel assessed outcomes on objective criteria, although not clear the extent to which ORR was confirmed after initial assessment. IRC assessed outcomes – Low – participants and personnel had no influence on independently assessed outcomes. Safety outcomes – Unclear – patients and personnel more likely to influence safety and PRO outcomes	The ERG agrees that safety and PRO outcomes are likely to be influenced by lack of blinding to a larger extent than objective outcomes. The ERG notes that it is possible for lack of participant blinding to influence outcomes, even ones that are independently assessed, although this influence is unlikely to be large.
Detection bias	Blinding of outcome assessment	High – outcome assessors were not independent for ORR or blinded to treatment for other outcomes. Safety outcomes – Unclear – patients and personnel more likely to influence safety and PRO	The ERG agrees that, for ORR, risk of bias is increased in this study due to lack of independent confirmation.
	Long enough follow up for important events to occur	Unclear – no calculation of number of events required	The ERG agrees that this is unclear due a lack of a calculation of number of events required.
Attrition bias	Incomplete outcome data	Low– withdrawal reasons were not reported independently for the eligible subgroup. However, analyses were conducted in ITT sample and K-M analysis for analyses.	The ERG agrees that, as ITT analyses were conducted, risk of attrition bias is low. Reasons for withdrawal are available for the whole Study 101 population, but not the relevant sub-group.
Reporting bias	Selective reporting	Low – protocol checked, no evidence of selective reporting	The ERG found no evidence of selective reporting.

Trial name: Study 101	Item	Company rating	ERG comments
Other bias	Bias due to problems not covered elsewhere	High – no comparator or control group. Also, difficult to assess methods in relation to the population included in this SLR because it was a subgroup of a larger population.	The ERG agrees with the concerns raised by the company.

Source: Adapted from CS, Appendix D (Takeda Ltd)

As with the ALTA trial, the company states that the largest risk of bias in Study 101 is related to the fact that no comparators are included; the ERG agrees with this. With regard to other sources of bias, there is more risk and more unclear items for Study 101 than for ALTA (see Table 8). This is largely because only a sub-sample of Study 101 is evaluated, and whilst this is appropriate, it does mean that certain information is not available for the sub-sample of interest.

The ERG agrees with the company that there is a high risk bias in the Study 101 sub-sample due to potential lack of generalisability; the eligible sub-sample was small and the company report that no power calculation was used. The ERG also notes that it is unclear whether all eligible participants were approached and recruited to Study 101. In addition, although the participants in the Study 101 subgroup were selected according to appropriate inclusion/exclusion criteria and appeared to be largely representative of clinical practice, data for disease stage at baseline and smoking status were not reported.

The participants, study personnel, and outcome assessors in Study 101 were not blinded to treatment. The ERG agrees with the company that this is likely to have most impact on patient reported and safety outcomes, although, as with the ALTA trial, impact on other outcomes cannot be completely ruled out. The company highlights the fact that for ORR, outcome assessors were not blinded, and there appears to be no further confirmation of this outcome by independent means.

Study 101 was also assessed by the company to be of low risk of attrition and reporting bias. The ERG agree with this view; although reasons for withdrawal are not given for the included sub-group, ITT analyses were conducted. The ERG has checked the study results against the endpoints described in the study protocol (43)and results are available for all primary and secondary endpoints.

4.1.5.3 Summary of risk of bias in the brigatinib trials

The company provides a summary of the risk of bias assessment for the two brigatinib trials (Table 9). This summary indicates that risk of bias is low in the ALTA study and low or unclear in Study 101.

However, the ERG finds the more detailed tables provided in Appendix D of the company submission (adapted in Sections 4.1.5.1 and 4.1.5.2 of the ERG report) to be more useful in terms of providing a full evaluation of the risk of bias of these studies. Indeed, Table 9 does not highlight the specific areas where risk of bias is high, and it is important to acknowledge that there are areas of high risk of bias in both of these studies due to a lack of a comparator and also further areas in Study 101 (Table 8).

Table 9: Quality assessment results from the ALTA and Study 101

Critical appraisal	Brigatinib	
	ALTA	Study 101 *
Do the selected patients represent the eligible population for the intervention?	Yes	Yes
Was selection bias minimised?	Yes	Yes
Were all participants accounted for at study conclusion?	Yes	Yes
Did the setting reflect UK practice?	Yes	Yes
Were outcome measures reliable? Were all clinically relevant outcome measures assessed?	Yes	Unclear
Did the analysis include an intention-to-treat analysis?	Yes	Yes
Are the study results internally valid?	Yes	Unclear
Are the findings externally valid?	Yes	Unclear
* The quality assessment of Study 101 is based only on the subgroup of n=25 patients that were relevant		

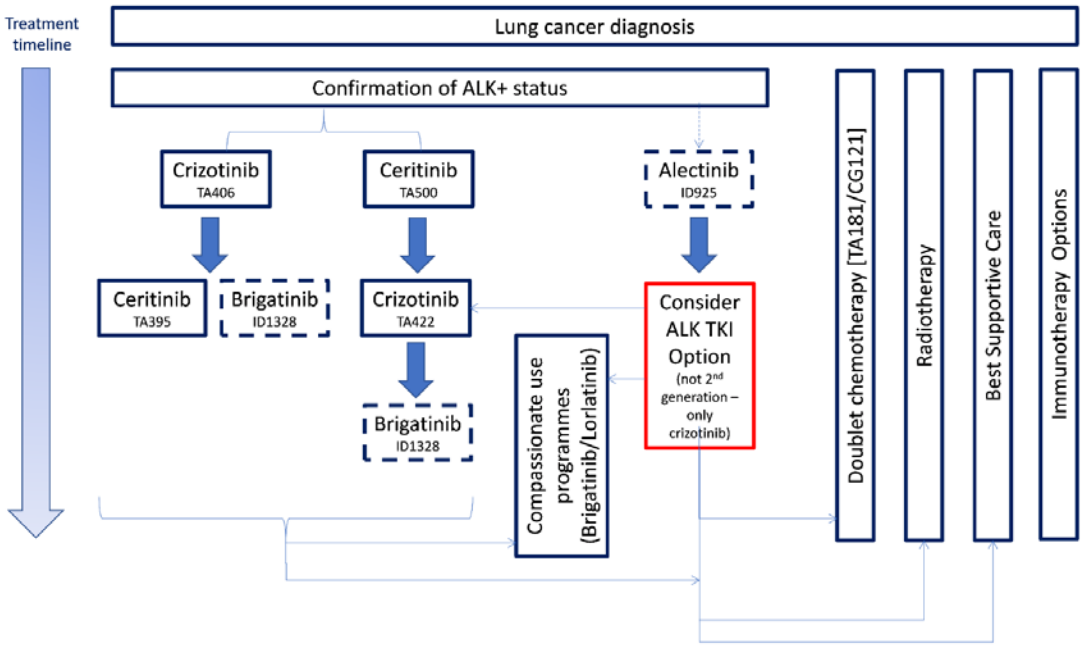
Source: CS, p33, Table 10 (Takeda Ltd)

4.1.6 Applicability to clinical practice

Clinical advisors to the ERG considered the inclusion criteria and patient characteristics to be satisfactorily representative of routine NHS practice. It was noted that a criterion of ECOG PS ≤2, as used in ALTA, may be more representative of the performance status of patients seen and treated in clinic than ECOG PS ≤1, as recruited in Study 101. The clinical advisors considered the treatment pathway presented in the CS (and reproduced in the figure below) to be relatively representative of current NHS practice. Crizotinib was seen as the current first-line treatment with ceritinib the usual second-line option. Crizotinib use is expected to decline in future due to the introduction and wider adoption of alternative first-line treatments, and this is acknowledged by the company, who say that crizotinib use “is likely to decrease

over time due to the diminishing use of crizotinib in light of the changing treatment landscape" (CS p16).

Figure 2 Treatment flow for ALK+ NSCLC patients



Source: CS, p16, Figure 1 (Takeda Ltd)

The treatment pathway presented allows for ceritinib to be used as first-line treatment (approved by NICE TA500, January 2018), but the clinical advisors to the ERG said that presently this was rarely used in practice as first-line treatment due to its poorer adverse event profile. They would rather keep it available as a second-line treatment following crizotinib. In addition, there is little evidence to support the use of crizotinib after ceritinib, although it remains a potential treatment option. It was also mentioned that additional treatment options such as alectinib, brigatinib and lorlatinib are sometimes available through schemes such as compassionate use programmes. However, availability of these schemes varies locally, can be time-limited, and cannot be considered standard practice.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.2.1 Clinical effectiveness results for brigatinib

4.2.1.1 Summary of efficacy results

Table 10 below provides a summary of the efficacy results for brigatinib in each of the two included studies. The ERG report includes solely the September 2017 results for ALTA,

since these are directly relevant for the ITCs and the economic model supplied in the CS Addendum.

Table 10 Efficacy summary from ALTA trial and Study 101

Trial	ALTA				Study 101
Assessment	INV		IRC		INV
	Arm A	Arm B	Arm A	Arm B	N=25
Median duration of follow-up, months	19.6	24.3	19.6	24.3	NR**
Confirmed ORR, % (95% CI)	45.5 (34.8-56.5)*	56.4 (45.2-67.0)*	50.9 (41.3-60.5)	56.4 (46.6-65.8)	76 (54.9-90.6)
Median duration of response in responders, months (95% CI)	12.0 (9.2-17.7)	13.8 (10.2-19.3)	16.4 (7.4-24.9)	15.7 (12.8-21.8)	26.1 (7.9-26.1)
Median PFS, months (95% CI)	9.2 (7.4-11.1)	15.6 (11.1-21.0)	9.2 (7.4-12.8)	16.7 (11.6-21.4)	16.3 (9.2-NE)
Median OS, months	29.5 (18.2-NR)	34.1 (27.7-NR)	---	---	NR (range:1.4-24.3)

Abbreviations: INV, investigator-assessed; IRC, independent review committee assessed; NE, not estimable; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression free survival. * 97.5% CI for primary endpoint. ** Median duration of follow-up is not reported independently for the relevant n=25 patients.

Source: CS, p35, Table 11 (Takeda Ltd)

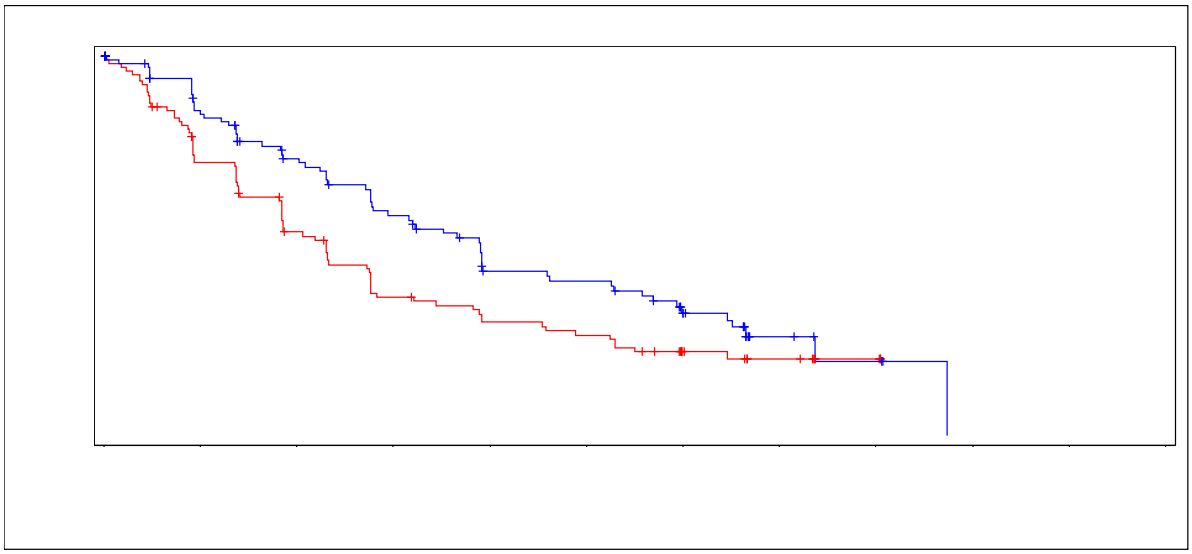
Study 101 provides only investigator-reported (INV) outcomes in this table, whereas INV and independent review committee assessed (IRC) outcomes are both available for ALTA, with the exception of overall survival (OS) for which only INV data are available.

The percentage of patients with confirmed objective response rate (ORR) is qualitatively substantially higher for Study 101 (76%) than for ALTA Arm B (56.4% for IRC). The 95% confidence intervals (CIs) do however overlap, suggesting that this difference is not statistically significant. The median duration of response in responders is also qualitatively substantially higher in Study 101 (26.1 months) than in Arm B of ALTA at September 2017 data cut (15.7 months using IRC data). Median progression-free survival (PFS) is numerically similar for ALTA ARM B (16.7 months for IRC) and Study 101 (16.3 months). Data are not reported in Study 101 for as full a set of covariates as in ALTA.

4.2.1.2 Further results from ALTA

The following figures show Kaplan-Meier (K-M) plots for ALTA using September 2017 data. The K-M plots, however, compare Arms A and B, and only Arm B is used in the ITC analyses and the economic model for this appraisal.

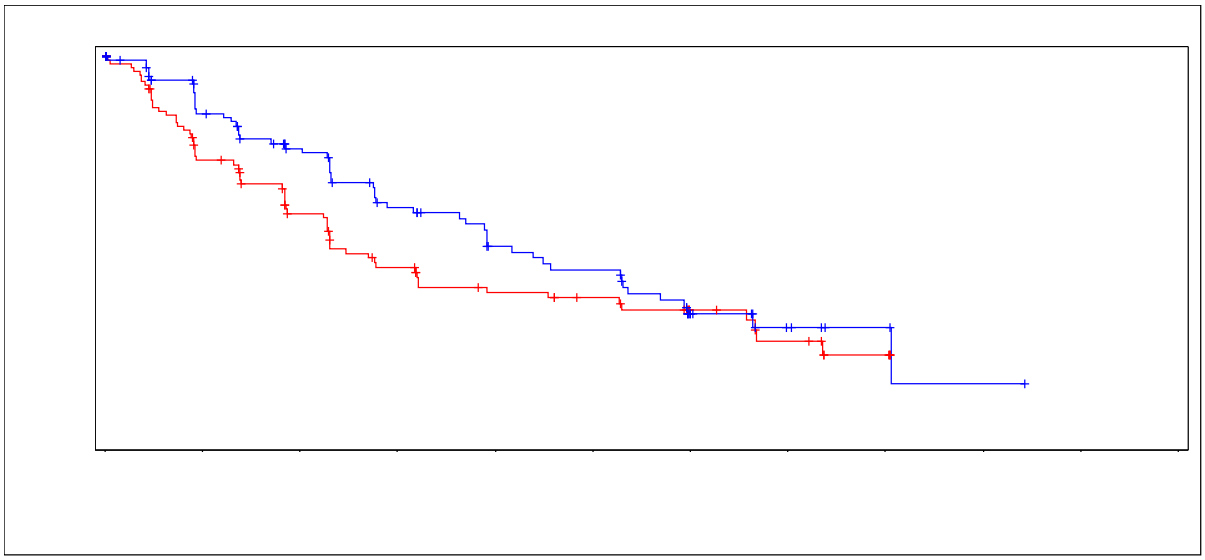
Figure 3. Kaplan-Meier plot of Investigator-assessed progression-free survival by treatment arm in ITT population (September 2017)



Source: CS, p46, Figure 10 (Takeda Ltd)

The figure above shows that for patients in Arm B of ALTA in the ITT population, the probability of INV PFS was around 0.5 at 15 months and 0.25 at 29 months.

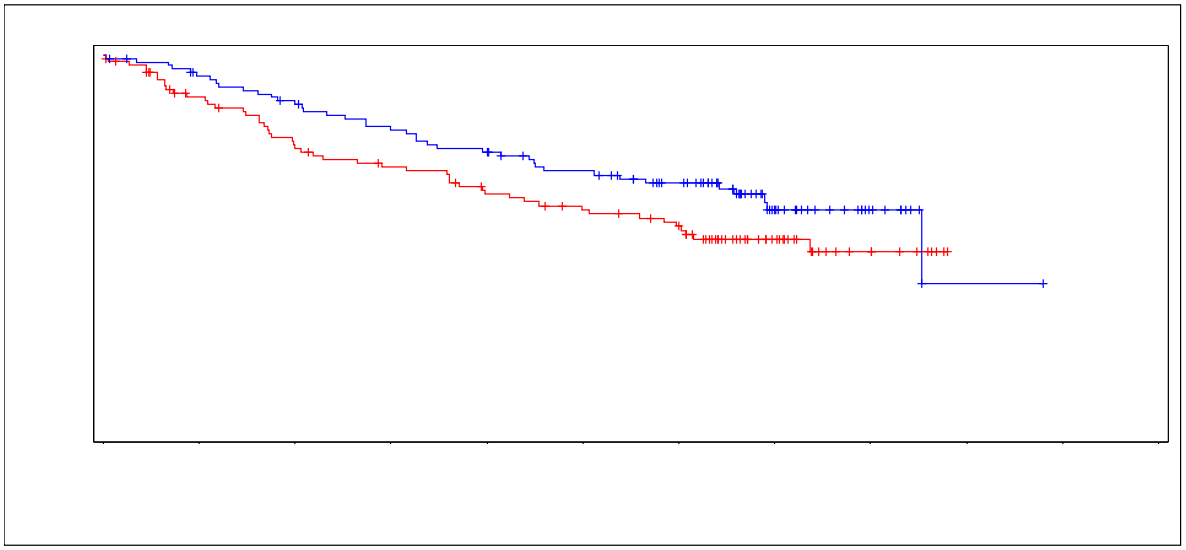
Figure 4. Kaplan-Meier plot of IRC-assessed progression-free survival by treatment arm in ITT population (September 2017)



Source: CS, p46, Figure 11 (Takeda Ltd)

The figure above shows that for patients in Arm B of ALTA in the ITT population, the probability of IRC PFS was around 0.5 at 15 months and 0.25 at 32 months.

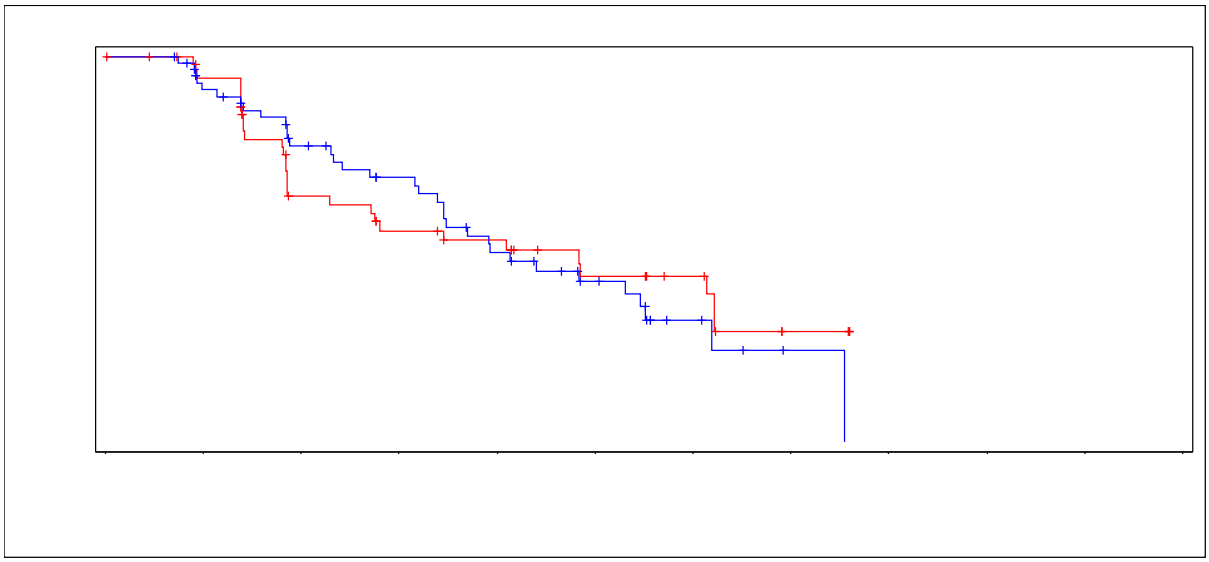
Figure 5. Kaplan-Meier plot of overall survival by treatment arm in ITT population



Source: CS, p47, Figure 12 (Takeda Ltd)

The figure above shows that for patients in Arm B of ALTA in the ITT population, the probability of OS is around 0.5 at 34 months, and does not fall to 0.25 in the data presented.

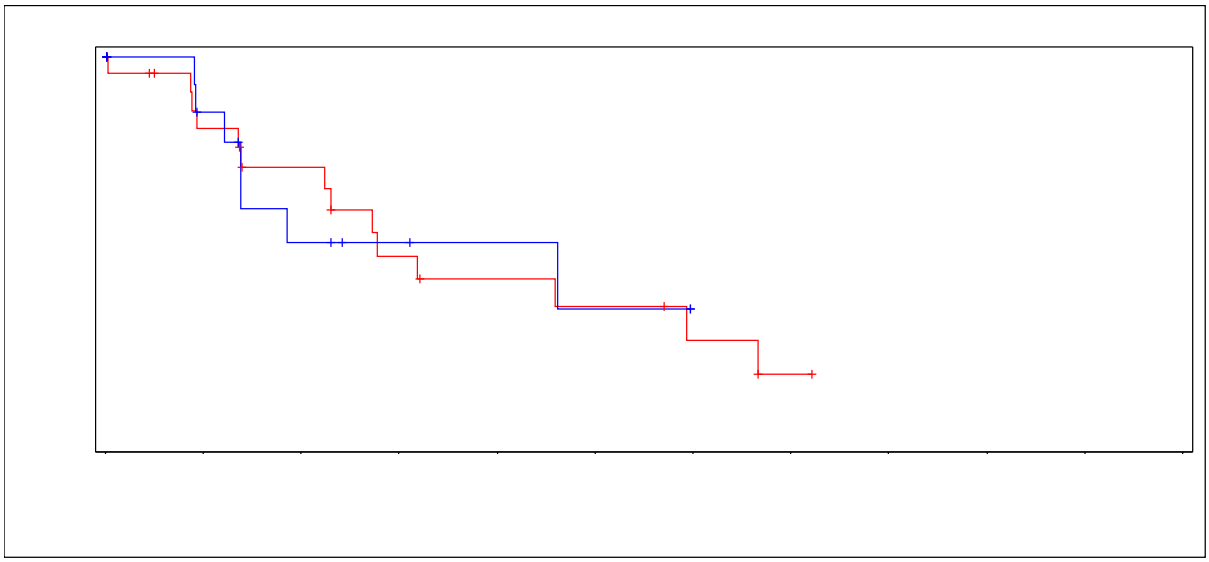
Figure 6. Kaplan-Meier plot of IRC-assessed systemic duration of response, by treatment arm, in the population with IRC-confirmed response, for ALTA



Source: CS, p40, Figure 5 (Takeda Ltd)

The figure above shows that for patients in Arm B of ALTA with IRC-confirmed response, the probability of continuing systemic response was around 0.75 at 8 months and 0.50 at 15 months.

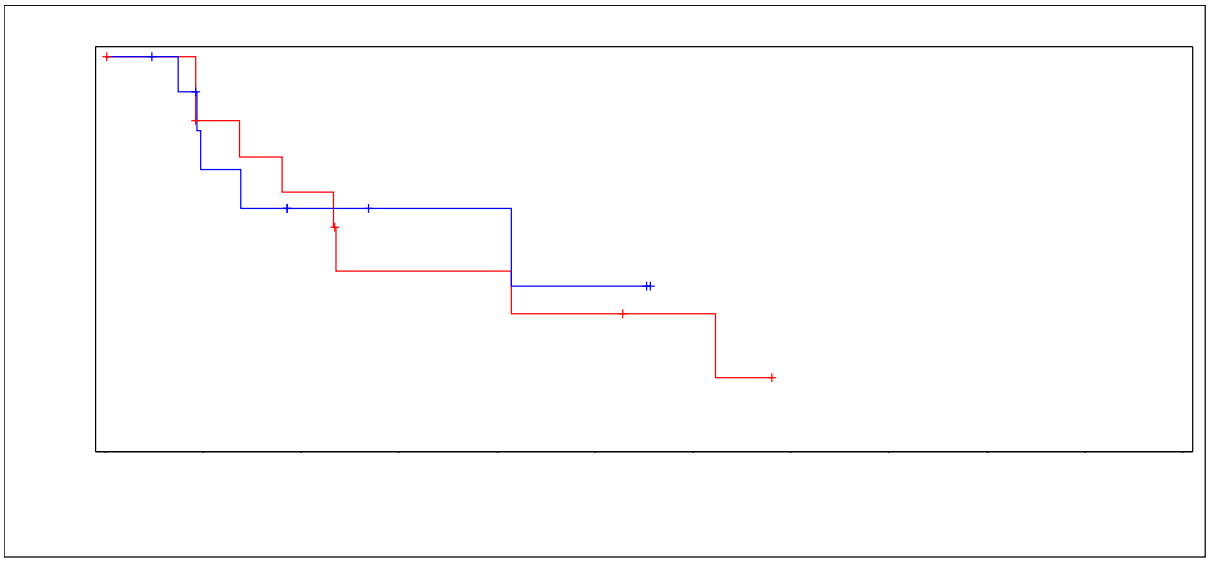
Figure 7. Kaplan-Meier plot of IRC-assessed CNS progression free survival in patients with measurable brain metastases at baseline



Source: CS, p43, Figure 6 (Takeda Ltd)

The figure above shows that for patients in Arm B of ALTA, the probability of CNS PFS in patients with measurable brain metastases at baseline was near-total up to 4 months, before falling to around 0.5 at 7 months and then after a plateau, falling again to around 0.35 from 18 to 24 months.

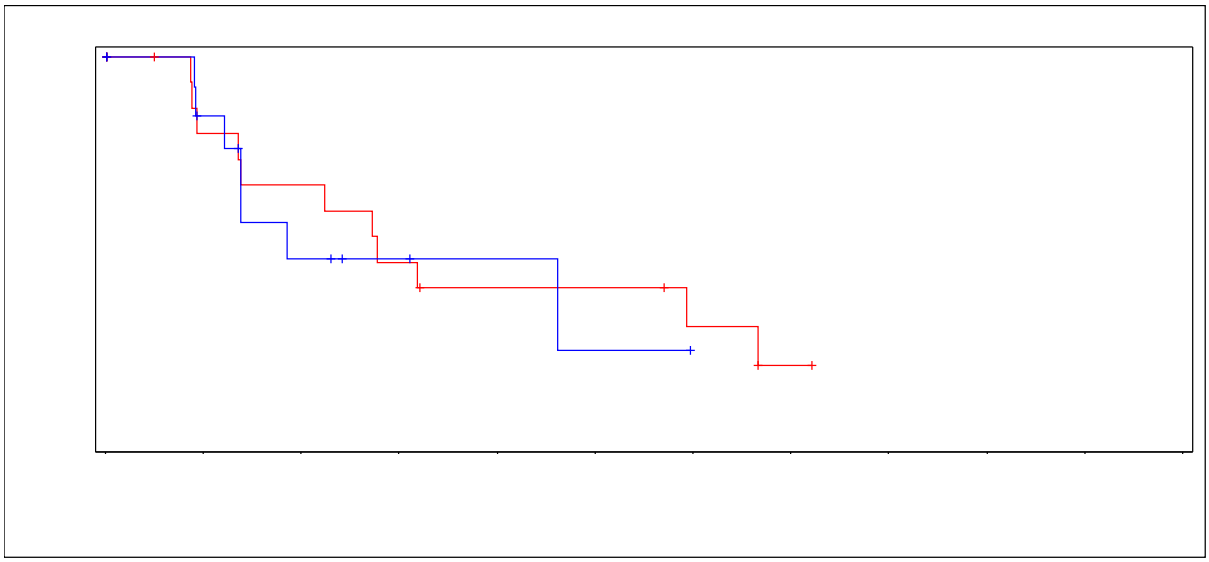
Figure 8. Kaplan-Meier plot of IRC-assessed CNS duration of response in patients with measurable baseline metastases and a confirmed CNS response



Source: CS, p43, Figure 7 (Takeda Ltd)

The figure above shows that for patients in Arm B of ALTA, the probability of continuing CNS response in patients with measurable baseline metastases and a confirmed CNS response was near-total up to 4 months, before falling to around 0.6 at 5 months and then after a plateau, falling again to around 0.45 between 16 and 22 months.

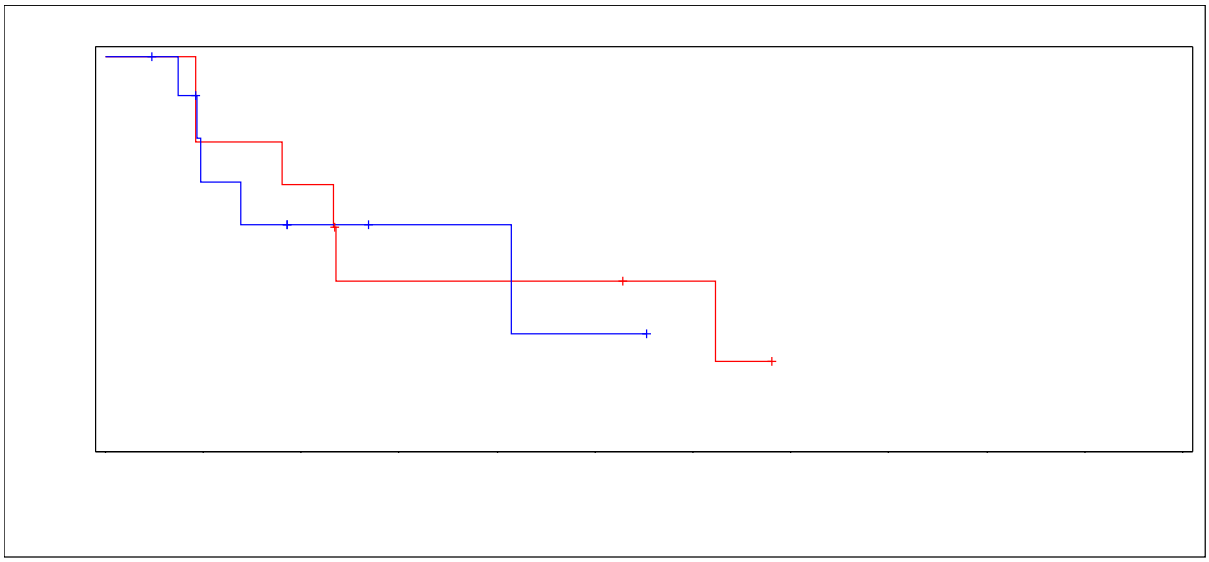
Figure 9. Kaplan-Meier plot of IRC-assessed CNS progression free survival in patients with measurable brain metastases at baseline



Source: CS, p44, Figure 8 (Takeda Ltd)

The figure above shows that for patients in Arm B of ALTA, the probability of CNS PFS in patients with measurable brain metastases at baseline was near-total up to 4 months, before falling to less than 0.5 at 7 months, and following a plateau, falling again to around 0.25 between 18 and 24 months.

Figure 10. Kaplan-Meier plot of IRC-assessed CNS duration of response in patients with active, measurable baseline metastases and a confirmed CNS response



Source: CS, p44, Figure 9 (Takeda Ltd)

The figure above shows that for patients in Arm B of ALTA, the probability of continued CNS response in patients with active, measurable baseline metastases and a confirmed CNS response was near-total up to 3 months, before falling to around 0.6 at 5 months, and following a plateau, falling again to around 0.25 between 17 and 22 months.

4.2.1.3 Further results from Study 101

There are no K-M plots available for Study 101. Health-related quality of life was not reported in Study 101. The tables below provide further information on response rates, overall survival and progression free survival. All are reported specifically for the subgroup of 25 patients relevant for this appraisal.

Table 11. Investigator-assessed response rates for selected patients receiving 90 → 180mg brigatinib in Study 101

Trial ID	Study 101
	ALK+ NSCLC patients with prior treatment with crizotinib in the 90 mg QD → 180 mg QD group
Analysis set N	25
Median months duration of follow up (range)	20.0 (range: 1–47.5)* (N=71)
Confirmed ORR % (CI 95%)	76.0 (54.9-90.6)
Disease control rate % (CI 95%)	88.0 (68.8-97.5)
CR %	12.0 (2.5-31.2)
PR %	68.0 (46.5-85.1)
SD %	8.0 (1.0-26.0)
PD %	8.0 (1.0-26.0)
Abbreviations: ALK+, anaplastic lymphoma kinase; CI, confidence interval; ITT, intention to treat; ORR, overall response rate; NR, not reported; NSCLC, non-small cell lung cancer. * Duration of follow-up was not reported for the sub-group of 25 patients pre-treated with crizotinib treated with the recommended dose (180mg with 7-day 90mg lead-in)	

Source: CS, p49, Table 17 (Takeda Ltd)

The follow-up duration data in the above table relates to the entire sample of Study 101, rather than the subgroup of 25 patients who are eligible for inclusion in this appraisal. The ERG considered that the company should have been able to provide this information specifically for the eligible subgroup using their IPD. Over three quarters of patients (76%) had confirmed ORR, while the disease control rate was 88%.

Table 12. Time to response and duration of response for selected patients receiving 90 → 180mg brigatinib in Study 101

Trial ID	Study 101
	ALK+ NSCLC patients with prior treatment with crizotinib in the 90 mg QD → 180 mg QD group
Analysis set, confirmed responders, N	20
Median (range) months duration of follow up	20.0 (range: 1–47.5)* (N=71)
Median TTR/months (range)	1.9 (1.2-6.0)
Median months (CI 95%) DOR	26.1 (7.9, 26.1; range: 3.5-26.1)
Abbreviations: ITT, intention-to-treat; NR, not reported; TTR, time to response; DOR, duration of response. * Duration of follow-up was not reported for the sub-group of 25 patients pre-treated with crizotinib treated with the recommended dose (180mg with 7-day 90mg lead-in)	

Source: CS, p49-50, Table 18 (Takeda Ltd)

Among the 20 confirmed responders, the median time to response (TTR) was 1.9 months with an IQR of 1.2-6.0.

Table 13. Overall survival for selected patients receiving 90 → 180mg brigatinib in Study 101

Trial ID	Study 101
	ALK+ NSCLC patients with prior treatment with crizotinib in the 90 mg QD → 180 mg QD group
Analysis set N	25
Median (range) months duration of follow up at assessment of outcome	20.0 (range: 1–47.5)* (N=71)
Median months overall survival (95% CI)	Not reached (21.4-NR) Range: 1.4 to 24.3
Number of events (%)	11 (44)
Abbreviations: CI, confidence interval; NR, not reached; QD, once daily. * Duration of follow-up was not reported for the sub-group of 25 patients pre-treated with crizotinib treated with the recommended dose (180mg with 7-day 90mg lead-in)	

Source: CS, p50-51, Table 19 (Takeda Ltd)

Overall survival ranged from 1.4 to 24.3 months.

Table 14. Investigator-assessed progression free survival for selected patients receiving 90 → 180mg brigatinib in Study 101

Trial ID	Study 101
	ALK+ NSCLC patients with prior treatment with crizotinib in the 90 mg QD → 180 mg QD group
Analysis set N	25
Median (range) months duration of follow up at assessment of outcome	NR - 20.0 (range: 1–47.5)* (N=71)
Median months PFS (95% CI)	16.3 (95% CI: 9.2, not reached; range: 0.5-27.8)
Number of events (%)	14 (56.0)
Abbreviations: ALK+, anaplastic lymphoma kinase positive; CI, confidence interval; NSCLC, non-small cell lung cancer; NR, not reported; PFS, progression free survival; QD, once daily. * Duration of follow-up was not reported for the sub-group of 25 patients	

Source: CS, p51, Table 20 (Takeda Ltd)

Median progression free survival (PFS) is reported as 16.3 months, with a range of 0.5-27.8 months.

4.2.1.4 Meta-analysis

The CS states that "No meta-analysis was performed because the brigatinib evidence was provided by the availability of individual patient data (IPD) from the two single-arm studies" (CS p51). The ERG consider this to be appropriate, and indeed it to be correct to say that no 'standard' meta-analysis of brigatinib trials was performed outside of the ITC process. However, the ERG notes that data from ALTA and Study 101 were pooled for use in ITCs and a meta-analysis was conducted to combine ITC analyses (see Section 4.4).

4.2.1.5 Subgroup analysis

The CS states that "No sub-groups were identified and included in specific subgroup analyses" (CS p51). The ERG considers this to be appropriate since the populations included in the CS match the NICE scope, and there are no clinically obvious subgroups for further analysis. However, it should be noted that the data from Study 101 included in the CS already represent a subgroup of the total trial population.

4.2.2 Safety of brigatinib

The company provides a summary table of adverse events for one of the two brigatinib studies (ALTA) and for the two comparator studies (ASCEND-2 and ASCEND-5) – see Table 15. Safety data for Study 101 were provided in text only due to a lack of adverse events data for the sub-sample of participants relevant to this STA. Safety data for the whole Study 101 sample receiving brigatinib are described in section 4.2.2.1.2.

The ERG note that the data provided for both brigatinib and ceritinib, appear to be correct based on available data from other sources. With regard to common adverse events (nausea, diarrhoea, vomiting) it appears that brigatinib is better tolerated than ceritinib. Dose reductions and interruptions were also lower for the participants receiving brigatinib (ALTA trial) than in those receiving ceritinib (ASCEND-2 and ASCEND -5), although serious adverse events appear to be slightly higher with brigatinib. Data on cough, dyspnoea and pneumonia were not included by the company in Table 15, but these data were provided elsewhere in the company submission. Across the ALTA study arms, 34.2% experienced cough, and 25.6% dyspnoea, which is higher than in the ceritinib studies. With regards to pneumonia, treatment-emergent occurrence ≥ grade 3 with brigatinib was 3.7% in Arm A and 5.5% in Arm B and pneumonia as a serious adverse event was 3.7% in Arm A and 8.2% in Arm B, which is similar to the value given for ceritinib in ASCEND-2.

The ERG notes that patient deaths are not included in summary Table 15. Patient deaths in the brigatinib studies are covered in section 4.2.2.1.

It is important to consider that median follow-up is longer in the ALTA trial than in the two ceritinib trials, and this may account for some of the differences in the safety data. Median follow-up in months was 19.6 (0.1-35.2) and 24.3 (0.1-39.2) for ALTA Arm A and Arm B respectively, 11.3 (0.1-18.9) for ASCEND-2 and 16.6 (IQR 11.6-21.4) for ASCEND-5.

Table 15: Comparative safety and tolerability of brigatinib and ceritinib

Intervention	Brigatinib		Ceritinib	
Trial	ALTA		ASCEND-2	ASCEND-5
	Arm A	Arm B		
Analysis population	109	110	140	115
Median follow-up (range)	19.6 (0.1-35.2)	24.3 (0.1-39.2)	11.3 (0.1-18.9)	16.6 (IQR 11.6-21.4)
No. SAEs	52 (47.7)	56 (50.9)	57 (40.7)	49 (42.6)
No. of TEAEs	109 (100.0)	110 (100.0)	135 (96.4)	110 (95.6)
Patients experiencing AEs ≥grade 3, n (%)	64 (58.7)	72 (65.5)	100 (71.4)	104 (90.4)
Dose reduction/interruption due to AEs, n (%)	Reduction 10 (9.2) Interruption 44 (40.4)	Reduction 33 (30.0) Interruption 65 (59.1)	Reduction 76 (54.3) Interruption 106 (75.7)	Reduction 70 (61) Combined reduction & interruption 92 (80.0)
Discontinuation due to AEs	4 (3.7)	12 (10.9)	11 (7.9)	6 (5.0%)

Special AEs of interest specific to brigatinib: EOPE			Cough 30 (21.4) Dyspnoea 29 (20.7) Pneumonia 10 (7.1)	Cough 16 (14) Dyspnoea 20 (17.4)
Special AEs of interest specific to ceritinib: G.I. disorders, any grade	Nausea 41 (37.6) Diarrhoea 30 (27.5) Vomiting 39 (35.8)	Nausea 52 (47.3) Diarrhoea 48 (43.6) Vomiting 33 (30.0)	Nausea 114 (81.4) Diarrhoea 112 (80.0) Vomiting 88 (62.9)	Nausea 76 (66.1) Diarrhoea 83 (72.2) Vomiting 60 (52.2)
Abbreviations: AE, adverse event; EOPE, early onset pulmonary events; GI, gastro-intestinal; SAE, serious adverse events; TEAE, treatment emergent adverse events;				

Source: CS, p82, Table 28 (Takeda Ltd)

Further safety data were provided by the company for brigatinib, and these data are provided and critiqued in section 4.2.2.1. No further data were provided for ceritinib.

4.2.2.1 Safety and tolerability of brigatinib

4.2.2.1.1 ALTA

The company provide safety data for 219 of the 222 participants in the ALTA study (three participants in Arm A did not receive brigatinib). In addition to the data summarised in Table 15, the company also provide data on the most common TEAEs of any grade (i.e. those that occurred in >20% of patients across the study: nausea (42.5%), diarrhoea (35.6%), cough (34.2%), headache (32.9%), vomiting (32.9%), fatigue (27.9%), dyspnoea (25.6%), blood creatine phosphokinase (CPK) increased (25.6%), and decreased appetite (24.7%). [redacted] (38)

The company tabulated the TEAEs Grade ≥3 that were experienced by ≥2% of patients across both study arms in the ALTA trial. These are provided in Table 16. Serious adverse events in the ALTA trial are given in Table 17. The ERG has checked the data in these tables against the CSR.(38) [redacted] (38)

Table 16: Grade ≥3 Treatment-emergent adverse events experienced by ≥2% of patients, by treatment arm

Preferred term	ALTA	
	Arm A	Arm B
Neoplasm progression	17 (15.6)	8 (7.3)
Blood creatine phosphokinase increased	5 (4.6)	14 (12.7)
Hypertension	6 (5.5)	9 (8.2)
Pneumonia	4 (3.7)	6 (5.5)
Lipase increased	5 (4.6)	4 (3.6)
Pneumonitis*	3 (2.8)	4 (3.6)
Neutrophil count decreased	4 (3.7)	2 (1.8)
Malignant pleural effusion	3 (2.8)	3 (2.7)
Dyspnoea	3 (2.8)	2 (1.8)
Hyponatraemia	2 (1.8)	3 (2.7)
Rash	1 (0.9)	4 (3.6)
* 3 patients in Arm B had pneumonitis which occurred during the first 7days of treatment (i.e., at 90 mg QD). One of the patients in Arm A had pneumonitis >1 month after escalation to 180 mg QD due to disease progression at 90 mg QD.		

Source: CS, p71, Table 24 (Takeda Ltd)

The company highlight the fact that neoplasm progression is part of progressive disease but was recorded as an adverse event, and that this disease progression accounts for several of the TEAEs ≥3 Grade 3 (see Table 16), SAEs (see Table 17) and two of the Arm B treatment discontinuations (see Table 15) in the ALTA trial.

Table 17: Serious adverse events experienced in ≥2% patients, by treatment arm

Preferred term	ALTA	
	Arm A	Arm B
Neoplasm progression	18 (16.5)	8 (7.3)
Pneumonia	4 (3.7)	9 (8.2)
Pneumonitis*	2 (1.8)	9 (8.2)
Malignant pleural infusion	4 (3.7)	4 (3.6)
* 6 of 9 patients in Arm B had pneumonitis occur during the first 7 days of treatment (i.e. at 90mg), One of the patients in arm A had pneumonitis >1 month after escalation to 180mg due to disease progression at 90mg.		

Source: CS, p72, Table 25 (Takeda Ltd)

The company state that all early onset pulmonary events (EOPE) followed treatment initiation and not dose escalation to 180mg, or re-initiation of treatment after interruption. Of the 219 patients in the ALTA safety population, there were four participants with a definite EOPE, and ten with a possible EOPE. Of these 14 patients, 9 were in Arm B of the ALTA trail (8.0% of all Arm B participants in the safety data set), although all of these occurred within the first 7 days of treatment (i.e. when the dose was 90 mg QD), with the median time to EOPE onset being Day 2 (range Day 1-9). Of the 14 participants who were EOPE cases, eleven were SAEs, seven were grade ≥3, and all of these seven discontinued brigatinib. Four of these patients experienced pneumonitis, one experienced radiation pneumonitis and another experienced pneumonia. As previously mentioned (in section 4.2.2) one of these patients died after developing pneumonia (7 days after start of treatment with brigatinib). Across the 14 patients with an EOPE, eleven (78.6%) received steroids and four (28.6%) received antibiotics. The ERG has checked this data against the CSR.(37)

The company highlight that in multivariate analyses age (≥65years and continuous 10-year increases) was associated with a higher rate of EOPE, and in adjusted stepwise logistic regression analysis, both age and shorter interval (<7 days) between last dose of crizotinib and first dose of brigatinib were significantly associated with an increased rate of EOPE. Due to this they recommend close monitoring of patients upon initiation of brigatinib and particularly a) of respiratory symptoms after the initiation of brigatinib, b) if they have any of the risk factors stated, and c) during the first week of treatment. The company recommends that these symptoms are managed through dose interruption and rapid clinical evaluation.

[redacted]

[redacted]

4.2.2.1.2 Study 101

As mentioned above, adverse events were not reported for the sub-sample of Study 101 participants relevant to this STA.

Data are provided in the company submission for the whole Study 101 sample who received ≥1 dose of brigatinib (n=137). In this sample median duration of brigatinib exposure was 227 (range, 1–1443) days, median dose intensity was 170.7 (range, 19– 300) mg/day and median relative dose intensity was 98.2%. AE led to dose reduction in 13.1% of patients in this sample. The ERG has checked these data against the CSR.

[redacted]

The company do report other data for the subset of patients in Study 101 who received brigatinib at a dose of 90 mg QD → 180 mg QD: 71.9% experienced TEAEs grade ≥3, with 59.4% experiencing TEAEs that led to dose interruption, reduction, or discontinuation and 34.4% experiencing SAEs. The ERG has checked these data against the CSR.(41) The company also report data from the whole study sample who received brigatinib with regards to EOPE (n=137): 8.0% of patients had a pulmonary TEAE that was either a possible or definite EOPE, median time to onset of the pulmonary TEAE (after introduction of brigatinib) was on Day 2 (range, 1–4 days). In all of these patient cases, the EOPE was a SAE, and in all but one case it was a grade ≥3 TEAE, and in two of these cases patient death occurred. However, the company highlight that none of the subset of patients in Study 101 who received brigatinib at a dose of 90 mg QD → 180 mg QD (n=32, n=7 not relevant to this STA) experienced an EOPE. The ERG has checked these data against the CSR.(41)

The ERG report that in the whole study sample receiving Brigatinib (at varying doses), 16 deaths occurred, although 8 were due to neoplasm progression.(1)

[redacted]

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

4.3.1 Search strategy for indirect treatment comparison

Evidence to inform indirect treatment comparison (ITC) analyses was identified from the main SLR, which the ERG critique above in section 4.1.1. No separate search was conducted for the ITC analyses, and the ERG considered this to be an appropriate approach.

4.3.2 Assessment of the feasibility of conducting network meta-analysis

Network meta-analysis (NMA) is a technique that can be used to simultaneously compare three or more treatments to produce a network of pooled effect estimates.(44) While a gold-standard in many HTA contexts, NMA is not applicable to the current submission, since a sole intervention (brigatinib) is compared to a sole comparator (ceritinib). Therefore the ERG agrees with the company's decision to not conduct NMA.

4.3.3 Study selection criteria for indirect treatment comparison

Since NMA was not appropriate, the company had to consider alternative approaches to conducting ITC analyses. It was necessary to conduct ITC analyses because of the absence of head-to-head trials between the intervention and comparator treatments. Additionally, the submitting company only had access to IPD for its own trials for brigatinib and not for the comparator ceritinib trials. Therefore, based on the NICE DSU TSD18 recommendations,(45) a matched-adjusted indirect comparison (MAIC) analysis was used to perform ITC taking into account differences between the brigatinib and ceritinib studies. Additionally, a naïve ITC was also performed without population adjustment.

Studies for the ITC analyses were selected from the SLR as discussed in Section 4.1.2 above. The criteria included studies for both brigatinib and ceritinib. As discussed above in Section 4.1.2, the ERG considered the inclusion criteria to be largely appropriate. No separate set of criteria for inclusion in the ITC were outlined in the CS beyond those for the SLR. The ERG considers this to be an appropriate approach.

4.3.4 Studies included in the Indirect Treatment Comparison

Two brigatinib studies were included in the ITC analyses. These were ALTA and Study 101, and both are considered by the ERG to be single-arm for the purposes of this appraisal in terms of use in ITC analysis and clinical inputs to the economic model, since Arm A of ALTA does not fit the NICE scope for this appraisal. Details of the design and key results of these brigatinib studies are provided above in section 4.2.

4.3.4.1 Design of included ceritinib studies

The table below provides an overview of the design and outcomes of the two ceritinib studies including in the ITC analyses, compared with the two brigatinib studies.

Table 18. Methods and outcomes of studies included in the indirect treatment comparison

Trial	ALTA	Study 101	ASCEND-5	ASCEND-2
Intervention/comparator	Brigatinib	Brigatinib	Ceritinib vs. Chemotherapy (docetaxel or pemetrexed)	Ceritinib
Study design	Multi-national, multi-centre, non-comparator trial	Open-label, dosing trial	RCT	Single-arm
Phase	2	1/2	3	2
Eligible patients (n)	222	25	231	140
Population	Locally advanced or metastatic ALK+ NSCLC investigator determined disease progression while receiving crizotinib	Subgroup of patients with locally advanced or metastatic ALK+ NSCLC that progressed while on crizotinib	ALK+ NSCLC who received prior treatment with at least one previous platinum-based chemotherapy regimen and previous crizotinib	ALK+ NSCLC who received prior treatment with ≥1 previous platinum-based chemotherapy regimen and previous crizotinib
Location and setting	71 cancer centres (USA n =15; Canada n =1; Europe n =38; Australia n = 6; Asia n = 11)	9 cancer centres in USA and Spain	110 sites across USA, Belgium, Canada, France, Germany, Hong Kong, Ireland, Israel, Italy, Japan, Republic of Korea, Lebanon, Netherlands, Portugal, Russian Federation, Singapore, Spain, Switzerland, Turkey, UK	51 global sites across Canada, France, Germany, Hong Kong, Italy, Japan, Republic of Korea, Netherlands, Singapore, Spain, United Kingdom, United States
Dosing regimen	Oral brigatinib 90mg once daily Oral brigatinib180mg once daily with 7 –day lead in of 90mg once daily	Oral brigatinib 90mg once daily Oral brigatinib 180mg once daily with 7 –day lead in of 90mg once daily	Oral ceritinib 750mg daily Intravenous Chemotherapy pemetrexed 500mg/m2 or docetaxel 75mg/m2 every 21 days	Oral ceritinib 750mg daily

Median duration of follow-up	May 2016 data cut: 7.8 months (0.1 -16.7) 8.3 months (0.1 to 20.2) February 2017 data cut: 16.8 months 18.6 months	NR for eligible subgroup **	16.6 months (IQR 11.6-21.4) 16.4 months (IQR11.4-21.4)	11.3 months (0.1-18.9)
Primary outcome	Investigator-assessed RECIST v1.1-defined ORR, confirmed at least 4 weeks from initial response in the ITT population.	Investigator-assessed ORR per RECIST v1.1	IRC-assessed (masked), RECIST v1.1-defined PFS in the ITT population	Investigator-assessed RECIST v1.1-defined ORR, confirmed at least 4 weeks from initial response.
Secondary outcomes	IRC-assessed confirmed ORR; CNS response (IRC assessed intracranial ORR & PFS in patients with active brans mets); DOR; PFS; OS; Safety and tolerability; QoL	Safety and tolerability; IRC-assessed: Best overall response; DOR; PFS; Time to treatment failure; OS; Systemic ORR	IRC-assessed: OS; ORR; DOR; DCR; TTR; Intracranial responses; Safety; QoL	OS; DCR; TTR; DOR; PFS; Intracranial response rates (in patients with baseline brain mets.) Safety; Patient reported outcomes
Abbreviations: ORR, objective response rate; PFS, progression-free survival; OS, overall survival; DOR, duration of response; TTR, time to response; INV, investigator; IRC, independent review committee; ITT, intent-to-treat; RECIST, Response Evaluation Criteria In Solid Tumours; QoL, quality of life; DCR, Disease Control rate				

Source: CS Appendix, p59-60, Table 12 (Takeda Ltd)

The clinical effectiveness evidence for ceritinib in the ITC is based on two studies, which are both single-arm studies for the purposes of this appraisal. ASCEND-2 is listed as an RCT in the table above, but the comparator is chemotherapy, which is not an eligible technology. ASCEND-5 is a single arm study.

The sparsity of the evidence should be noted, and it is challenging to conclude that single-arm studies alone represent a robust body of evidence. Since there is no common comparator for the brigatinib and ceritinib trials, this has a number of important limitations including precluding the use of anchored MAIC, which NICE DSU TSD 18 recommendations consider to be more robust than unanchored MAIC analysis.

There are no randomised controlled trials (RCTs) included for the purposes of this appraisal. RCTs have a traditional status as a gold standard for the evaluation of health technologies.(46) It is important to note that there is evidence that well-designed observational studies may not systematically overestimate treatment effects compared to RCTs.(47) However, the studies included in this appraisal do not have the benefits of well-designed observational studies as outlined in Concato *et al* (47) and Barnish and Turner.(48)

There are data from a total of 247 brigatinib patients available for this appraisal compared to 371 patients for ceritinib. Both ceritinib trials include some UK centres, while ALTA includes only one UK centre, and Study 101 includes no UK centres. It is, however, noted that the primary endpoint for ASCEND-5 is IRC- assessed PFS, whereas the other three trials used INV outcomes as the primary outcomes. Both ceritinib studies provide data on median follow-up duration, and this is longer for ASCEND-5 than ASCEND-2 (16.6 vs 11.3 months).

4.3.4.2 Results of included ceritinib studies

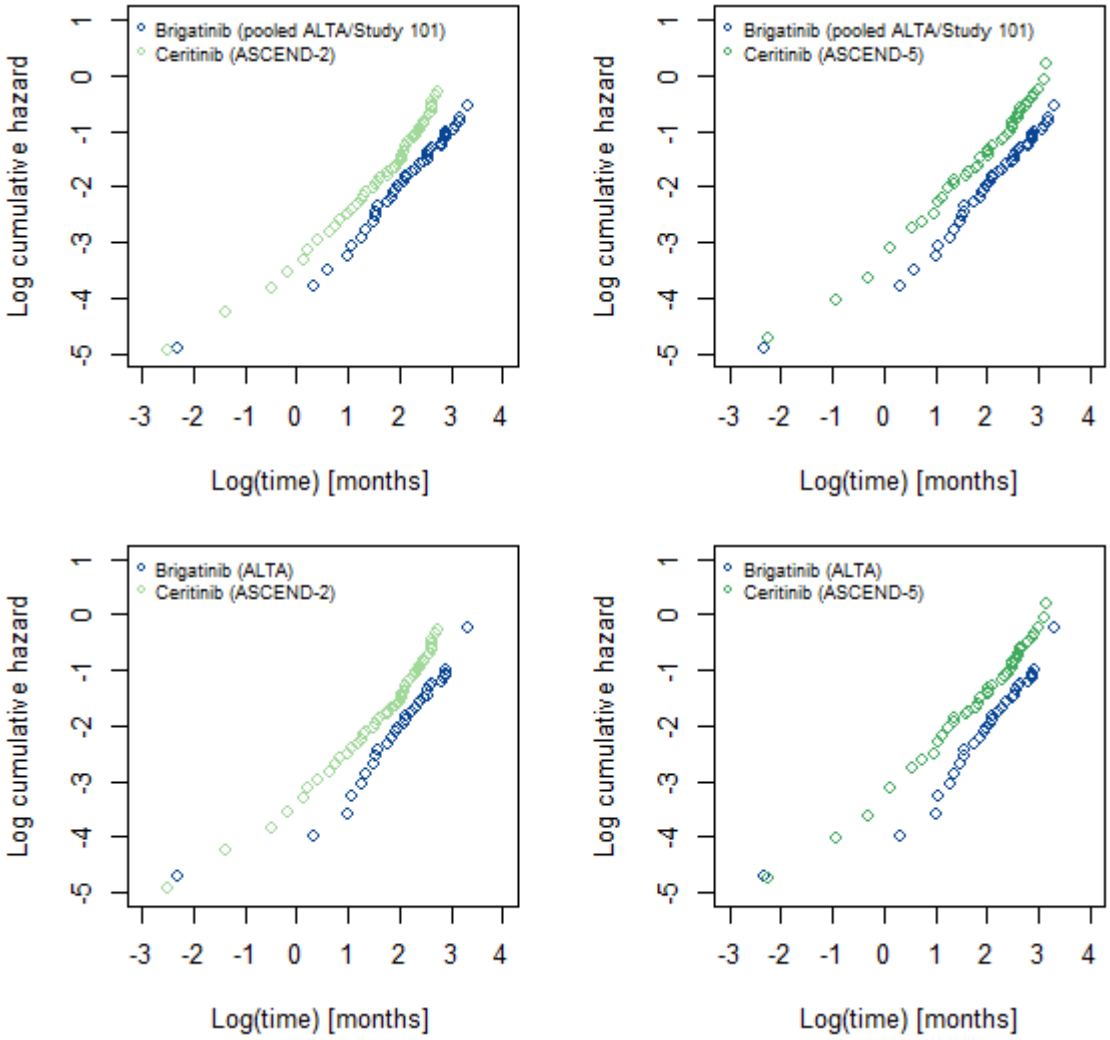
The CS includes the results of analysis conducted using reconstructed ceritinib datasets that were "recreated from published data" (e.g. CS Appendix, p66, Table 15). The table below and log cumulative hazard plots suggest an advantage for brigatinib over ceritinib in unadjusted analysis in terms of median OS.

Table 19. Summary of observed median overall survival

Brigatinib				Ceritinib			
Analysis	**Source**	**Median (months)**	**95% CI (months)**	**Analysis**	**Source**	**Median (months)**	**95% CI (months)**
Naïve	Pooled ALTA / Study 101	NE	[27.6, NE]	Recreated from published data	ASCEND-2	14.9	[13.5, NE]
Full		27.6	[27.6, NE]				
Reduced		27.6	[27.6, NE]				
Naïve	ALTA	27.6	[27.6, NE]				
Full		27.6	[27.6, NE]				
Reduced		27.6	[27.6, NE]				
Naïve	Pooled ALTA / Study 101	NE	[27.6, NE]	Recreated from published data	ASCEND-5	18.1	[13.4, 23.9]
Full		NE	[27.6, NE]				
Reduced		NE	[27.6, NE]				
Naïve	ALTA	27.6	[27.6, NE]				
Full		27.6	[27.6, NE]				
Reduced		27.6	[27.6, NE]				
Abbreviations: CI, confidence interval; NE, not estimable; OS, overall survival.							

Source: CS Appendix, p66, Table 15 (Takeda Ltd)

Figure 11. Log cumulative hazard plots for overall survival; unadjusted brigatinib data vs. reconstructed ceritinib data from ASCEND-2 and ASCEND-5



Source: CS Appendix, p67, Figure 7 (Takeda Ltd)

Similarly, as seen in the table and log cumulative hazard plots below, brigatinib appears to have an advantage over ceritinib in terms of PFS.

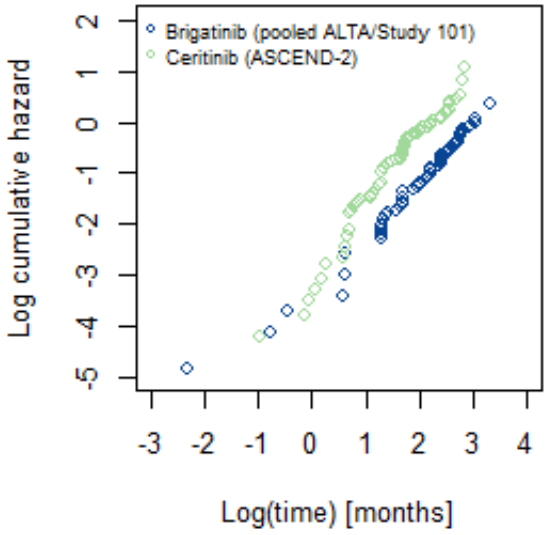
Table 20. Summary of observed median progression-free survival (PFS)

Brigatinib					Ceritinib				
Analysis	**Source**	**Measure**	**Median (months)**	**95% CI (months)**	**Analysis**	**Source**	**Measure**	**Median (months)**	**95% CI (months)**
Naïve	ALTA	INV	15.6	[11.1, 21.0]	Recreated from published data	ASCEND-2	INV	5.7	[5.4, 7.6]
Full			15.6	[11.1, NE]					
Reduced			15.6	[11.1, 21.1]					
Naïve	Pooled ALTA / Study 101		15.6	[12.6, 21.0]					
Full			15.6	[11.1, 21.1]					
Reduced			15.6	[11.1, 21.1]					
Naïve	ALTA	IRC	16.7	[12.6, NE]	Recreated from published data	ASCEND-5	IRC	5.4	[4.1, 6.9]
Full			18.3	[16.7, NE]					
Reduced			18.3	[15.6, NE]					

Abbreviations: CI, confidence interval; INV, investigator-assessed PFS; IRC, Independent Review Committee-assessed PFS; NE, not estimable; PFS, progression-free survival.

Source: CS Appendix, p71, Table 16 (Takeda Ltd)

Figure 12. Log cumulative hazard plots for progression-free survival; unadjusted brigatinib data vs. ceritinib data from ASCEND-2 and ASCEND-5



Source: CS Appendix, p72, Figure 9 (Takeda Ltd)

4.3.5 Risk of bias for studies included in the Indirect Treatment Comparison

The company assessed risk of bias for all four studies included in the MAIC analyses. A critique of the risk of bias assessment for the two brigatinib studies (ALTA and Study 101) is provided in section 4.1.5. This section provides a critique of the two ceritinib studies included in the MAIC analyses (ASCEND-2 and ASCEND-5) and a summary of risk of bias across all four studies.

For the purposes of this STA, and thus for quality assessment purposes, the ERG consider the two ceritinib studies to be single-arm trials. While ASCEND-2 is a single-arm Phase 2 trial of ceritinib, ASCEND-5 is in fact an RCT of ceritinib versus chemotherapy. Chemotherapy is not a comparator in this STA. Therefore, only the ceritinib data from ASCEND-5 are relevant. From this perspective the ERG consider that, as with the ALTA trial, the ASCEND-5 trial should be considered to be a single-arm study for this STA. The ERG note, however, that although the ALTA trial of brigatinib was quality appraised by the company as a single-arm trial, ASCEND-5 has been quality appraised as an RCT, which does not represent consistent practice.

To address this, the ERG has critiqued the quality appraisal of ASCEND-5 as per the company's methods (i.e. using the Cochrane Risk of Bias criteria for RCTs) and also provided a summary of the risk of bias data for this trial in the same format as for the other three single arm studies (see sections 4.3.5.2 and 4.3.5.3 respectively).

4.3.5.1 Quality assessment of ASCEND-2

The company produced a tabulated quality assessment of the single-arm study, ASCEND-2. Table 21 provides this assessment alongside ERG comments.

Table 21: Risk of bias in ASCEND-2

Trial name: ASCEND-2	Item	Company rating	ERG comments
Selection bias	Representative sample selected from a relevant population	Low – representative sample, from multi centres, enrolled at similar Stage of disease and functional level stated. Patients had similar prior treatment	The ERG agrees that participant characteristics appear to be largely consistent with clinical practice The ERG notes that it is unclear whether all eligible patients were recruited.
	Explicit inclusion/exclusion criteria	Low – patients selected according to inclusion/exclusion criteria specified in protocol.	The ERG agrees with this rating: inclusion/exclusion criteria appear to be appropriate, and participants were selected using these criteria.
	If comparisons of sub-series are being made, was there sufficient description of the series and the distribution of	NA	NA

Trial name: ASCEND-2	Item	Company rating	ERG comments
	prognostic factors?		
Performance bias	Blinding of participants and personnel	Efficacy outcomes Low – patients and personnel not blinded to treatment but were unlikely to influence objective efficacy outcomes Safety outcomes – Unclear – patients and personnel more likely to influence safety and PRO	The ERG notes that even objective outcomes might be influenced by lack of blinding. However, this is unlikely to have a large influence on these outcomes. The ERG agrees that safety and PRO outcomes are likely to be influenced by lack of blinding to a larger extent than objective outcomes but that the extent of this remains unclear.
Detection bias	Blinding of outcome assessment	Risk of bias was unclear for the primary outcome of ORR because investigators assessed responses. However, responses were confirmed at least 4 weeks from initial response and additional IRC-assessed ORR supported investigator-assessed ORR Safety outcomes – Unclear – outcome assessors were not blinded but unclear the extent to which these could be influenced – objective criteria used.	The ERG agrees with the company's assessment.
	Long enough follow up for important events to occur	Low – power calculation included assessment of how many events required.	The ERG agrees with the company's assessment.
Attrition bias	Incomplete outcome data	Low – patients with unknown best overall response	The ERG notes that analyses were conducted in participants who received ≥ 1 dose of ceritinib. It

Trial name: ASCEND-2	Item	Company rating	ERG comments
		were counted as non-responders and the analyses were conducted in ITT population.	appears that this applied to all enrolled patients.
Reporting bias	Selective reporting	Low – protocol checked, no evidence of selective reporting	The ERG found no evidence of selective reporting.
Other bias	Bias due to problems not covered elsewhere	High – no comparator or control group.	The ERG agrees that there is high risk of bias where no comparator is included.

Source: Adapted from CS, Appendix D (Takeda Ltd)

As with the two brigatinib trials, the company states that the largest risk of bias in the ASCEND-2 is related to the fact that no comparators are included. The ERG agree with this assessment. With regard to other sources of bias, risk is generally low, but sometimes unclear (see Table 21).

With regard to the risk of selection bias, the ERG notes that it is unclear whether all eligible participants were approached and recruited to the ASCEND-2 trial. However, the participants were selected according to appropriate inclusion/exclusion criteria and appeared to be largely representative of clinical practice.

With regard to blinding, the participants, study personnel and outcome assessors were not blinded to treatment for the primary study outcome. The ERG agrees with the company that the lack of patient, personnel and assessor blinding is likely to have most impact on patient reported and safety outcomes, although impact on other outcomes cannot be completely ruled out. Some of the response-related end-points were assessed by a blinded IRC and this may have mitigated bias to some extent, although it is unclear how blinding of the committee occurred in this single-arm study.

ASCEND-2 was also assessed by the company to be of low risk of attrition and reporting bias. Participants must have received ≥ 1 dose of ceritinib to be included in the analyses. The study authors report that all enrolled participants received ceritinib.(12) The ERG agrees, therefore, that analyses were conducted on an ITT sample. The ERG has checked the study results against the endpoints described in the study protocol (49)and no evidence of selective reporting was found.

4.3.5.2 Quality assessment of ASCEND-5

The company produced a tabulated quality assessment of ASCEND-5. The company evaluated ASCEND-5 as an RCT, although only a single-arm is used in this STA. Table 21 provides the company's assessment alongside ERG comments.

Table 22: Risk of Bias in ASCEND-5 (assessed as an RCT)

Trial name: ASCEND-5	Item	Company rating	ERG comments
Selection bias	**Random sequence generation**	Low – Block randomisation using interactive response technology	The ERG agrees with the company's assessment. Also, randomisation was stratified by WHO performance status and the presence of brain metastases.
	Allocation concealment	Low – central sequence generation therefore randomisation could not be predicted by sites	The ERG agrees with the company's assessment.
Performance bias	**Blinding of participants and personnel**	Efficacy outcomes – Low – patients and personnel knew the treatment assigned. However, efficacy outcomes are unlikely to be influenced because judged by IRC. Safety outcomes – Unclear – patients and personnel more likely to influence safety and PRO outcomes	The ERG notes that even objective outcomes may be influenced by lack of blinding. However, this is unlikely to have a large influence on these outcomes. The ERG agrees that safety and PRO outcomes are likely to be influenced by lack of blinding to a larger extent than objective outcomes but that the extent of this remains unclear.
Detection bias	**Blinding of outcome assessment**	Efficacy outcomes – IRC-assessed (i.e. efficacy) Low Safety outcomes – Unclear – investigator assessed but objective criteria used to categorise AEs.	The ERG agrees that risk of detection bias is low for the efficacy outcomes and that it is unclear as to what extent the lack of blinding would have influenced safety outcomes.
Attrition bias	**Incomplete outcome data**	Low – Analyses performed on ITT population, reasons for discontinuation are clearly documented and equal across arms.	The ERG agrees with the company's assessment.
Reporting bias	**Selective reporting**	Low – Protocol assessed against published results. No	Although all primary and key secondary outcomes were

		evidence of selective reporting.	reported, the ERG note that Intracranial Disease Control Rate (IDCR) was not reported.
Other bias	**Bias due to problems not covered elsewhere**	Unclear – Difficult to assess other sources of bias without further details (e.g. CSR or statistical analyses plan).	The ERG agrees with the company's assessment.
Abbreviations: AE, adverse events; CSR, clinical study report; ITT, intention to treat; PRO, patient reported outcomes.			

Source: Adapted from CS, Appendix D (Takeda Ltd)

The company judged that, when evaluated as an RCT, ASCEND-5 was at low risk of selection bias (random sequence generation and allocation concealment were appropriately conducted). The ERG agrees with this view. With regards to performance and detection bias, the company point out that although lack of blinding can increase risk of bias, this is still likely to be low for efficacy outcomes where results were primarily determined by a blinded IRC. Whilst the ERG largely agrees with this, it should be noted that lack of blinding of participants and study personnel can still impact upon results, even those that are 'objective'. Although this impact is likely to be small, it cannot be completely ruled out. The company highlight that lack of blinding is likely to have a greater impact on safety and quality-of-life outcomes, and the ERG agrees with this.

The company rate the risk of attrition bias in ASCEND-5 as low, and the ERG agrees with this rating. Although all main outcomes were reported, the ERG found that one of the secondary outcomes mentioned in the study protocol was not reported (Table 22).(50) The ERG agrees with the company that it is difficult to assess additional sources of bias based solely on the information available.

For consistency with the other three studies (including ALTA, which is also an RCT where only one arm has been used in the ITC analyses), the ERG also rated the quality of ASCEND-5 according to the company's modified criteria for single-arm studies. These ERG ratings are given in

Table 23 (note that only items not already assessed above are rated).

Table 23: Risk of Bias in ASCEND-5 (assessed as a single-arm study)

Trial name: ASCEND-2	Item	Rating
Selection bias	Representative sample selected from a relevant population	ERG rating - Low - participant characteristics appear to be largely consistent with clinical practice The ERG notes that it is unclear whether all eligible patients were recruited, although participants were randomly assigned to the ceritinib study arm
	Explicit inclusion/exclusion criteria	ERG rating - Low - inclusion/exclusion criteria appear to be appropriate, and participants were selected using these criteria.
	If comparisons of sub-series are being made, was there sufficient description of the series and the distribution of prognostic factors?	ERG rating - Low – patients were randomly assigned to the ceritinib and chemotherapy arms and these arms were similar in terms of prognostic factors
Performance bias	Blinding of participants and personnel	As with Table 22
Detection bias	Blinding of outcome assessment	As with Table 22
	Long enough follow up for important events to occur	OS data were immature
Attrition bias	Incomplete outcome data	As with Table 22
Reporting bias	Selective reporting	As with Table 22
Other bias	Bias due to problems not covered elsewhere	As with Table 22

Source: Adapted from CS, Appendix D (Takeda Ltd)

4.3.5.3 Summary of risk of bias in studies included in the MAIC

In summary, the largest potential source of bias (for all four studies) derives from the fact that all data were from either single-arm studies (Study 101 and ASCEND-2), or studies which, for the purposes of this STA can only be considered as single-arm studies (ALTA and

ASCEND-5). Although MAIC analyses aim to mitigate bias to some extent, by matching participants on key prognostic factors, other differences between the single-arm groups cannot be accounted for (e.g. differences due to specific sites or specific study methods).

Aside from this issue, when assessed as single-arm studies, there was generally low or unclear risk of bias across studies (see Table 7, Table 8, Table 21 and

Table 23). However, for Study 101, the risk of bias due to lack of blinding of the outcome assessors was rated as high. In this study, the data informing the ORR were not independently assessed or checked (e.g. by an IRC). Risk of bias was also rated as high for Study 101 because only a small sub-sample of the study was eligible for the appraisal and no power calculation was used to ascertain sufficient sample size.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

4.4.1 Summary of analyses undertaken

The company's MAIC analysis proceeded in the following steps:

(1) Identify an appropriate set of prognostic or effect-modifying covariates which should be balanced by a MAIC analysis.

(2) Estimate MAIC weights using Brigatinib IPD data and Ceritinib aggregate data using methodology described by Signorovitch *et al* and covariates identified in step 1.(51)

(3) Generate IPD outcome data for the Ceritinib studies (ASCEND2/5) from published Kaplan-Meier curves, using an algorithm described by Guyot *et al*.(52)

(4) Apply Cox regression to the survival data (step 3) to estimate hazard ratios, using MAIC weights (step 2).

(5) Bayesian meta-analysis of log hazard ratios from step 4 using treatment-contrasts setup with both fixed effects and random effects models.

A naïve version of the ITC analysis was also produced, in addition to the MAIC analysis. Bayesian meta-analyses were performed using both naïve and MAIC ITC models.

4.4.2 Use of unanchored MAIC

NICE DSU TSD 18 recommends the use of anchored comparisons where possible and that 'unanchored indirect comparisons may only be considered in the absence of a connected network of randomised or where there are single-arm studies involved' (DSU TSD18 p61).

The CS presents an ITC of 4 studies which included, for brigatinib, an RCT comparing two dosing regimens and a single-arm dosing trial, and for ceritinib, an RCT and a single-arm trial. Furthermore two single arm studies are included.

Of these, the randomised comparisons are between brigatinib (two dosing arms) and ceritinib (drug vs chemotherapy). There is no common comparator between these. That is, an anchored comparison that would have allowed an inference about the relative effect (of the form $\Delta_{BC} = (\bar{Y}_B - \bar{Y}_0) - (\overline{Y_C} - \bar{Y}_0)$, see DSU18 section 1.2) in which a common control arm

Y_0 'anchors' the comparison, is not possible. Indeed, all studies are considered as single-arm for the purposes of this appraisal, since no available comparator arm fell within the NICE scope for this appraisal.

The ERG therefore agrees that unanchored is the appropriate form of MAIC in this case.

4.4.3 Proportional hazards assumption in ITC analysis

The CS estimates hazard ratios between MAIC-adjusted IPD data on survival in the treatment population and (reconstructed) IPD survival data in the comparator population. The estimation makes use of Cox regression and an accompanying assumption of proportional hazards. In order to assess whether this assumption is reasonable, the log cumulative hazard is plotted against log time and conformity with a parallel pattern is assessed. Ideally this assessment would test the unadjusted hazards, so the ERG performed this test (results are presented in Section 5.2.6.3) and found hazards to be roughly parallel (proportional). And as stated in the CS, no serious violations in the form of crossing-over of curves were detected.

4.4.4 Effect modifier selection

The company identified 20 potential effect modifier and prognostic variables (summarised in Appendix D Table 13). These were filtered on the basis of (i) collinearity/correlation amongst them (ii) their prognostic strength according to interviews with clinicians, and (iii) availability of information across the treatment/comparators. A final 'full' set of 8 covariates was obtained for use in the MAIC analyses, where a narrower 'reduced' set was used in analyses including Study 101, for which more limited covariate information was available.

The full covariate set (CS Appendix, p62-64, Table 13) was:

1. ECOG PS
2. Presence of brain metastases
3. Number of prior anti-cancer regimens received
4. Age
5. Smoking history status
6. Crizotinib as last treatment before next TKI
7. Gender
8. Receipt of any prior chemotherapy

The reduced covariate set (CS, p.61) was:

1. ECOG PS
2. Presence of brain metastases

3. Age
4. Crizotinib as last treatment before next TKI
5. Gender
6. Receipt of any prior chemotherapy

(a) The submission states (B2.9.3) that the initial selection of 20 'were factors which were available in the ALTA trial'. It is not clear whether the initial selection was based solely on the ALTA trial. The ERG notes that in an unanchored indirect comparison population adjustment methods should adjust for all effect modifiers and prognostic variables (DSU18) so consideration ought to also have been given to any others not part of ALTA itself.

(b) The selection process described by the company is only broadly described. The ERG agrees that strong collinearity and low prognostic strength as rated / ranked by clinicians may be defensible bases on which to reduce the covariate set. However the submission does not quantify the correlation ratings (mild/strong/very strong) given in Table 13 (CS Appendix D) nor the exact process when selecting from the number of clinicians (out of 5) rating as prognostic. The clinicians' rankings of prognostic importance were not supplied (except narratively in some entries in CS Table 13) nor the correlation quantities.

It is not entirely clear to what extent a lack of availability figured in the exclusion of covariates, but it appears that at least one prognostically important variable was excluded solely on the basis of lack of information ('best prior response to crizotinib' which is rated as prognostic by 5 clinicians and has a single 'mild' correlation with other potential covariates). This leaves the possibility of residual bias in at least one known prognostic variable excluded from the MAIC.

(c) Further exclusion was necessary within the full 8-covariate set for individual MAIC analyses where individual studies did not record covariate(s). These exclusions are detailed in the caption of CS Table 14 and can be inspected in Table 24. Only the comparisons between ASCEND-5 and ALTA allowed use of the full set; other comparisons excluded the proportion who never smoked, and in many cases the proportion with 3+ prior regimens as well.

4.4.5 Comparison of baseline characteristics after matching

In principle, a MAIC forms a reweighting of the IPD sample such that the aggregate statistics between treatment and comparator are balanced. The submission did not provide a table allowing comparison of the covariate distributions between the MAIC-adjusted population and the comparator population. The ERG believes this information should be made available

within any CS to assess the MAIC procedure: after MAIC adjustment, the aggregate summaries should be similar. The ERG requested and received IPD and analytical code from the company at the clarification stage. The ERG was able to reproduce this information using the weights produced by the supplied code and the results are shown in Table 24.

A summary of potential MAIC covariates is given in the CS (Appendix D, Table 13) and a comparison of the characteristics of included covariates is given in CS Table 21. Among the 12 that were excluded, Table 25 below shows that in 5 cases information on comparisons was available. The ERG believes it would have been more transparent to explicitly show and compare the characteristics of all (included or excluded) potential prognostic/effect modifying covariates. It is not expected this would alter interpretation in this case, since the reasons for exclusion appear to be satisfactorily explained within the CS.

Table 24*. Comparison of aggregate summaries of covariates between the MAIC-adjusted population and the comparator population*

Brigatinib population	Covariate set	Ceritinib population	Mean age	Proportion male	Proportion in ECOG2 versus ECOG 0-1	Proportion with brain metastases	Proportion with prior chemo	Proportion whose last treatment was Crizotinib	Proportion with 3+ prior regimens	Proportion never smoked
Alta	Full*	Ascend2	51 (51)	0.50 (0.50)	0.14 (0.14)	0.71 (0.71)	1.00 (1.0)	1.00 (1.0)	0.56 (0.56)	
pooled	Full*	Ascend2	51 (51)	0.50 (0.50)	0.14 (0.14)	0.71 (0.71)	1.00 (1.0)	1.00 (1.0)		
Alta	Red	Ascend2	51 (51)	0.50 (0.50)	0.14 (0.14)	0.71 (0.71)	1.00 (1.0)	1.00 (1.0)		
pooled	Red	Ascend2	51 (51)	0.50 (0.50)	0.14 (0.14)	0.71 (0.71)	1.00 (1.0)	1.00 (1.0)		
Alta	Full*	Ascend5	54 (54)	0.41 (0.41)	0.08 (0.08)	0.56 (0.57)	0.99 (0.99)	0.82 (0.82)	1.5e-06 (0)	0.62 (0.62)
pooled	Full*	Ascend5	54 (54)	0.41 (0.41)	0.08 (0.08)	0.57 (0.57)	0.99 (0.99)	0.82 (0.82)		
Alta	Red	Ascend5	54 (54)	0.41 (0.41)	0.08 (0.08)	0.57 (0.57)	0.99 (0.99)	0.82 (0.82)		
pooled	Red	Ascend5	54 (54)	0.41 (0.41)	0.08 (0.08)	0.57 (0.57)	0.99 (0.99)	0.82 (0.82)		

Notes. Where cells are blank, the corresponding covariate was not used in the MAIC. The MAIC-adjusted figures are shown for the IPD population with the comparator figures are adjacent in parentheses (from CS Table 21). *The company define the 'full' covariate set as 7 covariates when the comparator is ASCEND2 and 8 covariates when the comparator is ASCEND5 (see caption to CS Table 14). The value in the cells is the MAIC-adjusted brigatinib value and the adjacent value in brackets is the value from the ceritinib population.

Table 25. Potential prognostic/effect-modifying covariates excluded from MAIC analyses with indication of availability of information

	ASCEND2	ASCEND5	ALTA (Arm B)	Relevant subgroup of STUDY101	(Partial) comparison possible
Best prior response to crizotinib	X	X	X	X	X
Presence of active lesions on brain	X	X	X	X	X
Receipt of prior radiotherapy	√	√	√	√	√
Number of metastatic sites	X	X	X	X	X
Time from Crizotinib to next TKI	X	√	X	X	X
Disease stage at entry	√	√	√	X	√
Prior platinum therapy	√	√	√	X	√
Liver metastases	√	X	X	X	X
Histology class	√	√	√	X	√
Race	√	√	√	√	√
Lung metastases	√	X	X	X	X
Bone metastases	√	X	X	X	X

Source: CS Appendix D, Table 13 for ASCEND2 and ASCEND5; CS Table 8 for ALTA and STUDY 101 (Takeda Ltd)

The CS did, however, include other assessments of ITC model fit. The use of naïve ITC alone was recognised as a limitation in TA395 for ceritinib (CS, p94, Table 31), since “bias may have been introduced for heterogenous [sic] patient populations and retrospective nature of included studies”. In order to address this limitation from a previous related appraisal, the CS also includes population-adjusted MAIC analyses.

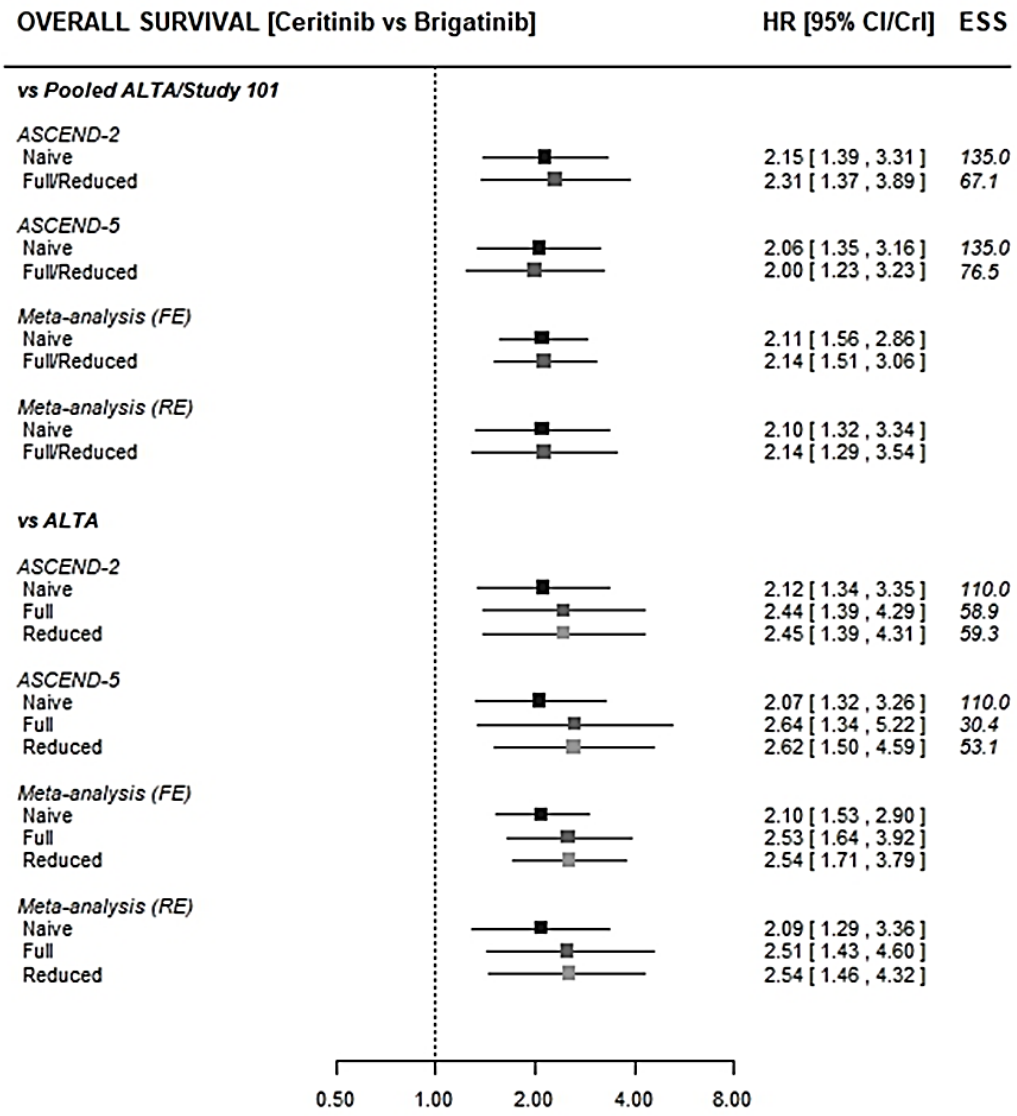
The CS itself acknowledges that there are limitations with regard to the extent of overlap between the patient populations for brigatinib and ceritinib. Assessing the weight distributions from the MAIC analysis, the CS concludes that “the medians are heavily skewed towards zero (0.03) and a large proportion of patients have been given a weight of close to zero meaning that these patients may be different in terms of patient characteristics compared to the ASCEND-2 and ASCEND-5 studies” (CS Appendix, p75). The effective sample sizes (ESS) in the MAIC analyses are also modest (see Appendix 5), indicating that there is sub-optimal overlap between the brigatinib and ceritinib populations. The figure below depicts the weight distribution and ESS:

In light of the limitations associated with both naïve ITCs and MAIC analyses in the context of this appraisal, the ERG agrees with the company that offering both approaches is the best and most informative course of action, although the ERG considers that neither may be entirely robust.

4.4.6 Results of ITC analyses

The results of the company’s naïve and MAIC ITC analyses for OS are provided below in. It is important to note that the figures provided by the company also include the results of the Bayesian meta-analysis of ITC results, which the ERG critique separately below in sections 4.4.7 and 4.4.8.

Figure 13. Summary of ITC results – overall survival

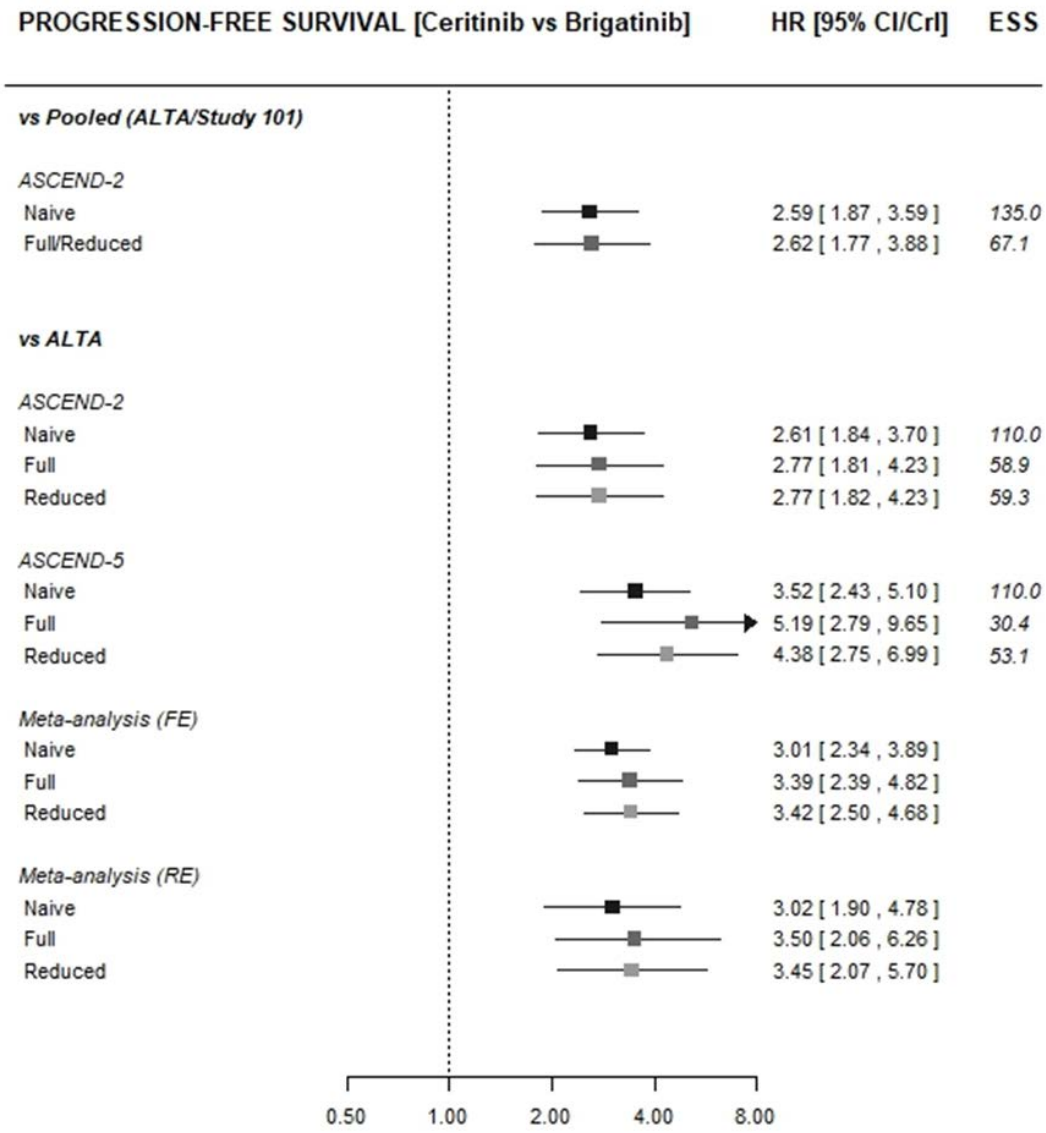


Abbreviations: CI, confidence interval; CrI, credible interval; ESS, effective sample size; FE, fixed-effect; HR, hazard ratio; RE, random-effects. Notes: Naïve estimates denote comparison without adjusting for prognostic factors. Full MAIC estimates denote analysis adjusting for all prognostic factors which were available per study; ASCEND-2: age, gender, ECOG PS, presence of brain metastases, receipt of prior chemotherapy, receipt of crizotinib as last treatment, number of prior anti-cancer regimens; ASCEND-5: age, gender, ECOG PS, presence of brain metastases, receipt of prior chemotherapy, receipt of crizotinib as last treatment, number of prior anti-cancer regimens, smoking status. Reduced MAIC estimates denote analysis adjusting for prognostic factors which were commonly reported across all studies: age, gender, ECOG PS, presence of brain metastases, receipt of prior chemotherapy, receipt of crizotinib as last treatment. Point estimates denote HR of ceritinib vs. brigatinib; estimates to right of dashed vertical line (HR>1) favour brigatinib and estimates to left of dashed vertical line (HR<1) favour ceritinib

Source: CS Addendum, p5, Figure 3 (Takeda Ltd)

The results in Figure 13 are consistently statistically significantly in favour of brigatinib over ceritinib in terms of OS regardless of whether ASCEND-2 or ASCEND-5 is used as a comparator; regardless of whether Pooled ALTA/Study 101 data are used or solely ALTA data; regardless of whether a full MAIC, reduced MAIC or naïve ITC is used; and regardless of whether a fixed or random effects model was used.

Figure 14. Summary of ITC results – progression-free survival



Abbreviations: CI, confidence interval; CrI, credible interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ESS, effective sample size; FE, fixed-effect; HR, hazard ratio; RE, random-effects. Notes: naïve estimates denote comparison without adjusting for prognostic factors. Full MAIC estimates denote analysis adjusting for all prognostic factors which were available per study; ASCEND-2: age, gender, ECOG PS, presence of brain metastases, receipt of prior chemotherapy, receipt of crizotinib as last treatment, number of prior anti-cancer regimens; ASCEND-5: age, gender, ECOG PS, presence of brain metastases, receipt of prior chemotherapy, receipt of crizotinib as last treatment, number of prior anti-cancer regimens, smoking status. Reduced MAIC estimates denote analysis adjusting for prognostic factors which were commonly reported across all studies: age, gender, ECOG PS, presence of brain metastases, receipt of prior chemotherapy, receipt of crizotinib as last treatment. Point estimates denote HR of ceritinib vs. brigatinib; estimates to right of dashed vertical line (HR>1) favour brigatinib and estimates to left of dashed vertical line (HR<1) favour ceritinib.

Source: CS Addendum, p8, Figure 7 (Takeda Ltd)

As above for OS, the ITC results in Figure 14 for PFS are consistently in favour of brigatinib, irrespective of which analytical approach is used.

Table 26. Summary of ITC results – objective/overall response rates

Brigatinib (observed data)				Ceritinib (observed data)				OR [95% CI/CrI] ceritinib vs. brigatinib		
Trial	**Measure**	**n/N**	**%**	**Trial**	**Measure**	**n/N**	**%**	**Naïve**	**MAIC [full]**	**MAIC [reduced]**
ALTA	INV	62/110	56.4	ASCEND-2	INV	54/140	38.6	0.49 [0.29, 0.81] ESS=110	0.54 [0.30, 0.97] ESS=58.9	0.52 [0.29, 0.93] ESS=59.3
ALTA	IRC	62/110	56.4	ASCEND-5	IRC	45/115	39.1	0.50 [0.29, 0.84] ESS=110	0.38 [0.18, 0.80] ESS=30.4	0.52 [0.29, 0.95] ESS=53.1
Pairwise meta-analysis (fixed-effect)								0.49 [0.34, 0.71]	0.48 [0.30, 0.76]	0.52 [0.35, 0.80]
Pairwise meta-analysis (random-effects)								0.49 [0.29, 0.82]	0.47 [0.26, 0.85]	0.53 [0.30, 0.92]

Abbreviations: CI, confidence interval; CrI, credible interval; INV, investigator-assessed ORR; IRC, Independent Review Committee-assessed ORR; n, number of people achieving ORR; N, total sample size; OR, odds ratio; ORR, objective/overall response rate.

Source: CS p66 Table 22 (Takeda Ltd)

Furthermore, Table 26 shows consistently favourable results for brigatinib in terms of response rate. Across the OS, PFS and response rate analyses, the impact of different analytical options on the ITC analyses appears limited.

4.4.7 Methodology for meta-analysis of ITC analyses

The company used meta-analysis methodology to produce an evidence synthesis of the ITC analyses that compared pooled IPD data from ALTA and Study 101 against data from ASCEND-2 with the ITC analyses that compared pooled IPD data from ALTA and Study 101 against data from ASCEND-5.

The CS reports that meta-analysis was conducted separately on the data from the naïve ITC and from the MAIC (CS Appendix, p61). The ERG consider it appropriate to keep the naïve ITC and the population-adjusted MAIC analysis separate. The Clarification response from the company made it clear that the meta-analyses of ITC analyses were Bayesian. The ERG considered a Bayesian approach to be appropriate, in line with NICE DSU TSD 2 recommendations,(53) although this is in the context of meta-analysis of individual trials rather than meta-analysis of ITCs. Moreover, a Bayesian approach to meta-analysis is beneficial for incorporating uncertainty in the context of small sample sizes.(54)

NICE DSU TSD 18 endorses the idea of performing "identical MAICs based on each IPD population, and then pool the relative effect estimates (on the linear predictor scale) with standard meta-analysis methods" (p42), which suggests that the idea of meta-analysing ITC analyses is in itself acceptable.

However, there are some specific issues that the ERG noted with regard to the methodology and/or reporting of the meta-analysis of ITC analyses.

1. The same sample of brigatinib patients pooled from ALTA and Study 101 was used in ITC analyses against ASCEND-2 and against ASCEND-5. Therefore, when these ITCs were meta-analysed, there was an issue with correlated data since the brigatinib patients contributed twice. This issue persists when Study 101 is excluded, since ALTA patients still contribute twice. This can lead to overstatement of the evidence base.(55) NICE DSU TSD 2 states that if a correction is not introduced, the "posterior sampling in addition retains the correlation between parameters that is induced by their joint estimation from the same data" (NICE DSU TSD 2, p41). Using WinBUGS code provided with the submission, the ERG noted that no correction for correlated data had been incorporated. The ERG considered that this omission would be likely to render the confidence intervals unrealistically precise, through underestimating the true uncertainty in the HR between brigatinib and ceritinib.
2. Data from ALTA and Study 101 were pooled prior to entry into ITC analyses (where data were available, so effectively only for the OS outcome as seen below – although ALTA-only results were also presented), and then ITC analyses were meta-analysed. NICE DSU TSD 18 criticises treatment comparison analysis where "multiple

populations with IPD were available" (NICE DSU TSD 18, p42), which is the case for ALTA and Study 101 and "the populations were simply pooled and treated as one large population [with]…seemingly no attempt to account for the clustering of individuals within the component trials" (NICE DSU TSD 18, p42). NICE DSU TSD 18 says that it is preferable to perform a series of MAICs without first pooling data and then to meta-analyse these MAICs.

3. Regarding the choice of distribution of priors in the Bayesian meta-analysis, the CS states that "The informative prior distribution used for the between-study deviation is proposed by Ren *et al*"(56) and that "This prior was a lognormal distribution, with mean -2.56 and variance of 1.74^2 as proposed by Turner *et al*.(57) which was then truncated so that the HR in one study would not be ≥10 times than in another. It represented the beliefs that heterogeneity being low is 15%, being moderate is 78%, and being high is 7%". However, the ERG note that the option from Turner et al selected by the company was a relatively generic distribution, and that an option is available specifically for pharmacological data. On balance, the ERG do not consider that the alternative prior would make a substantial difference to the clinical effectiveness results, although do not have the data to demonstrate this.

4.4.8 Results of meta-analysis of ITC analyses

The CS reported the results of the meta-analyses of ITC analyses in the forest plot showing the ITC results themselves, as seen above. However, for clarity the ERG produce Table 27 below with solely the meta-analysis results.

Table 27 Results of company ITC meta-analyses

	Overall survival (HR; 95% CI/CrI)	Progression-free survival (HR; 95% CI/CrI)	Objective/overall response rate (OR; 95% CI/CrI)
Vs pooled ALTA/Study 101			
Reduced MAIC (Fixed)	2.14; 1.51-3.06	NR	NR
Reduced MAIC (Random)	2.14; 1.29-3.54	NR	NR
Naïve ITC (Fixed)	2.11; 1.56-2.86	NR	NR
Naïve ITC (Random)	2.10; 1.32-3.34	NR	NR
VS ALTA alone			
Full MAIC (Fixed)	2.53; 1.64-3.92	3.39; 2.39-4.82	0.48; 0.30-0.76
Full MAIC (Random)	2.51; 1.43-4.60	3.50; 2.06-6.26	0.47; 0.26-0.85
Reduced MAIC (Fixed)	2.54; 1.71-3.79	3.42; 2.50-4.68	0.52; 0.35-0.80
Reduced MAIC (Random)	2.54; 1.46-4.32	3.45; 2.07-5.70	0.53; 0.30-0.92
Naïve ITC (Fixed)	2.10; 1.53-2.90	3.01; 2.34-3.89	0.49; 0.34-0.71
Naïve ITC (Random)	2.09; 1.29-3.36	3.02; 1.90-4.78	0.49; 0.29-0.82

Abbreviations: HR = hazard ratio, OR = odds ratio, CI = confidence interval, CrI = credible interval, NR = not reported.

Source: Adapted from CS Addendum, p5, Figure 3; p8, Figure 7; p10, Table 1 (Takeda Ltd)

The CS labels the reduced model versus pooled ALTA/Study 101 as ‘Full/Reduced’ – however, it is reduced, since the full covariate set is not available for Study 101. Fixed and random refer to the meta-analysis of the ITCs, rather than to the ITCs themselves. INV data are reported here. In the table above, a HR >1 favours brigatinib and an OR <1 favours brigatinib. Reduced MAIC refers to the MAIC analysis in which a limited covariate set was used – the full covariate set was not available for analyses involving Study 101.

The table above provides clear evidence that the clinical effectiveness analyses provided by the company show a favourable result for brigatinib, and that there is generally considerable consistency across the analytical options. When comparing against ALTA alone, the naïve analysis is notably more conservative than the MAIC analyses for OS, although it still demonstrates a clearly statistically significant effect in favour of brigatinib.

4.4.9 Overall comment on ITC analyses

The ERG agrees that the appropriate form of MAIC in this case is unanchored. The ERG investigated the MAIC analysis and found the distributions of included covariates to be well-matched for the adjusted IPD and aggregate populations. A large number of potential prognostic covariates were considered and most exclusions were given justification (see below), which strengthens the conclusions of the ITCs.

The ERG sought clarification about the production of error estimates made in the MAIC. Technically the uncertainty provided in the original CS should be estimated e.g. by use of sandwich estimators. Doing so increases the confidence intervals but does not alter broad interpretations of the MAIC analysis made in the CS. However the ERG notes that the DSU18 recommends 'full propagation of uncertainty through to the final estimates'. The slightly increased variances have not been further propagated through to the (Bayesian) meta-analysis in the CS (Figure 16) or the economic model.

The filtering process of the initial set of 20 covariates to 8 (CS Appendix D, Table 13) is only broadly explained in the CS, but the ERG agrees that collinearity and prognostic strength are defensible principles within this process. It appears that most exclusions could be supported on these grounds, though in at least one case an exclusion appeared to be made mainly on the basis of missing information. Further missing information meant that most MAIC analyses reduced the included 8-covariate set to 6 or 7. In summary, a small number of variables were identified as prognostically important and not strongly correlated with other included covariates, but were nonetheless not adjusted for in the MAICs.

A concern with any MAIC analysis is the potential for residual imbalance in covariates that have not been identified and included. The success of the MAIC largely hinges on the inclusion of all appropriate effect modifiers/prognostic factors. Furthermore, as noted by the DSU18 a MAIC is 'not capable of adjusting for differences in, for example, treatment administration, co-treatments or treatment switching'. The DSU18 recommends that the likely extent of error due to unaccounted for covariates be quantified and suggests obtaining evidence of the company's treatment 'in a range of different studies in the target population'. This evidence appears not to be available at the present time. Under this circumstance, the DSU18 (p63) advises including the following caveat: 'the amount of bias (systematic error) in

these estimates is unknown, is likely to be substantial, and could even exceed the magnitude of treatment effects which are being estimated'.

However, the ERG also note that naïve ITC models are also provided. This allows comparison of results across different analytical approaches with different strengths and limitations. The ERG note the broad consistency of the results from the analysis using MAIC and naïve ITC approaches, and that the interpretation of the results was consistent regardless of the analytical approach taken.

4.5 Additional work on clinical effectiveness undertaken by the ERG

The ERG requested and received analytical code and individual patient data (IPD) from the company. The ERG replicated the company's statistical analyses, and did not encounter any substantial deviations from the results provided in the CS. The ERG also performed some additional analyses as below to verify the impact of specific analytical decisions made by the company.

NICE DSU TSD 18 states "typically standard errors for MAIC estimates are calculated using a robust sandwich estimator" (p27) and recommends its use (or bootstrapping or Bayesian methods; point 4, section 4.2.8). The ERG obtained clarification from the company that standard model-based rather than sandwich estimators were used in producing the estimates of uncertainty (95% CLs) the CS.

The ERG repeated the company's analysis (using the company-supplied code) to examine the consequences of specifying sandwich estimators for variance estimation, and the results are shown in Appendix 6, Figure 27. As expected the uncertainty is largely increased, but with no major alteration to interpretation.

The ERG noted that the weights option of the coxph() function in the R 3.5.0 survival package is minimally described in the associated package documentation, and the reference given therein was not accessible to the ERG in the time available.(58) Online comments by the author indicate that these weights should be interpreted as frequency weights rather than sampling weights, and the former would be inappropriate for the MAIC-adjusted Cox regression.(59) To probe this further the analysis was repeated in Stata 14.1 with the stcox() function after setting probability weights (pweights with stset()). The results are displayed in Appendix 6, Figure 28. Broadly, there are increases in the confidence intervals but no major changes to interpretation.

Therefore, the ERG does not propose an alternative ITC analysis and meta-analysis thereof than those offered in the CS.

5 Cost-effectiveness

5.1 ERG comment on companies review of cost-effectiveness evidence

5.1.1 Objective

The company conducted a systematic literature review of cost-effectiveness studies to identify and review literature relating to economic models for the treatment of ALK+ advanced or metastatic NSCLC. No issues were raised regarding the objective, strategy or appropriateness of the approach or methods used for the economic search.

5.1.2 Search strategy

The company presented a literature search protocol to support its review of cost effectiveness. The same protocol was also used for the review of quality of life and the review of costs, with no changes. This protocol included systematic searches of key biomedical databases using a literature search strategy and a search of additional websites, grey literature sources and conference abstracts from 2013 onwards. The literature search was carried out in July 2017.

The bibliographic database searching used a search strategy that took the following form:

1. ((controlled index terms for non small cell lung cancer) OR
2. free-text terms for nsclc and for anaplastic lymphoma kinase) AND
3. (a range of search terms for health economics, costs, quality of life, and decision models) AND
4. (limited to 2006 onwards).

The search strategy was applied in the following bibliographic databases: Medline-in-Process and Medline (Ovid), Embase (Ovid), EconLIT and The Cochrane Library.

The literature searching for cost effectiveness studies is reasonably well conducted and reported. However, there are a few concerns. The filter used to limit to economic studies is not a validated filter that we recognise. It is unclear why a validated search filter was not used. The three different searches were combined into one search using a variety of search terms but without using recognised filters for the different subject areas. This lack of differentiation and precision in the search terms used may mean that some studies were missed. Finally, searches for MeSH (Medical Subject Heading) terms were not carried out for some of the search terms in the protocol. This is not best practice and there is a risk that some relevant papers could be missed if MeSH terms are not searched.

5.1.3 Inclusion/exclusion criteria

Inclusion and exclusion criteria described in the company submission for the systematic review are reported in CS Document B Section 5, Appendix D (18), and are presented in Table 28. Search criteria regarding population, interventions and outcomes align with the systematic review objective. The ERG note that cost-effectiveness studies published as conference abstracts before January 2013, may have been published as full-text studies by the search date of this systematic review (July 2017).

The company state that the included economic studies were subsequently quality appraised using the checklist presented in the Methods for the Development of NICE Public Health Guidance (third edition).(60) Results were not reported.

Table 28 Inclusion/ exclusion criteria economic systematic review

	Inclusion	Exclusion
Population	ALK+ advanced or metastatic NSCLC	Non-ALK+ advanced or metastatic NSCLC Advanced or metastatic SCLC Early stage NSCLC Healthy volunteers Animal studies
Interventions	Active intervention	Screening for ALK-rearrangement and echinoderm microtubule-associated protein-like 4 (EML4) ALK fusion testing Biomarkers
Outcomes	Cost-effectiveness outcomes including: incremental cost per QALY	Studies with no outcomes of interest
Study types	Economic models	Interventional or observational study designs (registry, chart review, administrative claims) Systematic literature reviews
Publication types	Journal articles, reports, abstracts, posters and summaries	Letters, newsletters, bulletins, fact sheets, editorials and commentaries
Other	Papers published from 2006 (inclusive) to July 2017 Conference abstracts published within the last four years (January 2013-July 2017, inclusive) Sufficient information to determine model structure	Papers published before 2006 Conference abstracts published before 2013 Insufficient information to determine model structure

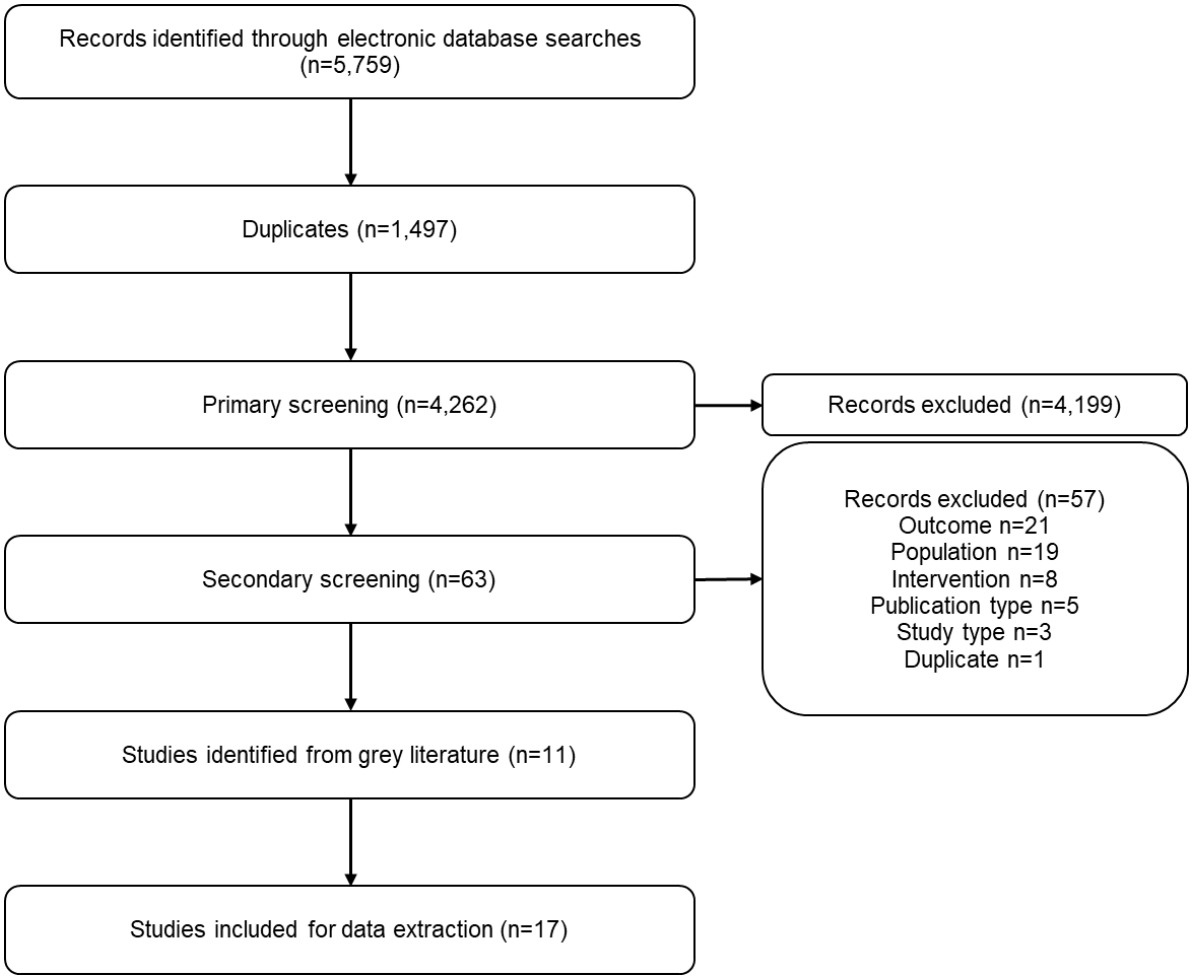
Abbreviations: ALK, anaplastic lymphoma kinase; NSCLC, non-small-cell lung cancer; QALY, quality adjusted life year; SCLC, small-cell lung cancer.

Source: CS Appendix G, p91 (Takeda Ltd)

5.1.4 Results

The PRISMA diagram presented in Figure 15 depicts the flow of information through the different phases of the systematic review, and summarises the reasons for study exclusion as reported by the company.(18)

Figure 15 PRISMA diagram



Abbreviations: n, number; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review

Source: CS. Appendix G, p92 (Takeda Ltd)

The company's systematic review of cost-effectiveness studies identified 17 studies evaluating interventions for ALK+ advanced NSCLC patients.(26, 61-75) The company data extraction summary tables can be found in Appendix 3 (Table 58).

Of the 17 identified, ten were HTA submissions, three abstracts, two posters and two full publication. Six came from electronic searches and 11 from grey literature searches and HTA websites. Summary information was presented by the company for only 16 studies (Table 29 NICE reference case checklistAppendix 4). If one was missed it is not known which or what it contained.

No studies were identified which evaluated brigatinib in the population of interest. Twelve of the identified studies used the AUC approach with 3 disease states to model treatment for the ALK+ advanced NSCLC. Eight of these studies used partitioned survival models. The ERG agrees that this finding lends credibility to the selection of an AUC partitioned survival model with three health states for evaluation of brigatinib.

In addition to the search for studies, the company summarised key issues raised in the appraisal of ceritinib in NICE TA395 at committee stage (CS p94 Table 31). These were available in the public domain. They outlined how the present submission addresses these issues of previous appraisals. (76) (76) (76) (77) (77) (77) (77)

5.1.5 Conclusions

ERG opinion:

- The company's search objective, strategy and inclusion and exclusion criteria aligned with the parameters of the scope of this appraisal.
- The systematic review of cost-effectiveness studies follows general systematic review guidelines and appears to be well-conducted. Quality assessment results and summary details of one included cost-effectiveness study are not reported.
- No economic studies were identified which evaluate the cost-effectiveness of brigatinib; but there exists sizable evidence to inform appropriate methods; and one fully published HTA is directly applicable to the ceritinib strategy in terms of indication, population, and setting: allowing for a well-informed approach to key assumptions.
- Existing economic evidence for the cost-effectiveness of ceritinib versus other comparators was identified in the economic search.

5.2 Summary and critique of companies submitted economic evaluation by the ERG

5.2.1 NICE reference case checklist

The conformity of the company's economic evaluation to the NICE reference case can addressed in Table 29.

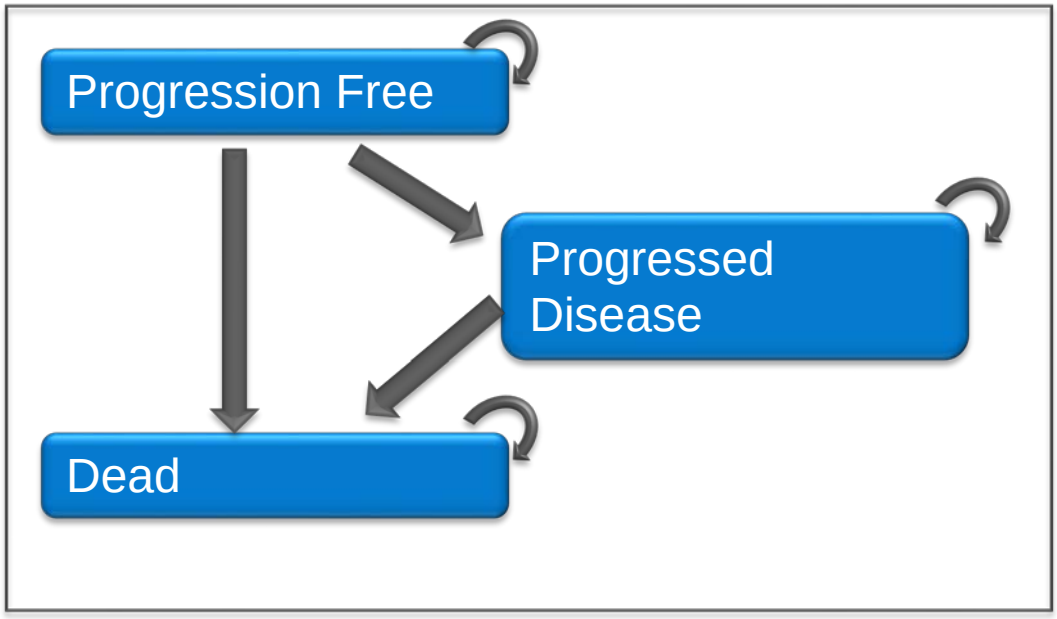
Table 29 NICE reference case checklist

NICE Reference Case Requirements	Comments	Issues arising
Defining the decision problem	The decision problem is defined as an evaluation of the clinical and cost-effectiveness of brigatinib for the treatment of anaplastic lymphoma kinase positive (ALK+) advanced non-small cell lung cancer (NSCLC) after crizotinib. This is consistent with the decision problem outlined in the NICE scope for this appraisal.	The comparator, ceritinib, has not been referred to within the statement of the decision problem (see section 5.1.4 of the NICE Reference Case Requirements).
Comparator(s)	As per NICE scope, ceritinib is used as the comparator for the clinical and cost-effectiveness evaluation of brigatinib.	
Perspective on outcomes	All relevant health outcomes are captured in this submission.	
Perspective on costs	Perspective largely focuses on NHS burden with limited emphasis placed on the perspective of Personal and Social Services. Social care costs associated with ALK+ NSCLC are relatively minor in comparison to NHS costs. Additionally social care resource use are likely to be similar for brigatinib and ceritinib and are therefore unlikely to have a major impact on ICER.	
Type of economic evaluation	The company presents a cost-utility analysis, results of this analysis are reported as ICERs in cost per QALY gained.	
Time horizon	A lifetime horizon is used. This is defined as 14.03 years, based on the prediction that 99% of patients in brigatinib arm would be dead at this point. This time horizon should be sufficient to capture all differences in costs and outcomes.	
Synthesis of evidence on health effects	The company conducted a systematic literature review to identify studies which evaluated brigatinib or ceritinib in the population of interest.	
Measuring and valuing health effects	The company submission uses QALYs to measure health benefits. Changes in health-related quality of life data were obtained from	

	participants in the ALTA study for the progression free period; and from the literature for the post-progression period.	
Source of data for measurement of health-related quality of life	HRQL data were obtained from the ALTA study as this was not reported in Study 101. This data was used to inform utility values for the pre-progression health state. Participants in this study completed the EORTC-QLQ-C30, results were converted to EQ-5D-3L utility values using a mapping algorithm published by Longworth *et al*. (2014). A systematic review was conducted to identify HRQL studies to inform the post-progression utility values. Eight studies met inclusion criteria. Chouaid *et al.* was chosen as this study used EQ5D and was chosen in a previous submission to NICE for ceritinib (TA395). A scenario analysis uses HRQL from Nafees *et al.* to estimate utility values post-progression.	Longworth *et al.* reports several methods of converting EORTC-QLQ-C30 results to EQ5D values therefore it is unclear what algorithm was used in this submission. Additionally the NICE reference case states that in cases where mapping functions are required to convert between health related quality of life measures, the decision regarding chosen algorithm should be justified and sensitivity analyses should explore alternative options. No justification was provided for the choice of function used, and no relevant scenario analyses presented.
Source of preference data for valuation of changes in health-related quality of life	EQ-5D UK tariff values were used to calculate utility values, and therefore utilities are representative of UK preferences.	
Equity considerations	Additional QALYs carried the same weight regardless of the characteristics of individual receiving health benefits.	
Evidence on resource use and costs	The submission reports that a systematic review was conducted to identify cost and resource use studies evaluating therapies for patients with ALK+ advanced or metastatic NSCLC, from a UK perspective. The company reports that eight studies were identified, however none of these studies reported treatment-specific or health state-specific resource use for this population. Consequently rate of resource use data was obtained from interviews with five UK clinicians. Costs were obtained from British National Formulary, eMIT, Personal Social Services Research Unit (PSSRU) or NHS Reference Costs. Therefore costs and resource use should be representative of UK practice.	
Discounting	Annual 3.5% discount applied to costs and QALYs.	
NICE, National Institute for Health and Care Excellence; NHS, National Health Service; PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.		

5.2.2 Model structure

Figure 16 Model Structure



Text boxes represent health states and arrows represent allowable movement. All patients start progression free at time zero, and Dead is the absorbing state.

Source: Adapted from CS p98, Figure 21 (Takeda Ltd)

The company have developed a cost-effectiveness model to calculate the incremental cost per quality-adjusted life year gained from using brigatinib as opposed to ceritinib as a second line treatment for patients with ALK+ advanced NSCLC, after treatment with crizotinib. This is an 'area under the curve' partitioned survival model with three health states: pre-progression, progressed and death (Figure 16). The proportion of patients on brigatinib in each of these states has been determined by fitting distributions to the trial data for overall survival and progression-free survival. In both cases, Gompertz distributions were chosen. Survival has been capped using ONS national lifetables and extrapolated over the model lifetime, based on the year by which 99% of patients have died. For the comparator treatment, the proportion of patients in each of the three health states is determined by applying hazard ratios for overall survival and progression-free survival to the respective distributions for brigatinib. At time zero, the proportion of patients in the progression-free state is equal to one. The resource use and HRQL of patients differ between the progression-free and progressed states, and terminal care costs are incurred 3 months prior to death. Costs of treatment and concomitant medications, and costs and utility decrements associated with adverse events, are incurred whilst patients are on treatment. It is assumed that the benefit of receiving treatment continues after treatment discontinuation. The cycle

length is equal to 28 days, and costs and HRQL outcomes are discounted at a rate corresponding to 3.5% per annum.

ERG opinion:

The structure of the model is consistent with that used in numerous previous submissions for cancer, including ALK+ lung cancer. The use of a partition survival model, rather than a Markov cohort model, means that the clinical endpoints are estimated and extrapolated using time-variant parametric distributions, rather than fixed transition probabilities, and this is fine, although not justified by the company. Length of time on treatment could have been modelled independently using a parametric distribution, but this was not done for the base case.

5.2.3 Population Interventions and comparators

Modelled population

The NICE scope defines the population for this technology appraisal of brigatinib as *"patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib."(17)*

In the company submission, clinical effectiveness data for brigatinib is derived from two studies, ALTA and Study 101 (CS, p101). ALTA recruited solely adult patients with locally advanced or metastatic ALK+ NSCLC previously treated with crizotinib, whereas only a small subgroup of Study 101 patients matched this description.

Clinical efficacy data for ceritinib are obtained from two studies, ASCEND-2 and ASCEND-5. Both recruited participants with ALK+ NSCLC previously treated with crizotinib who had subsequently experienced disease progression, in these two studies participants were previously treated with platinum-based chemotherapy.

ERG opinion:

Outcomes used as inputs in the model were drawn from participants of the included trials; they match the population described in the NICE Scope.

Modelled interventions

The proposed indication of brigatinib is as a second-line monotherapy for treating patients with ALK+ advanced or metastatic NSCLC, following crizotinib therapy. This drug is administered orally and recommended dosing regime is a 90mg dose once daily for a 7 day lead-in period, followed by a 180mg dose once daily. Brigatinib therapy should be continued as long as clinical benefit is observed.

In the ALTA trial, the received dosage in only one of the study arms was consistent with the proposed dosing regimen. Patients randomised to Arm B received a 180mg dose once daily, preceded by a 90mg dose once daily during a 7-day lead-in period. Patients randomised to Arm A received only a 90mg dose once daily throughout the duration of the study, so were not included.

Study 101 assessed three regimens: 90mg once daily, 180mg once daily and 180mg preceded by 90mg during a 7-day lead-in phase. In this study the subgroup of participants who matched the population defined by NICE scope totalled 71 participants, of whom 25 were assigned to the relevant dosing regimen.

For both ALTA and Study 101, the company submission considered only clinical efficacy evidence from participants that matched the population outlined in the NICE scope who received a dose consistent with proposed dosing regimen.

In respect to duration of therapy, the base-case assumes that brigatinib treatment is continued until progression, plus another 1.53 months. This is based on the difference in median ToT and median PFS observed in the ALTA trial, and explained by clinical feedback provided to the company stating that about six weeks is a standard period of follow-up post progression to treatment discontinuation at clinic (CS p100)

Comparators

Consistent with current clinical practice and in-line with the NICE scope, ceritinib is the comparator in this evaluation. Ceritinib is also a tyrosine kinase inhibitor which targets proteins associated with ALK-positive disease. It is administered orally and the recommended dose is 750mg once daily, however due to adverse events commonly experienced by patients the dose is frequently reduced, with the aim of increasing tolerability (ERG clinical advisors). Ceritinib therapy should be continued as long as clinical benefit is observed.

Clinical effectiveness evidence for ceritinib was obtained from two trials, ASCEND-2 and ASCEND-5 (CS, p101). In ASCEND-2 all patients received a 750mg dose of ceritinib once daily. Half of the participants enrolled in ASCEND-5 were randomised to receive 750mg of ceritinib once daily. All clinical efficacy data from ASCEND-2 and ASCEND-5 presented in the submission are based on dose regimens consistent with marketing authorisation and current clinical guidelines.

As was assumed for brigatinib there is the same period of 1.53 months post-progression for which ceritinib therapy is continued in the base case model. However, the model allows for the exploration of 14 other scenarios to explore the impact of various other ways of calculating time on treatment. Four are reported in addition to the base case:

1. Extrapolated ToT curves (capped by OS) for brigatinib with application of the PFS hazard ratio applied for ceritinib relative to brigatinib to the brigatinib ToT data for ceritinib (in absence of relative efficacy data for ToT)
2. Extrapolated ToT curves (capped by OS **and PFS**) for brigatinib with application of the PFS hazard ratio applied for ceritinib relative to brigatinib to the brigatinib ToT data for ceritinib (in absence of relative efficacy data for ToT)
3. Extrapolated ToT curves (capped by OS) for brigatinib and equal ToT assumed for ceritinib (capped by OS)
4. Extrapolated ToT curves (capped by OS **and PFS**) for brigatinib and equal ToT assumed for ceritinib (capped by OS and PFS).

ERG opinion:

The modelled population, intervention and comparators all match the NICE scope. The method used in the base case to estimate time on treatment uses PFS as a proxy rather than directly observed data, which is not generally preferable.

5.2.4 Perspective, time horizon and discounting

The company submission includes all pre-specified health-benefits relevant to patients. The base-case model uses a lifetime horizon which equates to 14.03 years, based on the prediction that 99% of patients in the brigatinib arm would have died by this point, and therefore simulates the disease long enough to capture the differences between strategies in costs and benefits. These are discounted using an annual rate of 3.5%.

Costs and resource use are focussed on those relevant to the perspective of the NHS, with fewer resources included that are relevant to the PSS perspective. The NICE reference case states that economic evaluations should consider costs and resource use from the perspective of Personal and Social Services, however in this case the balance may be reflective of the acute nature of the condition. The resource use and cost burden associated with lung cancer are predominantly placed on the NHS, and social care costs are relatively minor in comparison. End-of-life costs will be incurred by almost the same proportion of patients over the model horizon but because of the OS superiority of brigatinib they will be accrued at later in the brigatinib strategy. Consequently, end-of-life costs for brigatinib will be subject to more discounting than ceritinib and this would likely result in a minor reduction in social care costs for brigatinib although this difference is unlikely to have any major effect on the ICER.

ERG opinion:

- Perspective, time horizon and discounting are consistent with NICE reference case preferences.

5.2.5 Treatment effect

In the absence of head-to-head data, the company used unanchored indirect treatment comparisons (ITCs) for progression-free survival (PFS) and overall survival (OS). Overall response rate (ORR) in was used to inform the utility of the pre-progression health state. RCT data would have enabled an anchored and more reliable treatment comparison but none exist. As reported in section 4 the included trials were ALTA and Study 101 for brigatinib, and ASCEND-2 and ASCEND-5 for ceritinib. All four trials were used to generate the base case estimates of OS, but ASCEND-5 was not included in the estimation of PFS in the base case.

Matching-adjusted indirect comparison (MAIC) was used to reduce bias and improve comparability between trials.(51) The technique removes imbalances in those patient baseline characteristics by re-weighting the impact of those prognostic factors and treatment-effect modifiers that influence the selected outcome. See section 4.4 for a critique of the company's MAICs. An ITC of the population adjusted outcomes produced hazard ratios for PFS and OS which were applied to the baseline extrapolations of the same for brigatinib to produce the comparator survival curves.

The company selected Investigator (INV) reported results across the trials used to generate extrapolated outcomes, in preference to those of the Independent review committee (IRC). This dictated which trials could be used to inform the PFS estimates (OS/death does not require independent review). ALTA and ASCEND-2 reported both INV and IRC results; Study 101 only reported INV results; and ASCEND-5 only reported IRC results. Generally the preference is for IRC results for model inclusion since these are considered less open to local bias. However, in order that the PFS outcomes could be included for the subgroup of 25 patients in Study 101 the company opted for the INV results from ALTA and ASCEND-2 to match that available for Study 101. A comparison of the ALTA INV and IRC datasets showed inferior median PFS (15.6 months versus 16.7 months), and no difference in detection of overall response (56.4% both datasets). However, the inclusion of Study 101 is at the expense of the inclusion of the larger and better quality ASCEND-5 trial, and the preferred IRC selection, so the ERG reject the approach taken in the company model base case.

5.2.5.1 Synthesis of OS estimates

The two MAIC adjusted Kaplan-Meier curves of OS were produced for the pooled ALTA/Study 101 brigatinib patient group; one for the adjustment to ASCEND-2; and one for the adjustment to ASCEND-5 (*ERG opinion:*

- MAIC has a small impact on the relative OS treatment effect (1% decrease in the ICER).

Figure 17). The company conducted MAIC population adjustments using two alternative sets of prognostic factors and treatment effect modifiers, due to the differences between baseline patient characteristics of brigatinib and ceritinib trials (See Section 4.4). The base case used the full set. As expected both the unadjusted and adjusted pooled brigatinib curves showed superior survival versus ceritinib. The company scenario analysis for the OS HR that used the meta-analysis of unadjusted pooled brigatinib outcomes (naïve analysis), produced a higher hazard ratio (brigatinib versus ceritinib) compared to the meta-analysis for the base case ITC, which used a full MAIC (HR of 0.48 for naïve versus 0.40 with MAIC). This indicates that the MAIC adjustment to OS on brigatinib increase the relative treatment effect on survival (this can be seen in *ERG opinion:*

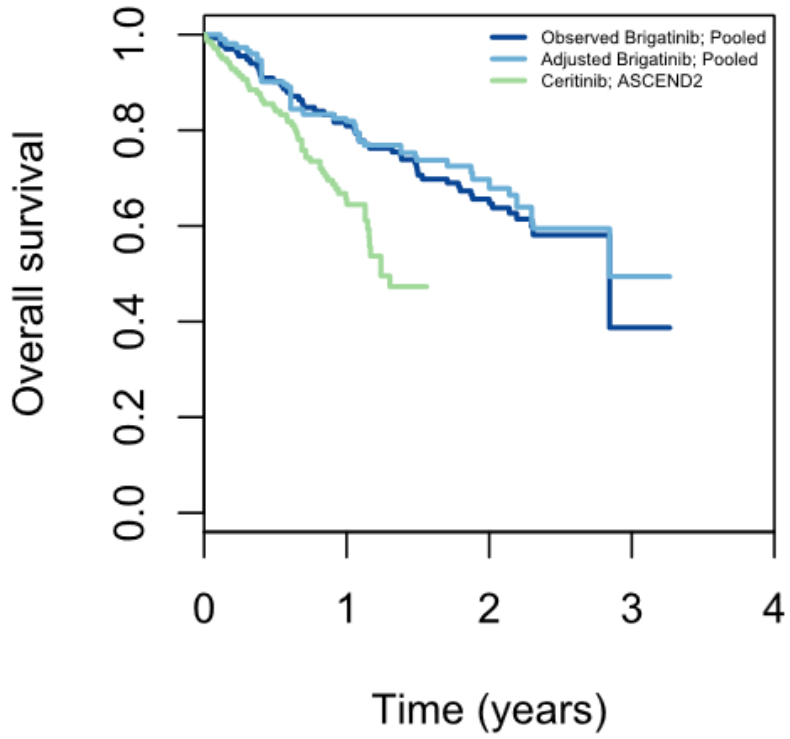
- MAIC has a small impact on the relative OS treatment effect (1% decrease in the ICER).

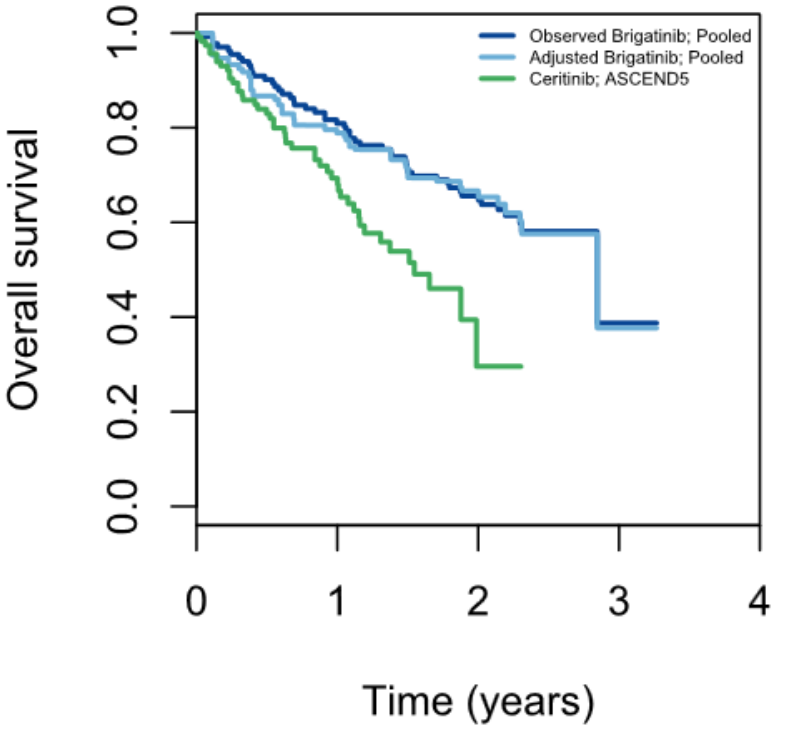
Figure 17 as the difference in the area under the light blue and dark blue plots). See section 4.4.2 for detail of the concerns with the MIAC method, and CS p109 Table 38 for full details of ITC scenario analyses.

ERG opinion:

- MAIC has a small impact on the relative OS treatment effect (1% decrease in the ICER).

Figure 17 Observed and MAIC Kaplan-Meier curves of overall survival based on pooled ALTA/Study 101 and reconstructed ASCEND-2 and ASCEND-5





Abbreviations: MAIC, matching-adjusted indirect comparison; OS, overall survival

Source: CS Addendum page 3 (Takeda Ltd).

5.2.5.2 Synthesis of PFS estimates

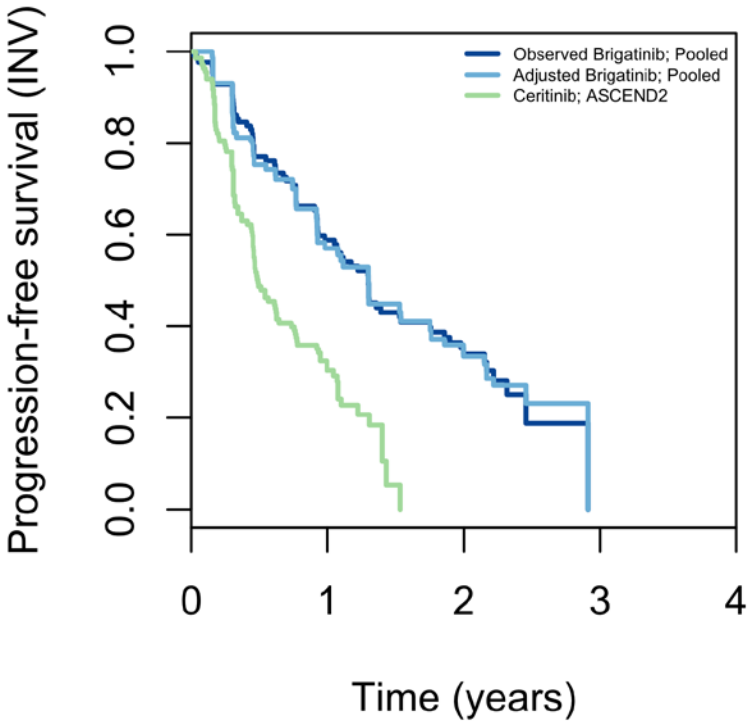
As stated above the ITC used to produce the hazard ratio determining the comparator PFS from the baseline (brigatinib) strategy did not use all the available trial information: whilst Study 101 (n=25) was included, ASCEND-5 was not (n=115). This was an unreasonable approach, because ASCEND-5 is a larger and more reliable study than Study 101.

An adjusted KM curve was constructed and is presented below alongside the ASCEND-2 plot and the unadjusted pooled brigatinib plot (Figure 18). This MAIC shows little change in PFS between observed results and adjusted estimates. Indeed, the company scenario analysis of PFS HR, which drew on the ITC of unadjusted pooled brigatinib outcomes (naïve analysis) versus ASCEND-2, produced only a slightly higher hazard ratio (brigatinib versus ceritinib) compared to base case ITC using MAIC adjustment (HR of 0.38 for naïve versus 0.39 with MAIC). This confirms that the MAIC adjustment to OS on brigatinib improved this outcome only slightly (as can be seen in Figure 18 – the light blue and dark blue plots are near overlapping). Any extension of the progression-free period is associated with increased life-time utility, but it is also associated with a comparatively longer period of expense on treatment.

ERG opinion:

- MAIC has little impact on the relative PFS treatment effect (<1% impact on the ICER).

Figure 18 Observed and MAIC Kaplan-Meier curves for PFS (INV-assessed) based on pooled ALTA/Study 101 and reconstructed ASCEND-2



Abbreviations: INV, investigator; MAIC, matching-adjusted indirect comparison

Source: Company submission, Addendum p6 (Takeda Ltd).

5.2.6 Extrapolation of PFS and OS

The underlying trials have short follow-up periods, which makes the extrapolation periods relatively long. Extrapolation under these conditions attracts significant uncertainty to the ICER, particularly the extrapolation of OS.

5.2.6.1 Long-term OS

Parametric extrapolation was applied to the unadjusted pooled brigatinib KM OS plot to estimate long-term survival. Since the company's model base case time horizon was 14.03 years – the point at which 99% of patients were predicted to have died in the brigatinib arm – it was necessary to extrapolate OS reported in the trial follow-up period through to at least this time interval. Brigatinib was the baseline strategy so the length of extrapolation was 12 years (14.03 years minus 24.3 months follow-up in ALTA), representing 86% of the time horizon. By the end of follow-up 40/110 (36.4%) of patients in Arm B ALTA had died, and 11/25 (44%) patients in the Study 101 sub-group had died.

A set of seven parametric distributions (exponential, Weibull, Gompertz, gamma, log-normal, log-logistic and generalized gamma) were fitted to the pooled plot for each clinical outcome (OS and PFS INV), in line with the NICE Decision Support Unit (DSU) guidance.(77)

Goodness-of-fit was assessed statistically using Akaike information criterion (AIC) and Bayesian information criterion (BIC) (Table 30), then the clinical plausibility of resultant long-term estimates was tested using a panel of five clinicians (Table 31). Estimates of proportion alive at 3, 5, 10 and 20 years following treatment with brigatinib gave clinical context to the selection of best distribution, considering both statistical and clinical information. The Gompertz distribution was selected for the base case, being one of the best fits statistically and providing the closest estimates of long-term survival to the clinical panel average. The company's scenario analyses show this to be a conservative selection, providing the highest ICER of the tested distributions. This selection was also in contrast to the choice of Weibull for ceritinib in the technology appraisal in the same population and treatment line.(26) However, there is no available evidence to strongly support the use of an alternative choice. Selection of the Weibull instead of the Gompertz decreases the ICER by 11.8%, but clinician estimates from the company indicate that this would overestimate the proportion of patients alive at 10 years.

ERG opinion:

- The accuracy of the extrapolation of OS is very uncertain. Observation periods of trials are short, and the ability of clinicians to accurately forecast survival with a new treatment at second-line of advanced disease at 20 or even ten years is tenuous. Conclusions made on results based on a time-horizon of 14.03 years (the base case) should be treated with caution.

Table 30 Goodness-of-fit statistics for overall survival (OS), pooled brigatinib data

Model	AIC	BIC
Generalised gamma	666.23	674.94
Gamma	664.23	670.04
Log normal	667.52	673.33
Log logistic	664.37	670.18
Weibull	664.24	670.05
Gompertz	664.34	670.15
Exponential	662.43	665.34

Abbreviations: AIC, Akaike information criterion; BIC, Bayes information criterion

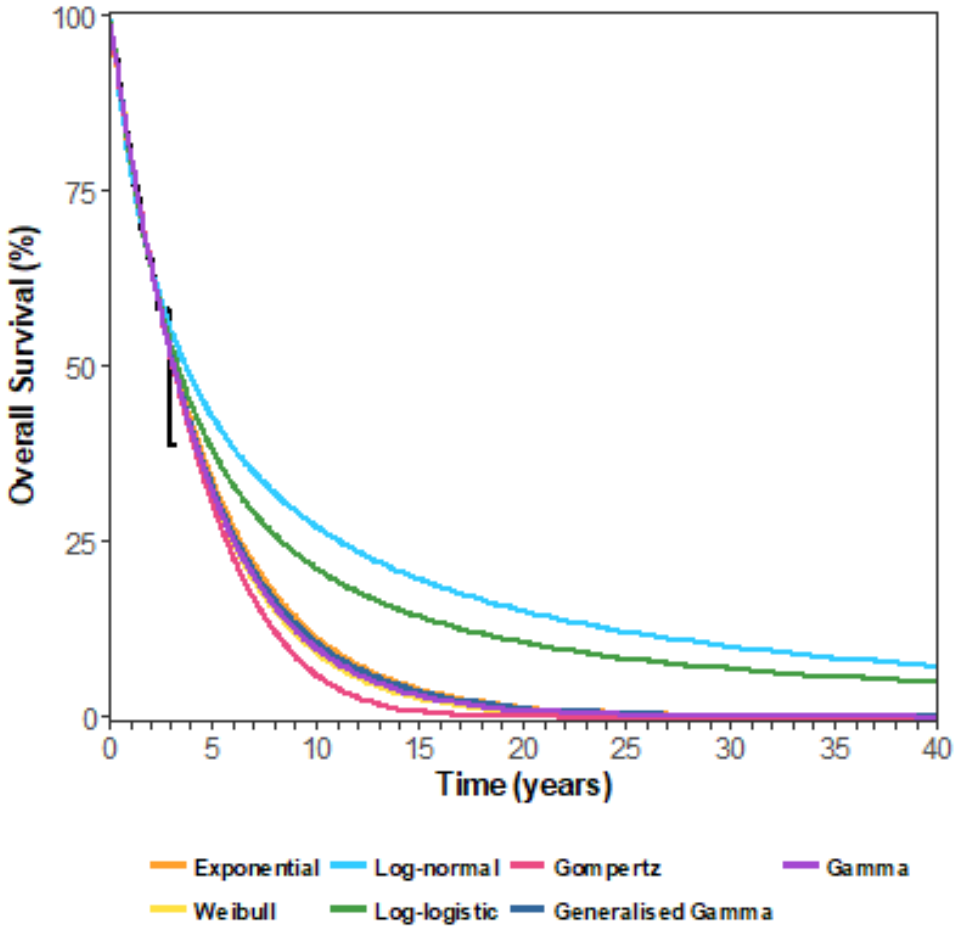
Source: CS Addendum, Table 2 (Update of original Table 33), (Takeda Ltd)

Table 31 Extrapolated long-term survival rates for brigatinib compared to clinician estimates, pooled data

	3-years	5-years	10-years	20-years
Extrapolated outcomes				
Generalised gamma	51.46%	32.64%	10.61%	1.19%
Gamma	51.29%	32.03%	9.68%	0.86%
Log-normal	55.14%	42.69%	27.10%	15.03%
Log-logistic	52.82%	37.89%	21.12%	10.51%
Weibull	51.20%	31.67%	9.12%	0.68%
Gompertz	51.05%	30.24%	5.90%	0.03%
Exponential	52.01%	33.63%	11.31%	1.28%
Clinician outcomes				
Clinician 1	50.00%	20.00%	<5%	<5%
Clinician 2	40.00%	20.00%	<5%	0.00%
Clinician 3	65.00%	50.00%	5.00%	0.00%
Clinician 4	60.00%	35.00%	7.50%	0.00%
Clinician 5	35.00%	17.50%	5.00%	0.00%
Average	50.00%	28.50%	5.83%	0.00%

Source: CS Addendum, Table 3 (Update of original Table 34), (Takeda Ltd)

Figure 19 Kaplan-Meier curve and fitted parametric distributions for OS, pooled data using the September 2017 data-cut from the ALTA trial



Abbreviations: OS, Overall survival. Note. Base case Gompertz in pink; lowest curve.

Source: CS Addendum, p12, Figure 9 (update of original Figure 23) (Takeda Ltd)

5.2.6.2 Long-term PFS

Parametric extrapolation was also applied to the unadjusted pooled brigatinib KM plot of PFS to estimate long-term progression. Whilst extrapolation of PFS extends to the same time horizon as OS (14.03 years), the proportion of patients who progress is higher than those who die so the effective period of extrapolation is shorter. Sixty-four/110 (58.2%) patients had progressed during follow-up in ALTA Arm B, and 14/25 (56%) in the Study101 sub-group.

The company's approach to the selection of parametric distribution for the extrapolation of the brigatinib follow-up period (baseline strategy) differed to the OS method. The company presented goodness-of-fit statistical test evidence only (Table 32), but the justification for the selection of the Gompertz distribution (of moderate statistical fit) was the desire to use the same distribution as OS, and thereby avoid implausible clinical scenarios. Such as the

avoidance of PFS and OS curve overlap: when there are more patients alive-and-progressed than there are alive. The ERG reject the rationale that the same functional form should be selected for one based on the other; and that clinical implausibility is not possible with paired selections. Clinical plausibility testing of PFS was not reported by the company, however the model has a safeguard whereby PFS cannot exceed OS whatever distributions are chosen.

Table 32 Goodness-of-fit statistics for progression-free survival (PFS) investigator assessed (INV), pooled data

Model	AIC	BIC
Generalised gamma	871.89	880.60
Gamma	869.91	875.72
Log normal	878.22	884.03
Log logistic	871.87	877.68
Weibull	869.90	875.72
Gompertz	870.57	876.38
Exponential	870.54	873.45

Abbreviations: AIC, Akaike information criterion; BIC, Bayes information criterion

Source: CS Addendum, Table 5 (update of original Table 36), (Takeda Ltd)

The statistical fit of the Gompertz is reasonable but was not the optimal statistical choice (4th for PFS INV, after exponential, Weibull, and gamma), and scenario analysis performed by the company shows that the Gompertz distribution is the least conservative of the seven with respect to the ICER. The next least conservative choice, Weibull, adds 5.8% to the ICER; and log-normal adds 48.2% to the ICER.

If PFS curve selection is considered in isolation then this selection favours the brigatinib strategy, however the base case PFS selection alongside Gompertz for OS together may be more conservative: when compared to Weibull/Weibull for example the ICER is changes from the base case £54,311 to £52,677 (ERG analysis). However, there is an indirect consequence of the conservative selection of Gompertz for OS: the Gompertz distribution has a thin ‘tail’ compared to Weibull or Gamma, used in the company base case it produces a low estimate for ceritinib OS. This has a favourable knock-on effect for the consideration of brigatinib as an end-of-life treatment.

ERG opinion:

- The selection of Gompertz for PFS extrapolation is not justified. This selection may seem acceptable in the light of the conservative selection of Gompertz for OS, but it has a secondary effect: it produces an estimate of OS for ceritinib which is closest to the life-expectancy criterion for end-of-life designation (24 months).

5.2.6.3 Comparison of long-term treatment effect

Hazard ratios for PFS and OS produced by the ITC analysis were applied directly to the extrapolated unadjusted brigatinib survival curves. The inherent assumption is that of proportional hazards, which should be tested for each outcome separately. The company tested the assumption of proportional hazards for unadjusted comparisons only, so the ERG tested the adjusted comparisons in an additional analysis. We found that the PH assumption held reasonably well for both outcomes, according to visual inspection. Plots of log - cumulative hazard versus log time, presented in Table 33, Table 34 and Table 35 show the curves for brigatinib and ceritinib are reasonably parallel in each case, as required by the proportional hazards assumption.

Table 33 PH test of PFS HR ceritinib versus ASCEND-2 adjusted brigatinib

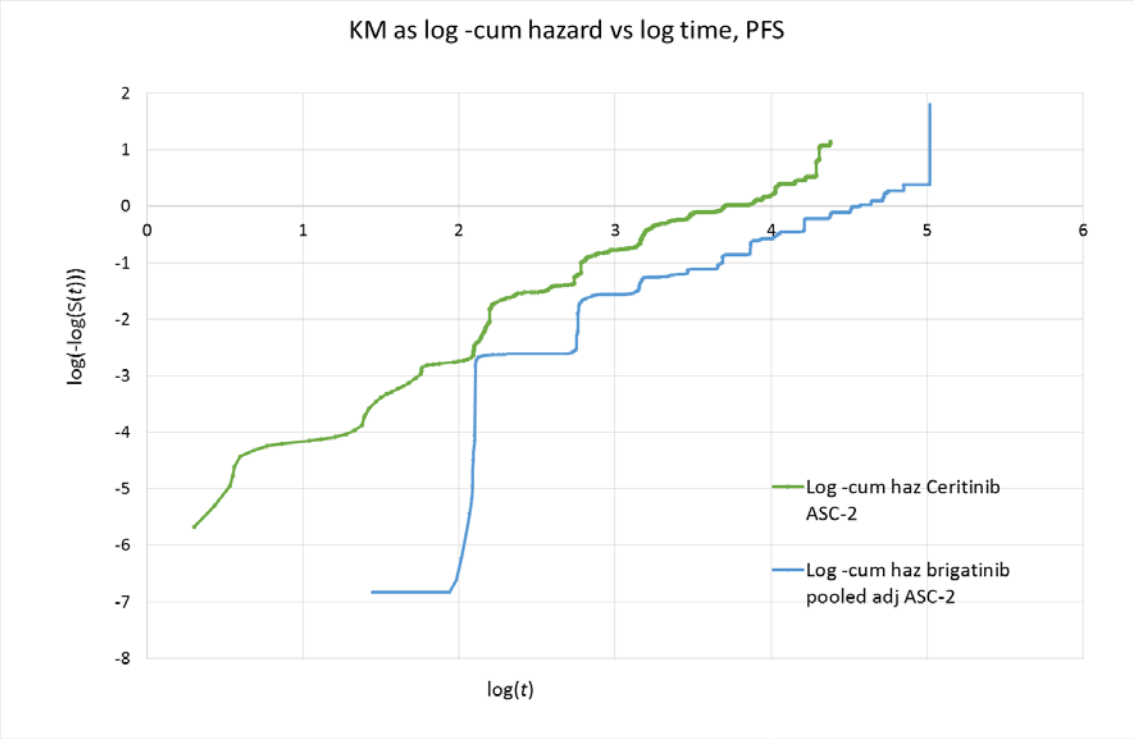


Table 34 PH test of OS HR ceritinib versus ASCEND-2 adjusted brigatinib

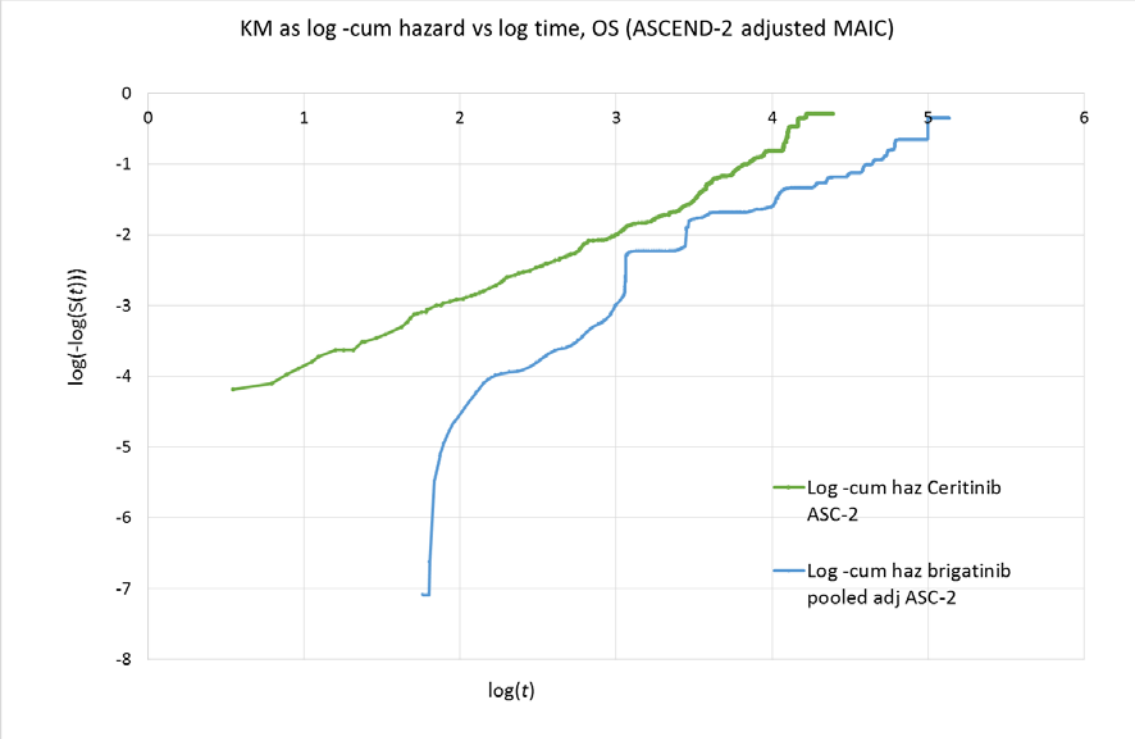
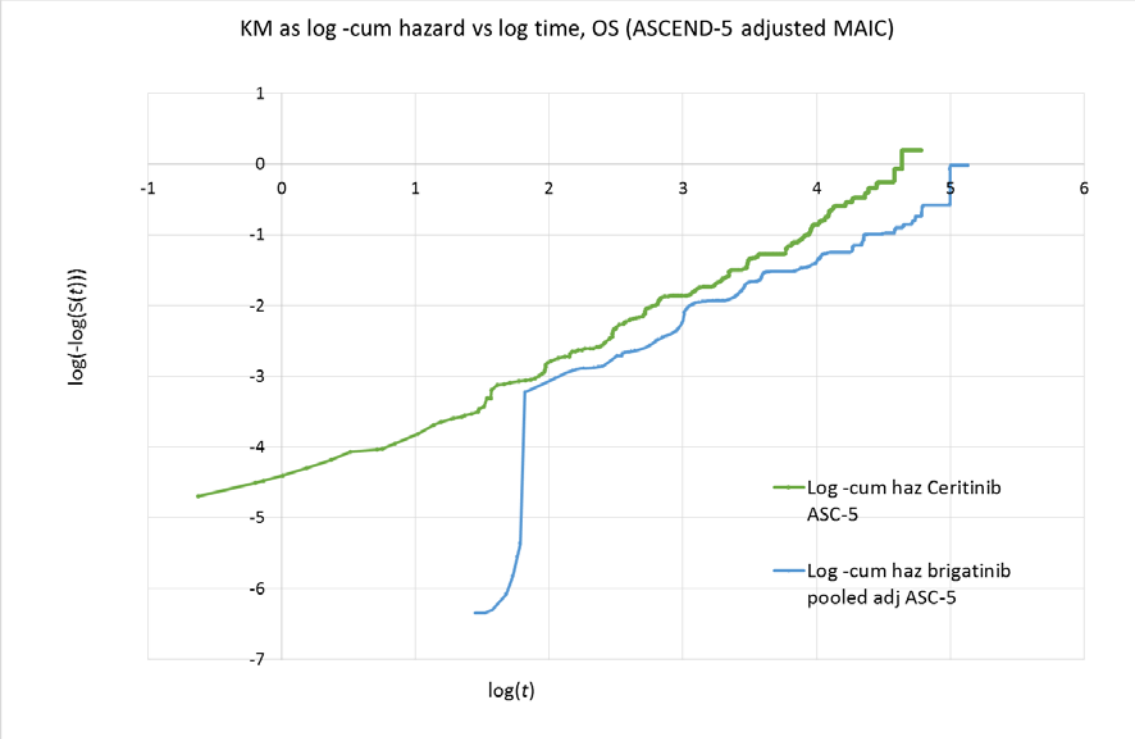


Table 35 PH test of OS HR ceritinib versus ASCEND-5 adjusted brigatinib



5.2.6.4 Continuation of benefit beyond progression

The ERG consider it plausible that the benefit of brigatinib gained over ceritinib during trial observation is carried through the model's lifetime horizon. However, we also consider it the most beneficial in terms of the cost-effectiveness of brigatinib. The NICE committee considering ceritinib in TA395 received expert clinical opinion that benefits of ceritinib treatment were unlikely to persist beyond the end of treatment.(78) The scenarios testing ceritinib in that case showed that reductions in the duration of benefit from full time horizon to 18 and 24 months had 'little impact' on the ICER. In this case, the company conducted scenario analyses of reduced treatment benefit which showed that the ICER increases appreciably (Table 36). Similarly, if the time horizon is reduced the ICER again increases (in these scenarios all costs and benefits yond the selected time horizon are eliminated).

ERG opinion:

- The ERG adopt the assumption that treatment benefits for both drugs extend beyond the end of treatment, although there is limited evidence for a strong position either way, other than expert clinical opinion, which the ERG found to be mixed.

Table 36 Results of company scenario analyses

Scenario	*Incremental Costs*	*Incremental QALYs*	*ICER*	*Difference from base case ICER*
Long-term treatment effect				
OS – Gompertz distribution				
Treatment benefit discontinues at 2-years	£38,200	0.3623	£105,434	94.13%
Treatment benefit discontinues at 3-years	£49,885	0.5469	£91,210	67.94%
Treatment benefit discontinues at 4-years	£55,439	0.6993	£79,282	45.98%
Treatment benefit discontinues at 5-years	£57,862	0.8199	£70,573	29.94%
Treatment benefit discontinues at 10-years	£60,809	1.0899	£55,793	2.73%
Time horizon				
5-year time horizon	£54,895	0.7593	£72,300	33.12%
10-year time horizon	£60,310	1.0791	£55,887	2.90%

Source: Extracted from CS, addendum, p32, Table 16 (Takeda Ltd)

5.2.6.5 Background mortality

People with ALK+ NSCLC may die of other causes, and these are included in the observed trial period. However, when OS is extrapolated the increase with age in the probability of death from other causes is not well accounted for. Extrapolating over long periods from short follow-up – as is the case here - attracts further uncertainty in long-term OS estimates. The base case makes no specific adjustment for background mortality, so the ICER may be underestimated, because treatments with superior survival benefit maintain life longer so that patients are more exposed to the risk of death from other causes.

ERG opinion:

The company have not adjusted for background mortality, and this may lead to an underestimation of the ICER. The company do not explain this omission.

5.2.7 Health related quality of life

Participants in the ALTA trial completed the EORTC-QLQ-C30 measure of health related quality of life on the first day of every treatment cycle. No data regarding participant quality of life were reported for participants in Study 101. A mapping algorithm published by Longworth *et al.* was used to convert EORTC-QLQ-C30 responses to EQ5D values.(79) UK tariffs were then used to convert scores to utility values, before an HRQL analysis was conducted to derive health state values (Table 37).

Table 37 Mapped utility values (relevant to pre-progression)

	Number of patients	Number of records	Mean (SD)	Range	Median [Q1-Q3]
Overall EQ-5D score (across a maximum of 35 cycles)	103	1712	0.755 (0.190)	[-0.297, 0.959]	0.783 [0.732, 0.896]
Baseline EQ-5D score	103	103	0.712 (0.219)	[-0.246, 0.951]	0.764 [0.652, 0.861]
Abbreviations: Q1, lower quartile; Q3, upper quartile; SD, standard deviation.					

Source: CS p116, Table 42 (Takeda Ltd)

The company conducted HRQL analyses to investigate the impact of response to treatment on HRQoL. The company designed four models, each defined according to a different combination of response granularity and response attainment in ALTA. Response level granularity was either low at two levels, or high at four levels. The two level approach comprised progression free response, or progressed 'response'. The four state category set disaggregated the progression-free state into complete, partial or stable response. Response attainment was either Standard (ORR at the time of EORTC survey), or Best (best ORR recorded for the patient over the entire follow-up period). The company base case implemented the analysis using the Standard 2-level model (model 2), in so doing defining pre-progression utility by ORR.

The company then conducted a linear mixed effects regression analysis to assess the impact on these utility values of several factors potentially prognostic on HRQL. Thirteen variables identified as potentially impacting HRQL were included in the company's analysis. When evaluating ORR (including the 2 category model used for the base case), ECOG PS

of 2 showed a reduction in HRQL versus a status of 0-1. Experience of at least one grade 3/4 adverse event, increase in age, male gender, presence of brain metastases, receipt of prior chemotherapy, and an increase in the time since receipt of prior crizotinib therapy all showed a trend of negatively impacting HRQL.

The company applied these adjustment value obtained using the Standard 2-level model, above, in order that the utility in the first cycle pre-progression represents a 'standard' patient, with the average characteristics observed in ALTA at baseline. For each covariate a corresponding utility increment or decrement was calculated and incorporated to produce a mean state utility of 0.744, giving a starting utility of 0.903, with decrements for aging were applied through the time in the state. A decrement for experiencing a serious adverse event (whilst on treatment only) was multiplied by the per-cycle probability of an event occurring, and by the weighted number of cycles events were observed in ALTA to endure. Table 38 presents mean baseline utilities in the model for the 'average' patient, and the estimates for ageing per cycle and occurrence of a serious adverse event.

The company used evidence from a systematic literature review (CS Appendix H) to inform progressed disease utility since ALTA effectively only followed patients to progression. Of the 16 studies included in the review two were chosen to for inclusion in the economic model. Chouaid *et al.* was used to inform utility values for the progressed disease health state in the base case, while Nafees *et al.* was used in scenario analyses.(80, 81). Both are studies of people with NSCLC, not specifically ALK+ NSCLC. The company rationalised the choice of Chouaid *et al.* on the basis that this study directly measured using EQ-5D, and was chosen to inform the same parameter in TA395. The utility decrement associated with progression in this study was carried forward to estimate the progressive-disease utility in the model base case. The company applied this decrement (0.15) to the progression-free estimate (0.793) to produce the estimate for the mean post-progression utility used in the model (0.643). The equivalent decrement for progression in the Nafees study was 0.180.

Table 38 Utility values at baseline and key adjustments

Health state	Mean value	Justification
Progression free (whether on brigatinib or ceritinib)	0.793*	To capture the relevant population to this submission, utility values based on mapped patient reported values from the ALTA clinical trial were used for progression-free.
Progressed disease (whether on brigatinib or ceritinib)	0.643*	Utility based on the progressed disease decrement published in Chouaid *et al*. (2013) (-0.15). This is in line with the NICE Methods Guide 2013 and the NICE submission for ceritinib [TA395]. Limited data associated with progressed disease from ALTA study. The data that are available reflects patients whose disease had progressed recently.
Age	-0.002	To capture the HRQL impact associated with increasing age. For every year increase in age utility will decrease by -0.0017 in the progression-free and the progressed disease health states
Adverse events	-0.0678	To capture the HRQL impact associated with grade 3/4 adverse events
Abbreviations: HRQL, health-related quality of life *Note, this is the mean utility value calculated from the mean of covariates in the data informing the HRQL analysis. Utility will change over time in the model based on progression, age and number of grade 3/4 adverse events		

Source: CS p124, Table 47 (Takeda Ltd)

ERG opinion:

- Changes in HRQL were obtained from a relevant patient population. Utility values were calculated from preference data representative of the UK population and based on choice experiments.
- Which mapping algorithm was used to convert EORTC-QLQ-C30 to EQ-5D is unclear, the choice of algorithm was not justified, and no sensitivity analyses explored the impact of alternative mapping functions.
- The statistical derivation of utility for patients in the progression free health state (mean=0.793) (using ORR to define utility, and adjusting for the range of baseline characteristics in the source trial ALTA) appears reasonable on the basis that the

resultant estimate of the mean is reasonably consistent with other estimates used in studies identified in the utility SLR.

- The estimate of the progression increment was based on Chouaid *et al*. The result is a higher estimate of progression state mean utility (mean=0.643) than found in the two included empirical studies; Chouaid (0.46) and Nafees (0.473). This could underestimate the ICER because strategies with superior OS cumulate more QALYs compared to a scenario using a lower estimate, however these are studies of the general NSCLC population, which might be considered to have a greater morbidity burden.

5.2.8 Resources and costs

This section breaks down the costing analysis into cost of intervention (ALK+ targeted treatment) and [other] health state costs.

5.2.8.1 Intervention costs

This is disaggregated into basic pricing of intervention, dose intensity, and time on treatment.

5.2.8.1.1 Basic pricing and PAS information

The company provide the dose, unit and pricing information for brigatinib alongside that for ceritinib. This is presented below (Table 39) with the CS estimates of dose intensity included.

Table 39 Intervention costing information taken into the model

	Brigatinib	Ceritinib
Unit dose	180mg once daily with a 7-day lead-in at 90mg	750mg orally once daily
Pack size	28 tablets (oral administration)	150 capsules (oral administration)
Unit cost at list price	£4,900 for a 28-tablet pack	£4,923.45 for three packs of 50 capsules (150mg)
Dosing cycle length	28 days	30 days
Cost per 28-days – dose intensity not applied	£4,900	£4,595.22
Average dose intensity	88.90% (ALTA trial, mean)	83.59% (ASCEND 2 and 5, weighted median)

	Brigatinib	Ceritinib
Cost per 28-days – dose intensity applied	£4,356.10	£3,841.24
Treatment duration	1.53 months post-progression*	1.53 months post-progression*
Source	Takeda UK	British National Formulary (BNF) accessed February 2018
Abbreviations: BNF, British National Formulary. * This is a set period added to the median progression-free period for the specified treatment.		

Source: Adapted CS Document B, Table 48 (Takeda Ltd)

Ceritinib packs contain 150 capsules for a 30-day treatment cycle at 5 capsules per day. The company model cycles are 28-days in length, so this is accounted for in their calculation of 28-day cost. Brigatinib tablets are purchased in packs of 28 tablets, recommended as once daily. Novartis Europharm Limited, the marketing authorisation holder for ceritinib have agreed a patient access scheme (PAS) with the Department of Health. In their CS, Takeda Pharma A/S, the marketing authorisation holder for brigatinib, state their intent to agree a PAS. Details of both can be found in the separate confidential appendices 1 and 2.

5.2.8.1.2 Mean dose intensity

The company apply a reduction to the cost of brigatinib of 88.9%, commensurate with the mean dose intensity observed in ALTA. However, according to the safety and tolerability report in the CS for ALTA the mean relative dosing intensity for patients in ALTA was 98.5%; and in the ALTA CSR AP26113-13-201 (final version) the mean relative dose intensity reported for Arm B was [redacted]% (observed total dose divided by expected total dose multiplied by 100%).

ERG opinion:

- The company's estimate of brigatinib MDI, used in the model, does not tally with the estimate found in the ALTA CSR. The CSR value is preferred and used in the derivation of the ERG base case.

5.2.8.1.3 Time on treatment

The company base case assumed the mean time spent on treatment was equal to the median progression-free period (pooled data for brigatinib data; Full RE MAIC ITC HR for ceritinib) plus 1.53 months post-progression. This additional period on treatment post-progression is the difference between the observed median time on treatment (ToT) and median PFS in ALTA. This is approach is not adequately justified by the company. Use of

the progression-free period rather than the actual time on treatment period is not discussed; only the size of the post-progression constant. ToT data for brigatinib was available for use in the base case but was preferred by the company for the development of their alternative treatment costing scenarios. In these scenarios the company extrapolated from a brigatinib (ALTA) ToT KM plot using the gamma statistical distribution. To this baseline a curve for ceritinib ToT was produced by applying the PFS hazard ratio (in the absence of relative efficacy data for ceritinib). This approach is preferred by the ERG for the base case since it has the benefit of estimating ToT independently of disease status. Advice to the ERG from clinical experts supports evidence from the ALTA and ASCEND trials, that treatment is often continued beyond radiological progression provided patients continue to receive clinical benefit (the company make the case for 1.53 months for both brigatinib and ceritinib, however the median duration of exposure to ceritinib in ASCEND-2 [8.8 months] is 3.2 months longer than the median PFS [5.7 months]). In variations of this scenario analysis the company explored capping for OS and PFS, and equating ToT for ceritinib to that of brigatinib.

ERG opinion:

- The ERG reject the company's method in favour of estimating ToT directly from ToT observation in the ALTA trial.

5.2.8.2 Health State Costs

The company reports that a systematic literature review was conducted to identify studies which report costs and resource-use associated with treating ALK+ advanced or metastatic NSCLC. Eight studies met inclusion criteria, seven of which were previously identified in the economic systematic review, however the company states that none of the included studies presented resource use data for ALK+ patients. So to inform resource use inputs in the economic model specific for ALK+ services, interviews were conducted with five UK clinicians. Unit costs associated with resource use were obtained from UK databases. Primary care, pharmacy, and other medical professional costs were obtained from Personal Social Services Research Unit. The cost of administration for drugs constituting best-supportive care were guided by the BNF and all other costs were obtained from NHS reference costs. Concomitant medications used by ≥5% of patients in the ALTA trial were included in the model; their costs were derived from the eMIT database, or the BNF as second preference.

The company take the view that resource use would be broadly similar for patients treated with either ceritinib or brigatinib, both pre- and post- progression (supported by expert clinical opinion obtained by the company). Notable additional costs may be incurred for patients

treated with ceritinib due its toxicity and subsequent management of adverse events, and this is supported by expert clinical opinion gathered by the ERG. Resource use data is presented in Table 40 and Table 41. Individual clinician estimates of the frequency of resource use per cycle were averaged; the range was used in one way sensitivity analyses.

The total cost associated with the pre-progression health state was £640.17 for the first cycle and £326.27 per cycle subsequently (28-day cycles). The total cost associated with progressed disease was calculated as £513.34 per cycle, this was applied irrespective of the treatment pre-progression, and for the brief period of ALK+ targeted treatment post-progression.

ERG Opinion:

- Base case costing of brigatinib and ceritinib through the time horizon may underestimate the ICER because of the method used to estimate times on treatment, and because the MDI of brigatinib may be too low (see comments in 5.2.8.1.2 and 5.2.8.1.3).
- All other resource use and cost estimates are reasonable.

Table 40 Pre-progression resource use

	Frequency first cycle	Frequency subsequent cycles	Unit cost first cycle	Unit cost subsequent cycles	Total cost first cycle	Total cost subsequent cycles	Source
Oncology outpatient visit	2.00	1.00	£219.19	£172.67	£438.38	£172.67	NHS Reference Costs (2016/17);(82) CL. WF01B, 370, Medical Oncology Non-Admitted F2F Attendance, First. NHS Reference Costs (2016/2017); CL, WF01A, 370, Medical Oncology Non-Admitted F2F Attendance, Follow up
Pharmacist	2.00	1.00	£44.00	£44.00	£88.00	£44.00	PSSRU (2017);(83) Cost per working hour of a band 6 nurse
GP visit	0.25	0.25	£37.00	£37.00	£9.25	£9.25	PSSRU (2017); per surgery consultation lasting 9.22 minutes, including direct care staff costs with qualification costs
Cancer nurse	0.42	0.42	£82.09	£82.09	£34.48	£34.48	NHS Reference Costs (2016/2017); CHS, N10AF, specialist nursing, cancer related, adult face to face
Complete blood count	2.00	1.00	£3.06	£3.06	£6.12	£3.06	NHS Reference Costs (2016/2017); DAPS, DAPS05, Haematology
Serum chemistry	2.00	1.00	£1.13	£1.13	£2.25	£1.13	NHS Reference Costs (2016/2017); DAPS, DAPS04, Clinical Biochemistry
CT scan	0.41	0.41	£110.04	£110.04	£45.31	£45.31	NHS Reference Costs (2016/2017); Total HRGs, SUMPRODUCT of RD20A, RD20b, RD20C, RD21A, RD21B, RD21C, RD22Z, RD23Z, RD24Z, RD25Z, RD26Z and RD27Z

X-ray	0.55	0.55	£29.78	£29.78	£16.38	£16.38	NHS Reference Costs (2016/2017); DADS, Direct Access Plain Film
Total cost per cycle:					£640.17	£326.27	
Abbreviations: CHS, community health services; CL, consultant led; CT, computerized tomography; DADS, directly accessed diagnostic services; DAPS, directly accessed pathology services; F2F, face-to-face; GP, general practitioner; HRG, health related group; NHS, National Health Service							

Source: CS page 126 Table 49 (Takeda Ltd)

Table 41 Progressed disease resource use

	Dose	Frequency per cycle	Unit cost	Total cost per cycle	Source
Resource use					
Oncology outpatient visit	NA	1.13	£172.67	£195.12	NHS Reference Costs (2016/17);(82) CL. WF01B, 370, Medical Oncology Non-Admitted F2F Attendance, First. NHS Reference Costs (2016/2017); CL, WF01A, 370, Medical Oncology Non-Admitted F2F Attendance, Follow up
GP visit	NA	0.28	£37.00	£10.43	PSSRU (2017);(83) per surgery consultation lasting 9.22 minutes, including direct care staff costs with qualification costs
Cancer nurse	NA	0.66	£82.09	£54.34	NHS Reference Costs (2016/2017); CHS, N10AF, specialist nursing, cancer related, adult face to face
Complete blood count	NA	0.60	£3.06	£1.84	NHS Reference Costs (2016/2017); DAPS, DAPS05, Haematology
Serum chemistry	NA	0.60	£1.13	£0.68	NHS Reference Costs (2016/2017); DAPS, DAPS04, Clinical Biochemistry

	Dose	Frequency per cycle	Unit cost	Total cost per cycle	Source
CT scan	NA	0.21	£110.04	£23.30	NHS Reference Costs (2016/2017); Total HRGs, SUMPRODUCT of RD20A, RD20b, RD20C, RD21A, RD21B, RD21C, RD22Z, RD23Z, RD24Z, RD25Z, RD26Z and RD27Z
X-ray	NA	0.12	£29.78	£3.57	NHS Reference Costs (2016/2017); DADS, Direct Access Plain Film
Dietician	NA	0.42	£84.85	£35.64	NHS Reference Costs (2016/17); CHS, AHP, A03, Dietitian
					Subsequent therapy
Home oxygen	NA	0.12	£111.65	£12.84	NHS Home Oxygen Service (2011) uplifted from 2009/10 prices to 2016/17 prices using PSSRU (2017)
Radiotherapy	NA	0.25	£130.85	£32.71	NHS Reference Costs (2016/2017); Total Outpatient Attendances, 800, Clinical Oncology (previously radiotherapy)
Steroids (dexamethasone)	0.5mg daily	14.00	£0.75	£10.50	BNF Accessed January 2018; 0.5mg tablets, 28 pack, pack cost £21.00; https://www.medicinescomplete.com/mc/bnf/64/PHP4364-dexamethasone.htm
NSAIDs (aspirin)	75mg daily	5.88	£0.04	£0.23	BNF Accessed January 2018; 75mg tablets, 28 pack, pack cost £1.12; https://www.medicinescomplete.com/mc/bnf/current/PHP2596-aspirin.htm#PHP2596-medicinalForms
Morphine (morphine sulphate)	40-60mg daily (average 50mg)	20.44	£5.78	£118.14	BNF Accessed January 2018; morphine sulfate 50mg/50ml solution for infusion vials, vial cost £5.78; https://www.medicinescomplete.com/mc/bnf/current/PHP2740-morphine.htm#PHP2740-medicinalForms

	Dose	Frequency per cycle	Unit cost	Total cost per cycle	Source
Bisphosphonate (alendronic acid)	10mg daily	1.60	£0.06	£0.09	BNF Accessed January 2018; alendronic acid 10mg tablets, 28 pack, pack cost £1.57; https://www.medicinescomplete.com/mc/bnf/current/PHP4656-alendronic-acid.htm
Denosumab	120mg every 4 weeks	0.04	£366.00	£13.91	BNF Accessed January 2018; Prolia 60mg/ml solution for injection pre-filled syringes, 1 pre-filed disposable injection £183.00; https://www.medicinescomplete.com/mc/bnf/current/PHP4691-denosumab.htm#PHP4691-medicinalForms
			Total cost per cycle:	£513.34	
Abbreviations: BNF, British National Formulary; CHS, community health services; CL, consultant led; CT, computerized tomography; DADS, directly accessed diagnostic services; DAPS, directly accessed pathology services; F2F, face-to-face; GP, general practitioner; HRG, health related group; NHS, National Health Service					

Source: CS, p130, Table 50 (Takeda Ltd)

5.2.9 Cost effectiveness results

5.2.9.1 Deterministic model

Summary results of the company's deterministic base case analysis are presented in Table 42. Based on the September 2017 data cut the ICER for brigatinib versus ceritinib was £54,311 per QALY gained. Incremental LYs gained were 1.58, and incremental QALYs gained were 1.12. The brigatinib strategy incurred £61,097 more resource than the ceritinib strategy. Benefits are cumulated fairly evenly either side of progression (Table 43): 57.5% of incremental QALYs are gained were in the progression-free health. The cost burden for both strategies is prior to progression (91.5% pre-progression; Table 44) and is dictated by the use and cost of ALK+ targeted treatment (84.5% of total increment; Table 45).

Table 42 Base case result of primary analysis (deterministic)

Technology	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Brigatinib	119,029	3.49	2.45				
Ceritinib	57,932	1.91	1.32	61,097	1.58	1.12	54,311

Source: Reproduced form CS addendum p27, Table 14 (Takeda Ltd)
Abbreviations: LY, Life Years; QALYs, Quality Adjusted Life Year; ICER, Incremental cost-effectiveness ratio

Table 43 Summary of QALY gain by health state

Health State	LYs brigatinib	LYs ceritinib	QALY brigatinib	QALY ceritinib	Incremental QALY	% Absolute increment	Adverse events brigatinib	Adverse events ceritinib
Progression-free state	1.54	0.72	1.22	0.57	0.65	57.5%		
Progressed disease state	1.95	1.19	1.24	0.76	0.48	42.5%		
Total	3.49	1.91	2.46	1.33	1.13	100%	-0.0079	-0.0064

Source: Data extracted from the CS revised model (September 2017 data cut) (Takeda Ltd)

Table 44 Summary of costs by health state

Health State	Cost (£) brigatinib	Cost (£) ceritinib	Increment (£)	% Absolute increment
Progression-free state	£98,025	£42,093	£55,932	91.5%
Progressed disease state	£19,514	£14,246	£5,268	8.6%
End of Life	£1,490	£1,594	-£104	-0.17%
Total	£119,029	£57,932	£61,096	100%

Source: Data extracted from the CS revised model (September 2017 data cut) (Takeda Ltd)

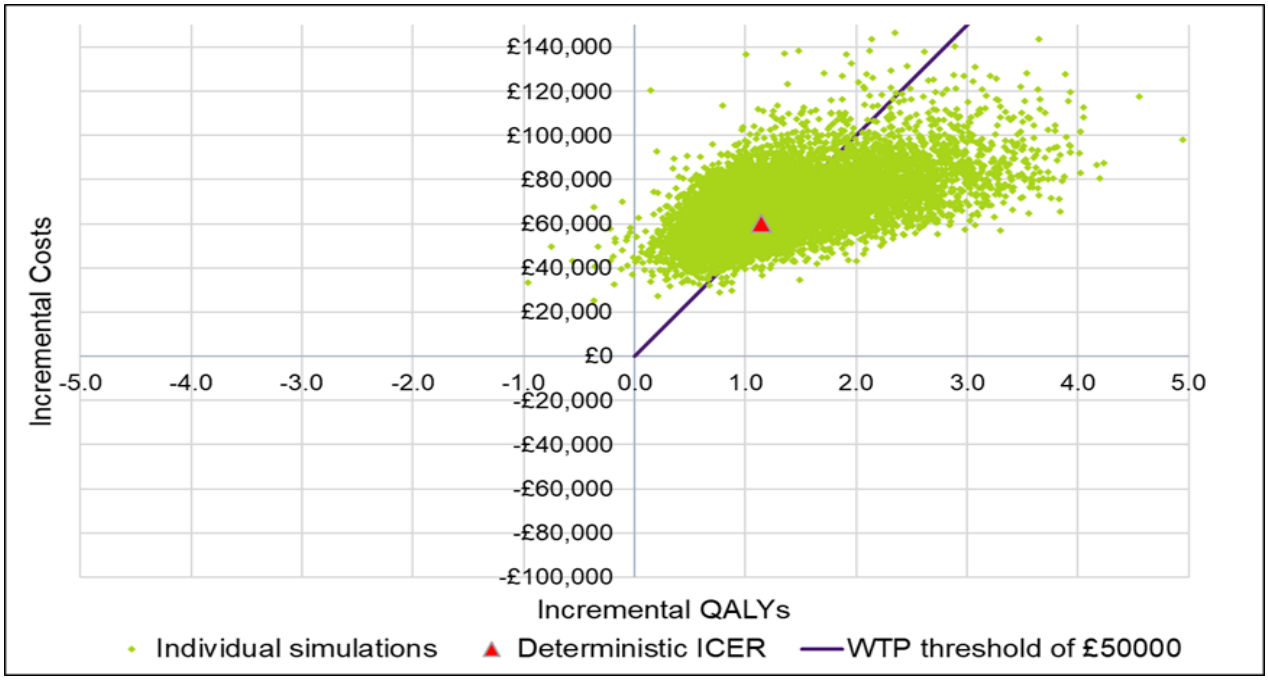
Table 45 Summary of estimated resource-use for brigatinib versus ceritinib

Resource use	Cost (£) brigatinib	Cost (£) ceritinib	Increment (£)	% Absolute increment
Progression-free state	£6,863	£3,373	£3,489	5.7%
Progressed disease state	£13,079	£7,956	£5,123	8.4%
Treatment	£93,680	£42,052	£51,628	84.5%
Concomitant medications	£1,231	£627	£604	1.0%
Terminal care	£1,490	£1,594	-£104	-0.2%
Adverse events	£2,687	£2,331	£356	0.6%
Total	£119,029	£57,932	£61,097	100%

5.2.9.2 Probabilistic model

Figure 20 displays the PSA findings on the cost-effectiveness plane; Figure 21 presents the cost effectiveness acceptability curves; and Table 46 presents the PSA summary result.

Figure 20 Probabilistic sensitivity analysis: incremental cost effectiveness plane for brigatinib versus ceritinib



Source: CS addendum p28, Figure 12 (Takeda Ltd)

Abbreviations: QALY, Quality-adjusted life year; ICER, Incremental cost-effectiveness ratio; WTP, willingness-to-pay.

Table 46 Probabilistic base case results

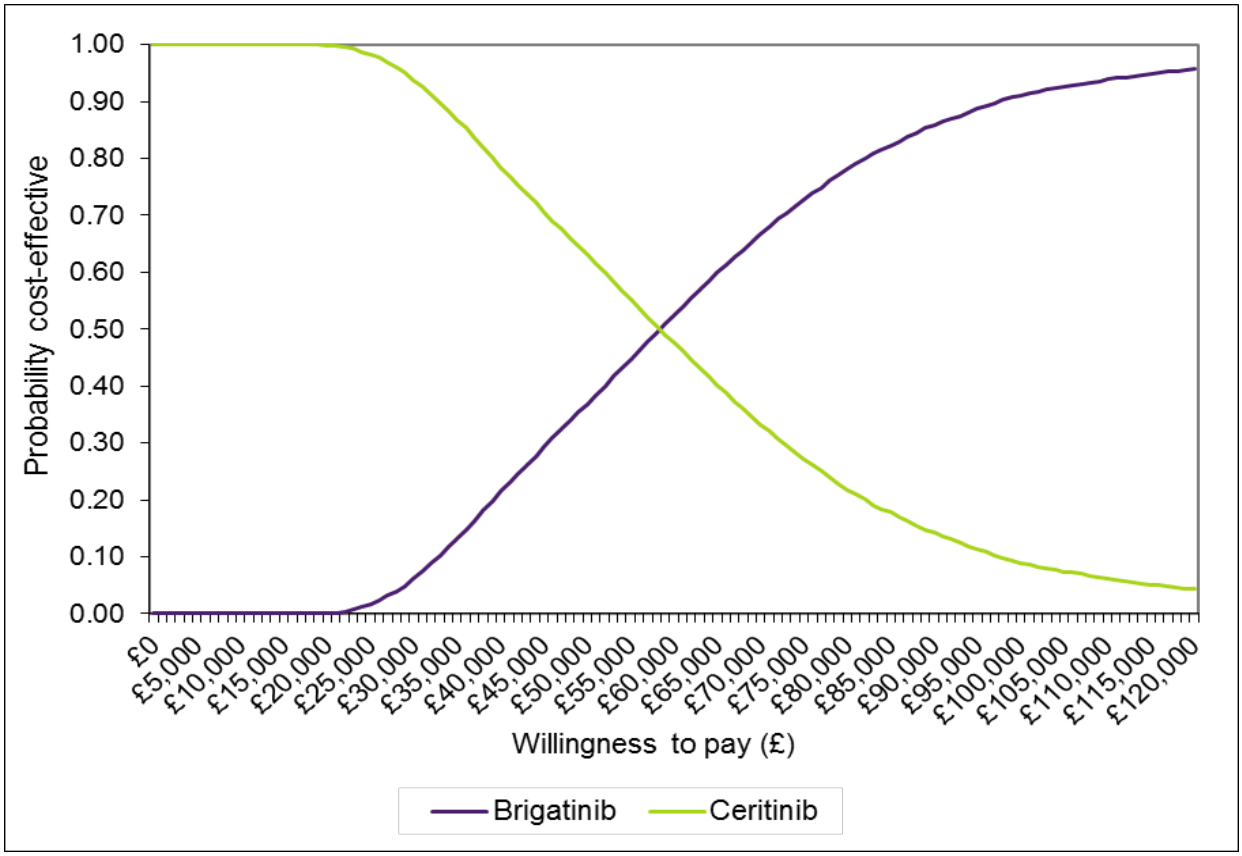
Contrast	Incremental costs (£), *mean± SD*	Incremental QALYs, *mean± SD*	ICER (£/QALY)
Brigatinib versus ceritinib	67,540± 14,270	1.30± 0.69	51,882

Source: Data extracted from the CS revised model (September 2017 data cut) (Takeda Ltd)

Abbreviations: ICER, incremental cost-effectiveness ration, QALY, Quality-adjusted life year; SD, Standard deviation.

The PSA ICER estimate is close to the deterministic base case estimate (£54,311 per QALY gained). The company do not comment on this difference, but in their PSA vary PFS and OS extrapolation distribution selection, as well as their parameters and the standard parameters, which may introduce some technical variance.

Figure 21 Cost effectiveness acceptability curve: brigatinib vs. ceritinib



Source: CS p142, Figure 27 (Takeda Ltd)

Abbreviations: CEAC, cost-effectiveness acceptability curve; OS, overall survival; PFS, progression-free survival

Based on these 10,000 PSA iterations and the list price for brigatinib and ceritinib, the CEAC suggests that there is a 36.87% likelihood of brigatinib being cost-effectiveness at a willingness-to-pay (WTP) of £50,000 per QALY.

5.2.10 Sensitivity analyses

Univariate deterministic sensitivity analyses were conducted by the company to explore the impact of different parameters on the ICER. Variables which had the highest impact are presented in Table 47. Results of deterministic analyses are presented in Table 48 and Figure 22. These results show that the parameter estimate of log (scale) for the Gompertz curve fitted to the OS data for brigatinib had the largest effect on ICER estimate. The parameter which had the second largest impact on ICER estimate was the hazard ratio calculated for OS (from the full-MAIC random effects meta-analysis of pooled OS data).

Scenario analyses were conducted across a range of important assumptions underlying the model. The ICER result of each of these are presented in Table 49 (135).

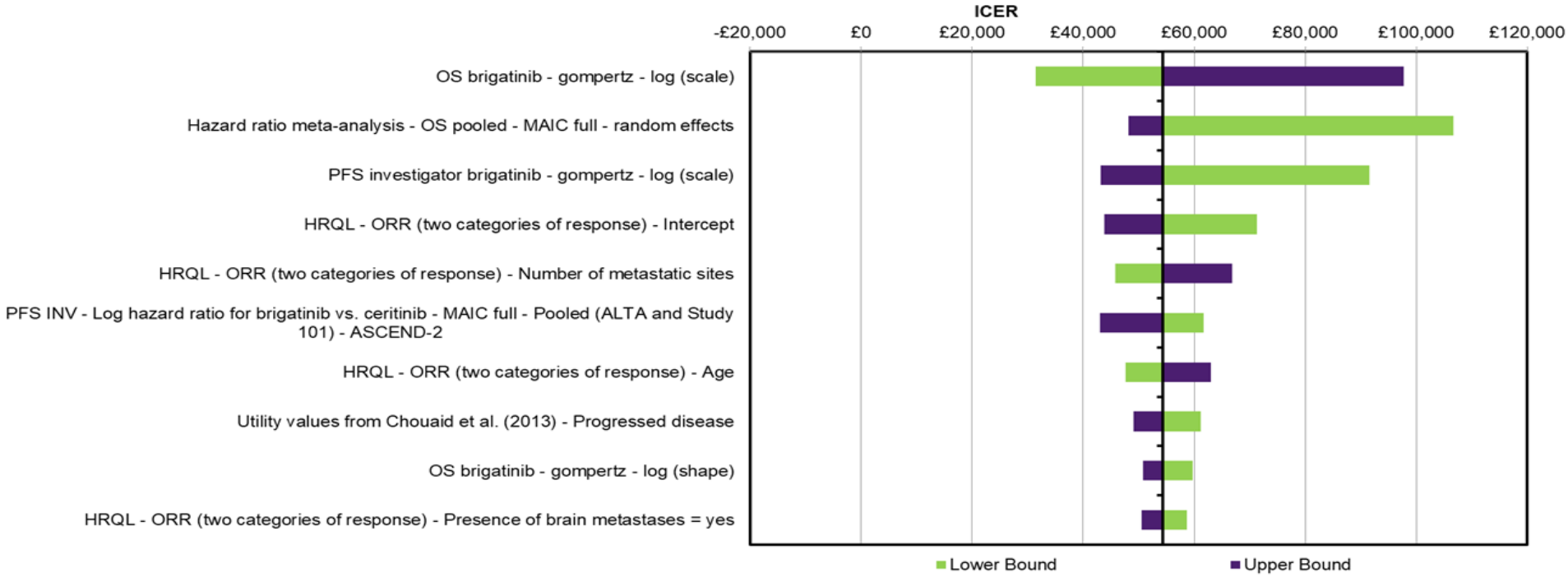
Table 47 Deterministic sensitivity analysis: variables and ranges explored

Variable	Base case	Lower bound	Upper bound
OS brigatinib - Gompertz - log (scale)	0.00	-0.01	0.01
HR meta-analysis - OS pooled - MAIC full - random effects	2.14	1.29	3.54
PFS investigator brigatinib - Gompertz - log (scale)	0.00	0.00	0.01
HRQL - ORR (two categories of response) - Intercept	0.57	0.4	0.74
HRQL - ORR (two categories of response) - Number of metastatic sites	0.019	0.06	-0.02
PFS INV - Log HR for brigatinib vs. ceritinib - MAIC full - Pooled (ALTA and Study 101) - ASCEND-2	-0.96	0.28	0.55
HRQL - ORR (two categories of response) - Age	-0.002	-0.0003	-0.0037
Utility values from Chouaid et al. (2013)[6] - Progressed disease	0.59	0.425	0.746
OS brigatinib - Gompertz - log (shape)	-5.54	-5.39	-5.7
HRQL - ORR (two categories of response) - Presence of brain metastases = yes	-0.08	-0.16	-0.01

Source: CS addendum p32, Table 15 (Takeda Ltd)

Abbreviations: ICER, incremental cost-effectiveness ratio; OS, overall survival; HR, hazard ratio; PFS, progression-free survival; HRQL, health-related quality of life; INV, investigator assessed; MAIC, matching-adjusted indirect comparison; ORR, overall response rate.

Figure 22 Tornado diagram: deterministic sensitivity analyses results



Source: CS addendum p31 Figure 14 (Takeda Ltd)

Abbreviations: ICER, incremental cost-effectiveness ratio; OS, overall survival; HR, hazard ratio; PFS, progression-free survival; HRQL, health-related quality of life; INV, investigator assessed; MAIC, matching-adjusted indirect comparison; ORR, overall response rate.

Table 48 Numerical results of deterministic sensitivity analyses

Variable	Lower Bound ICER estimate	Upper bound ICER estimate	Difference
OS brigatinib - Gompertz - log (scale)	£31,489	£97,791	£66,302
HR meta-analysis - OS pooled - MAIC full - random effects	£106,751	£48,210	£58,541
PFS investigator brigatinib - Gompertz - log (scale)	£91,559	£43,139	£48,419
HRQL - ORR (two categories of response) - Intercept	£71,272	£43,870	£27,403
HRQL - ORR (two categories of response) - Number of metastatic sites	£45,738	£66,839	£21,102
PFS INV - Log HR for brigatinib vs. ceritinib - MAIC full - Pooled (ALTA and Study 101) - ASCEND-2	£61,774	£43,020	£18,754
HRQL - ORR (two categories of response) - Age	£47,700	£63,049	£15,348
Utility values from Chouaid et al. (2013)6 - Progressed disease	£61,197	£49,114	£12,083
OS brigatinib - Gompertz - log (shape)	£59,678	£50,809	£8,869
HRQL - ORR (two categories of response) - Presence of brain metastases = yes	£58,726	£50,513	£8,213

Source: CS addendum p32 Table 15 (Takeda Ltd)

Abbreviations: ICER, incremental cost-effectiveness ratio; OS, overall survival; HR, hazard ratio; PFS, progression-free survival; HRQL, health-related quality of life; INV, investigator assessed; MAIC, matching-adjusted indirect comparison; ORR, overall response rate.

5.2.10.1 Scenario analyses

Presented in Table 49 is the full set of alternative scenarios presented by the company. Those marked with an asterisk (*) are those the ERG have assigned greater importance based on priority areas of assumption uncertainty: distribution selection for extrapolation; ITC data sources and impact of MAIC; time on treatment; treatment benefit discontinuation; and drug wastage. Of those selected, only the selection of Weibull in place of Gompertz for long-tern PFS and adoption of a naïve ITC for PFS HR reduce the ICER, all the other scenarios increase the ICER.

Table 49 Result of company scenario analyses in full

Scenario	Incremental costs	Incremental QALYs	ICER	Difference from base case ICER
Brigatinib outcomes				
Brigatinib OS data – pooled data for OS and PFS				
Generalised gamma	£62,962	1.3115	£48,006	-11.61%
Gamma	£62,549	1.2713	£49,200	-9.41%
Log-normal	£70,628	1.9812	£35,649	-34.36%
Log-logistic	£67,641	1.7694	£38,228	-29.61%
Weibull*	£62,298	1.2471	£49,955	-8.02%
Gompertz (base case)	£61,097	1.1249	£54,311	0.00%
Exponential	£63,452	1.3439	£47,216	-13.06%
Brigatinib OS data – ALTA data for OS and PFS				
Generalised gamma	£62,422	1.4302	£43,645	-19.64%
Gamma	£61,147	1.3030	£46,929	-13.59%
Log-normal	£68,954	2.0131	£34,252	-36.93%
Log-logistic	£66,145	1.7918	£36,917	-32.03%
Weibull	£60,988	1.2877	£47,361	-12.80%
Gompertz	£61,463	1.3298	£46,220	-14.90%
Exponential	£61,847	1.3665	£45,259	-16.67%
Brigatinib PFS INV data – pooled data for OS and PFS				
Generalised gamma	£66,077	1.1377	£58,080	6.94%
Gamma*	£67,136	1.1404	£58,869	8.39%
Log-normal	£98,164	1.2193	£80,511	48.24%
Log-logistic	£92,297	1.2041	£76,650	41.13%
Weibull*	£65,253	1.1356	£57,462	5.80%
Gompertz (base case)	£61,097	1.1249	£54,311	0.00%
Exponential	£74,053	1.1585	£63,924	17.70%
Brigatinib PFS INV data – ALTA data for OS and PFS				
Generalised gamma	£66,353	1.3424	£49,430	-8.99%
Gamma	£67,265	1.3447	£50,022	-7.90%
Log-normal	£99,436	1.4267	£69,697	28.33%
Log-logistic	£94,560	1.4141	£66,871	23.13%
Weibull	£65,341	1.3397	£48,771	-10.20%
Gompertz	£61,463	1.3298	£46,220	-14.90%
Exponential	£74,825	1.3645	£54,838	0.97%
Brigatinib PFS IRC data – ALTA data for OS and PFS				

Scenario	Incremental costs	Incremental QALYs	ICER	Difference from base case ICER
Generalised gamma	£73,192	1.3594	£53,842	-0.86%
Gamma	£72,810	1.3584	£53,600	-1.31%
Log-normal	£111,975	1.4579	£76,808	41.42%
Log-logistic	£103,966	1.4374	£72,328	33.17%
Weibull	£70,732	1.3531	£52,275	-3.75%
Gompertz	£66,510	1.3422	£49,552	-8.76%
Exponential	£81,084	1.3797	£58,769	8.21%
ToT scenarios				
Patients treated with brigatinib 1.53 months beyond progression and patients treated with ceritinib treated 1.6 months beyond progression	£60,809	1.1250	£54,053	-0.48%
Brigatinib extrapolated ToT curves (uncapped) and PFS HR applied to brigatinib ToT data for ceritinib*	£87,207	1.1223	£77,706	43.08%
Brigatinib extrapolated ToT curves (capped for PFS) and PFS HR applied to brigatinib ToT data for ceritinib	£62,528	1.1241	£55,624	2.42%
Brigatinib extrapolated ToT curves (uncapped) and ceritinib ToT equal to brigatinib's ToT (uncapped)	£26,911	1.1309	£23,797	-56.18%
Brigatinib extrapolated ToT curves (capped for PFS) and ceritinib ToT equal to brigatinib's ToT (capped for PFS)	£57,453	1.1249	£51,076	-5.96%
Relative efficacy				
OS				
Naïve ITC - ALTA - ASCEND-2	£61,010	1.1164	£54,651	0.63%
MAIC full - ALTA - ASCEND-2	£63,706	1.2599	£50,565	-6.90%
MAIC reduced - ALTA - ASCEND-2	£63,799	1.2629	£50,516	-6.99%
Naïve ITC - Pooled (ALTA and Study 101) - ASCEND-2	£61,151	1.1303	£54,102	-0.38%
MAIC full - Pooled (ALTA and Study 101) - ASCEND-2	£62,230	1.2030	£51,728	-4.76%
MAIC reduced - Pooled (ALTA and Study 101) - ASCEND-2	£62,230	1.2030	£51,728	-4.76%
Naïve ITC - ALTA - ASCEND-5	£60,776	1.0933	£55,590	2.35%
MAIC full - ALTA - ASCEND-5	£66,399	1.3374	£49,649	-8.58%
MAIC reduced - ALTA - ASCEND-5	£66,112	1.3298	£49,716	-8.46%
Naïve ITC - Pooled (ALTA and Study 101) - ASCEND-5	£60,735	1.0893	£55,758	2.66%
MAIC full - Pooled (ALTA and Study 101) - ASCEND-5	£60,378	1.0541	£57,280	5.47%
MAIC reduced - Pooled (ALTA and Study 101) - ASCEND-5	£60,378	1.0541	£57,280	5.47%
Meta-analysis ALTA - MAIC full - fixed effects	£64,870	1.2955	£50,073	-7.80%
Meta-analysis ALTA - MAIC full - random effects	£64,630	1.2885	£50,159	-7.64%
Meta-analysis ALTA - Naïve ITC - fixed effects	£60,919	1.1074	£55,012	1.29%

Scenario	Incremental costs	Incremental QALYs	ICER	Difference from base case ICER
Meta-analysis ALTA - Naïve ITC - random effects	£60,888	1.1044	£55,133	1.51%
Meta-analysis ALTA - MAIC reduced - fixed effects	£65,032	1.3001	£50,020	-7.90%
Meta-analysis ALTA - MAIC reduced - random effects	£65,045	1.3005	£50,015	-7.91%
Meta-analysis pooled data - MAIC full - fixed effects	£61,116	1.1269	£54,235	-0.14%
Meta-analysis pooled data - MAIC full - random effects (base case)*	£61,097	1.1249	£54,311	0.00%
Meta-analysis pooled data - Naïve ITC - fixed effects	£60,969	1.1123	£54,813	0.92%
Meta-analysis pooled data - Naïve ITC - random effects	£60,939	1.1093	£54,932	1.14%
Meta-analysis pooled data - MAIC reduced - fixed effects	£61,116	1.1269	£54,235	-0.14%
Meta-analysis pooled data - MAIC reduced - random effects	£61,097	1.1249	£54,311	0.00%
PFS				
Naïve ITC - ALTA - ASCEND-2	£60,898	1.1244	£54,161	-0.28%
MAIC full - ALTA - ASCEND-2	£62,728	1.1295	£55,536	2.26%
MAIC reduced - ALTA - ASCEND-2	£62,766	1.1296	£55,564	2.31%
Naïve ITC - Pooled (ALTA and Study 101) - ASCEND-2	£60,692	1.1238	£54,005	-0.56%
MAIC full - Pooled (ALTA and Study 101) - ASCEND-2 (base case)	£61,097	1.1249	£54,311	0.00%
MAIC reduced - Pooled (ALTA and Study 101) - ASCEND-2	£61,097	1.1249	£54,311	0.00%
Naïve ITC - ALTA - ASCEND-5	£69,310	1.1479	£60,381	11.18%
MAIC full - ALTA - ASCEND-5	£77,601	1.1710	£66,268	22.02%
MAIC reduced - ALTA - ASCEND-5	£74,290	1.1618	£63,945	17.74%
Meta-analysis ALTA - MAIC full - fixed effects	£68,332	1.1451	£59,671	9.87%
Meta-analysis ALTA - MAIC full - random effects	£69,162	1.1475	£60,274	10.98%
Meta-analysis ALTA - Naïve ITC - fixed effects	£65,164	1.1363	£57,347	5.59%
Meta-analysis ALTA - Naïve ITC - random effects	£65,220	1.1365	£57,389	5.67%
Meta-analysis ALTA - MAIC reduced - fixed effects	£68,535	1.1457	£59,819	10.14%
Meta-analysis ALTA - MAIC reduced - random effects	£68,757	1.1463	£59,980	10.44%
Long-term treatment effect				
OS – Gompertz distribution				
Treatment benefit discontinues at 2-years	£38,200	0.3623	£105,434	94.13%
Treatment benefit discontinues at 3-years	£49,885	0.5469	£91,210	67.94%
Treatment benefit discontinues at 4-years	£55,439	0.6993	£79,282	45.98%

Scenario	Incremental costs	Incremental QALYs	ICER	Difference from base case ICER
Treatment benefit discontinues at 5-years*	£57,862	0.8199	£70,573	29.94%
Treatment benefit discontinues at 10-years	£60,809	1.0899	£55,793	2.73%
OS – Weibull distribution				
Treatment benefit discontinues at 2-years	£38,306	0.3629	£105,567	94.37%
Treatment benefit discontinues at 3-years	£49,938	0.5473	£91,237	67.99%
Treatment benefit discontinues at 4-years	£55,468	0.7004	£79,191	45.81%
Treatment benefit discontinues at 5-years	£57,912	0.8243	£70,258	29.36%
Treatment benefit discontinues at 10-years	£61,385	1.1464	£53,546	-1.41%
OS – exponential distribution				
Treatment benefit discontinues at 2-years	£38,299	0.3637	£105,307	93.90%
Treatment benefit discontinues at 3-years	£50,012	0.5478	£91,300	68.11%
Treatment benefit discontinues at 4-years	£55,621	0.7032	£79,096	45.64%
Treatment benefit discontinues at 5-years*	£58,147	0.8323	£69,862	28.63%
Treatment benefit discontinues at 10-years	£62,058	1.1958	£51,895	-4.45%
Cost inputs				
End-of-life cost applied as a lump sum over 4-weeks	£61,149	1.1249	£54,357	0.08%
Include drug wastage*	£64,542	1.1249	£57,373	5.64%
Include administration costs for oral therapies*	£68,308	1.1249	£60,721	11.80%
Assume relative risks of unreported adverse events equal to zero for ceritinib	£61,991	1.1224	£55,232	1.70%
HRQL inputs				
ALTA data, ORR four categories and Chouaid et al. (2013)[6] for progressed disease	£61,097	1.1244	£54,335	0.04%
ALTA data, BoR two categories and Chouaid et al. (2013) for progressed disease	£61,097	1.1035	£55,368	1.95%
ALTA data, BoR four categories and Chouaid et al. (2013) for progressed disease	£61,097	1.1053	£55,276	1.78%
ALTA data, ORR two categories and Nafees et al. (2008)[9] for progressed disease	£61,097	1.1021	£55,434	2.07%
ALTA data, ORR two categories and progressed disease	£61,097	1.1931	£51,210	-5.71%
Utilities from Chouaid et al. (2013)	£61,097	1.0568	£57,813	6.45%
Utilities from Nafees et al. (2008)	£61,097	0.9096	£67,168	23.67%
Time horizon				
5-year time horizon	£54,895	0.7593	£72,300	33.12%
10-year time horizon	£60,310	1.0791	£55,887	2.90%

Abbreviations: BoR, best overall response; FE, fixed effects; HRQL, health-related quality of life; ICER, incremental cost-effectiveness ratio; IRC, independent review committee; MAIC, matching-adjusted indirect comparison; NHS, National Health Service; ORR, overall response rate; OS, overall survival; PFS, progression free survival; QALY, quality adjusted life year; RE, random effects; ToT, time on treatment

Source: CS addendum p32 Table 16 (Takeda Ltd)

5.2.11 Model validation and face validity check

Table 50 presents the incremental benefits of various ceritinib strategies as modelled in previous economic evaluations, extracted from included studies from the company's economic evaluation search.

Table 50. Life Years and QALYs gained for ceritinib previous strategies

Study	Setting	Life Years gained	QALYs gained
CS (Takeda Ltd)	**UK**	**1.91**	**1.29**
Balu et al. 2015	Mexico	NR	2.49
Carlson et al. 2017	USA	1.67	0.98
Hurry et al. 2016	Canada	1.61	0.86
NICE Technology Appraisal TA395, 2016	UK	1.77	1.08
Zhou et al. 2015	UK	1.77	0.94
Zhou et al. 2015	Canada	1.61	0.86

Source: CS page 159 Table 58 (Takeda Ltd)

Abbreviations: QALY, quality adjusted life year; SLR, systematic literature review.

The estimate of benefits for ceritinib in this *de novo* evaluation are generally consistent with those estimated elsewhere, including the UK studies Zhou *et al.* and NICE TA395,(8, 74) although the QALY may be slightly high in the overall context.

ERG opinion:

- The company model outcomes hold face value, and appear valid in the context of existing relevant economic evaluations. This should be taken on advice that the use of several methodological approaches by the company may underestimate the base case ICER. We refer you to the ERG base case.

5.3 Exploratory and sensitivity analyses undertaken by the ERG

The company model included multiple alternative settings, allowing for broad exploration of data sources and assumptions different to the base case. It was not necessary for the ERG to perform additional analyses to those already provided within the company model. Additional analyses might have been conducted to synthesise preferential estimates though, had time allowed.

The ERG are not in agreement with some important assumptions or their justification in the base case modelling of clinical effectiveness and resource consumption. Sections 5.3.1 and 5.3.2 detail the aspects of the company model that have been changed, using existing settings, to produce the ERG's preferred base case.

5.3.1 Clinical effectiveness

1. The data sources used for the simulation of PFS should include the ASCEND-5 trial in preference to Study 101. Because neither IRC nor INV reported data is available for all four included trials (Study 101 has only INV data and ASCEND-5 has only IRC data), the selection of trials to include is necessarily a trade-off of size, quality and preference for IRC reported outcomes. Using existing readily available analyses within the company model to include ASCEND-5, the optimal scenario is a meta-analysis of MAIC of ALTA versus ASCEND-2 using the INV data, and the MAIC of ALTA versus ASCEND-5 using IRC data. We prefer this scenario since the size and quality of ASCEND-5 is superior to Study 101 (refer to sections 4.1.5 and 4.4), and results for ASCEND-5 are reported by independent review committee.
    - Given this change, the base case ICER changes from £54,311 to £60,274
2. The extrapolation of PFS to the full time horizon should use the gamma distribution. This provides the best statistical fit to the observed data for time on treatment and the second best for PFS, after the exponential distribution. Unlike for the exponential distribution, the hazard rate is not assumed to be constant over time, as indicated by the empirical hazard plots. The ERG rejects the company's justification for Gompertz, which is that the distribution should match the one chosen for OS (this would be a valid justification for retaining the same distribution between strategies for a single outcome). No implausible scenario whereby there are more patients progression-free than alive is created.
    - Given this change, the base case ICER changes from £54,311 to £58,869 (and with the PFS data source change (1) = £64,686)

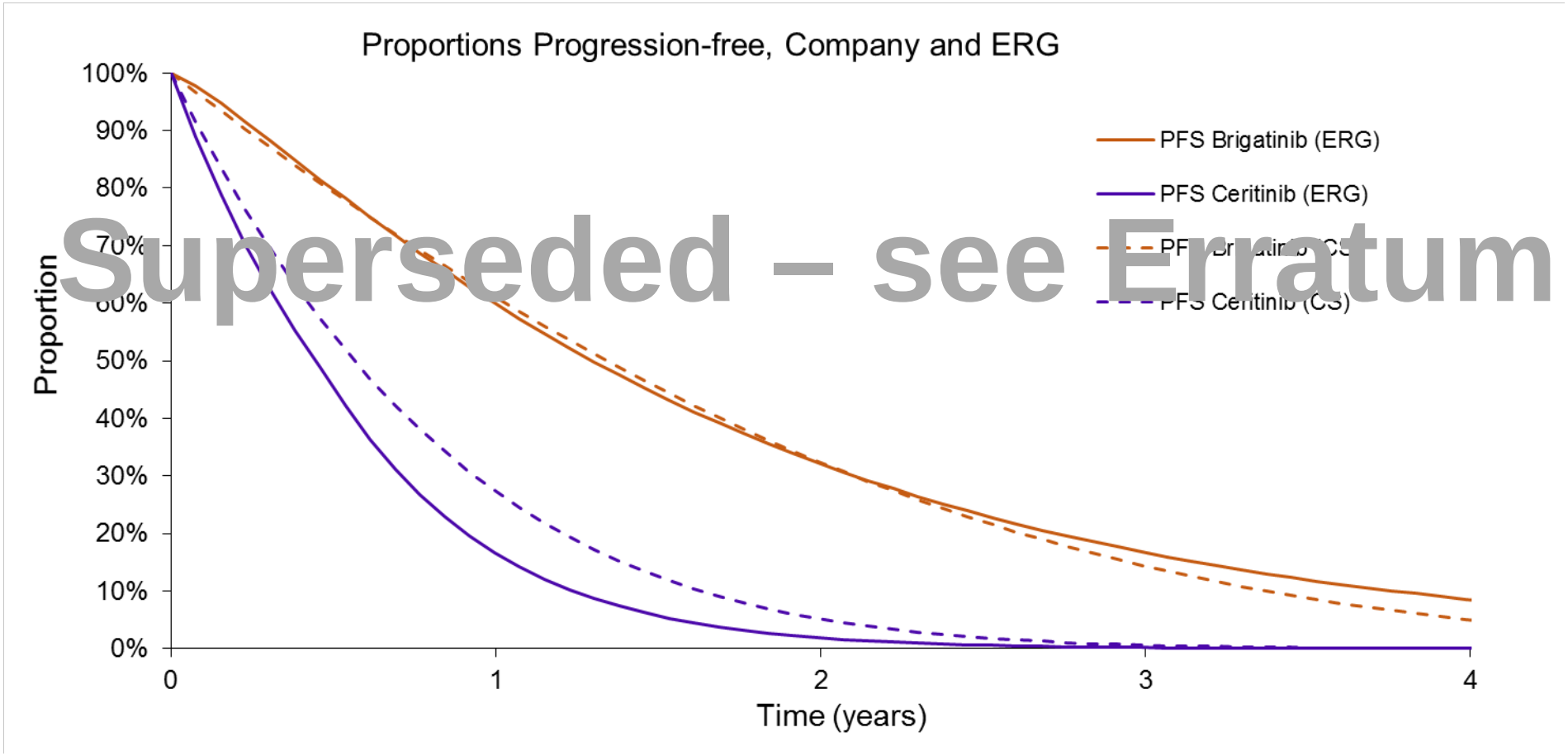
Company and ERG long-term PFS estimates are presented in Table 51. Two reasons lead to the differences observed (above): the inclusion of ASCEND-5 revised the ITC HR for PFS, so changing the relative position of the ceritinib strategy; and the gamma distribution changes the shape of the curves.

5.3.2 Costs and Resources

3. The estimate of time spent on treatment for each of the therapies can be improved given the availability of IPD data from ALTA, which was not used by the company for the baseline strategy (brigatinib) in their base case. The ERG believe it is preferable to extrapolate the observed ToT for brigatinib in ALTA (not available for Study 101), using the gamma distribution, rather than adopting the company's preferred assumption that all brigatinib patients discontinue 1.53 months after they progress (progression in the CS being extrapolated using the Gompertz distribution).(18) This direct approach is preferential because it ensures that the total costs in the model are consistent with the modelled clinical benefit of brigatinib, as both are taken from the same source: the brigatinib and ceritinib trials. Also, evidence from both ALTA and ASCEND-2, as well as clinical advice received by the ERG, supports the independence of time to discontinuation from time to progression. The CS calculates an additional period of 1.53 months from ALTA; and the ERG calculates the difference between median duration of exposure and median PFS in ACSEND-2 is 3.2 months (ERG scenario analysis). In the absence of a hazard ratio derived using time on ceritinib treatment it is necessary to use the PFS HR derived from the population-adjusted PFS ITC; the ERG base case adopts this approach. The company already present this, scenario in their submission.
    - Given this change, the base case ICER changes from £54,311 to £77,706 (and with the PFS data source change (1) and PFS distribution change (2) = £83,360)

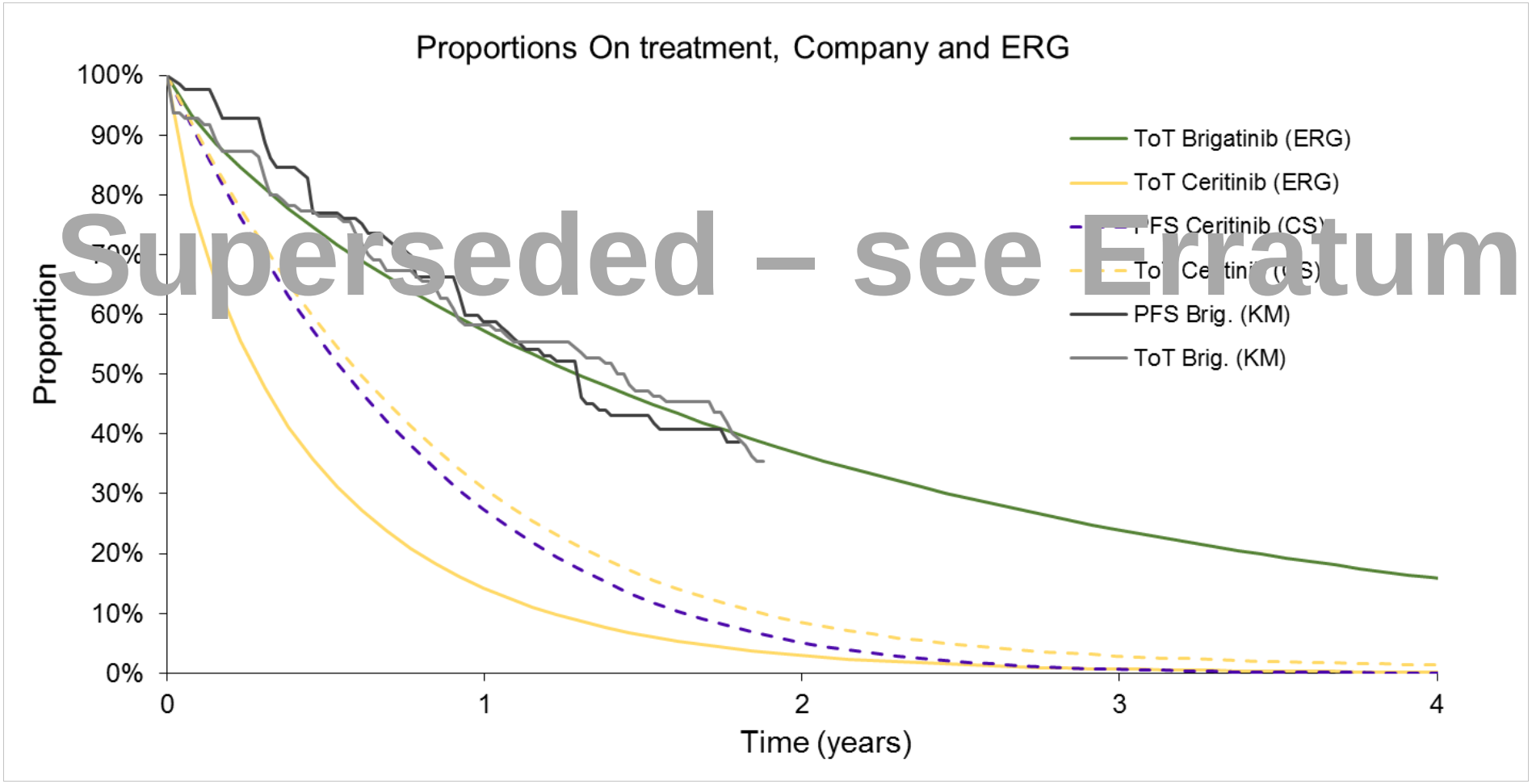
Below are the graphed company and ERG estimates for the proportion of patients remaining on treatment (Figure 23); and the proportion of patients remaining on treatment alongside the proportion progression-free (Figure 24, brigatinib; Figure 25, ceritinib).

Table 51 Long-term PFS estimates for strategies, company and ERG



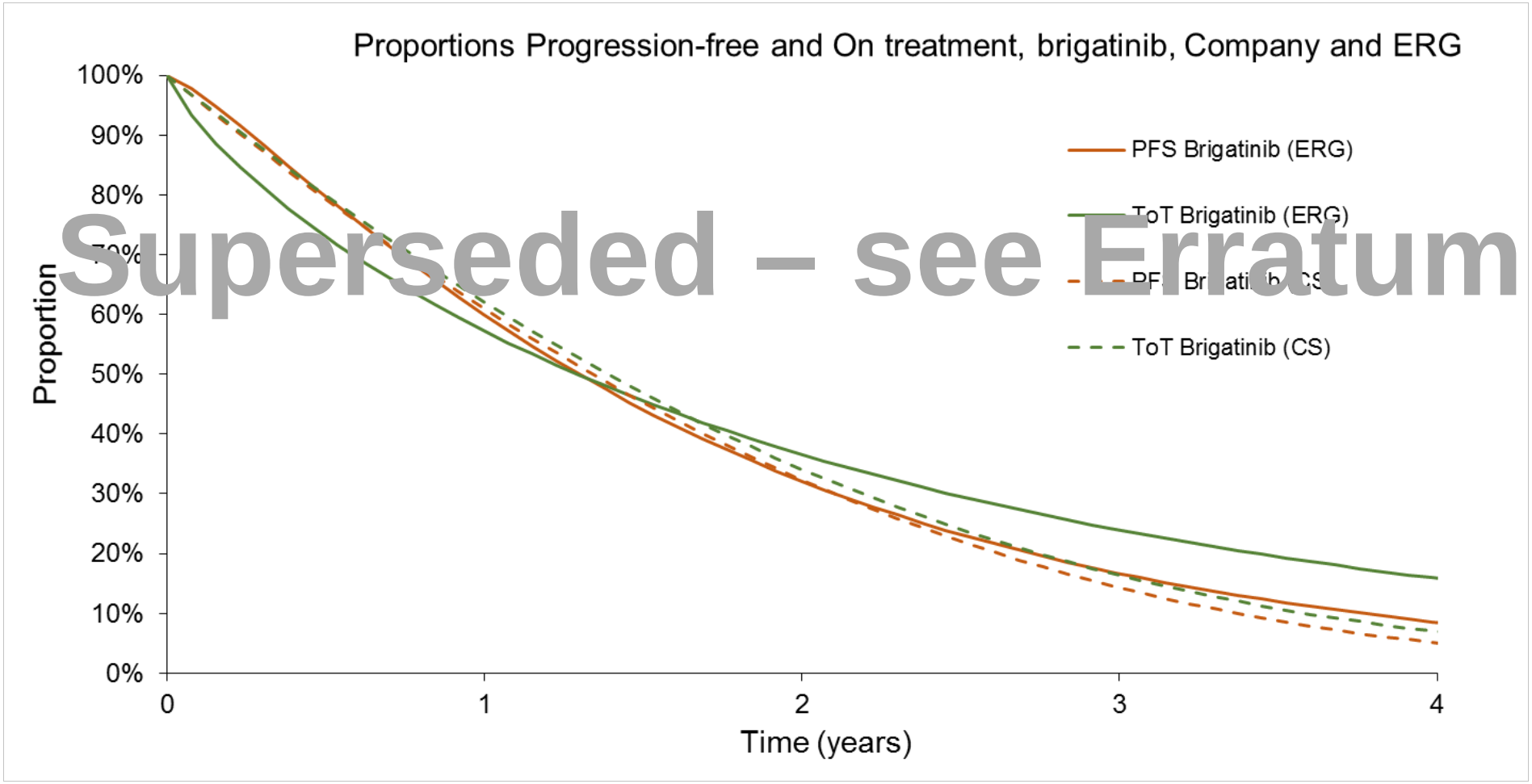
The combined effect of ERG base case changes 1 and 2 is to reduce the long term estimate of PFS on ceritinib; with a slight change to the brigatinib estimate.

Figure 23 TOT as a proportion of patients on treatments, Company and ERG estimates



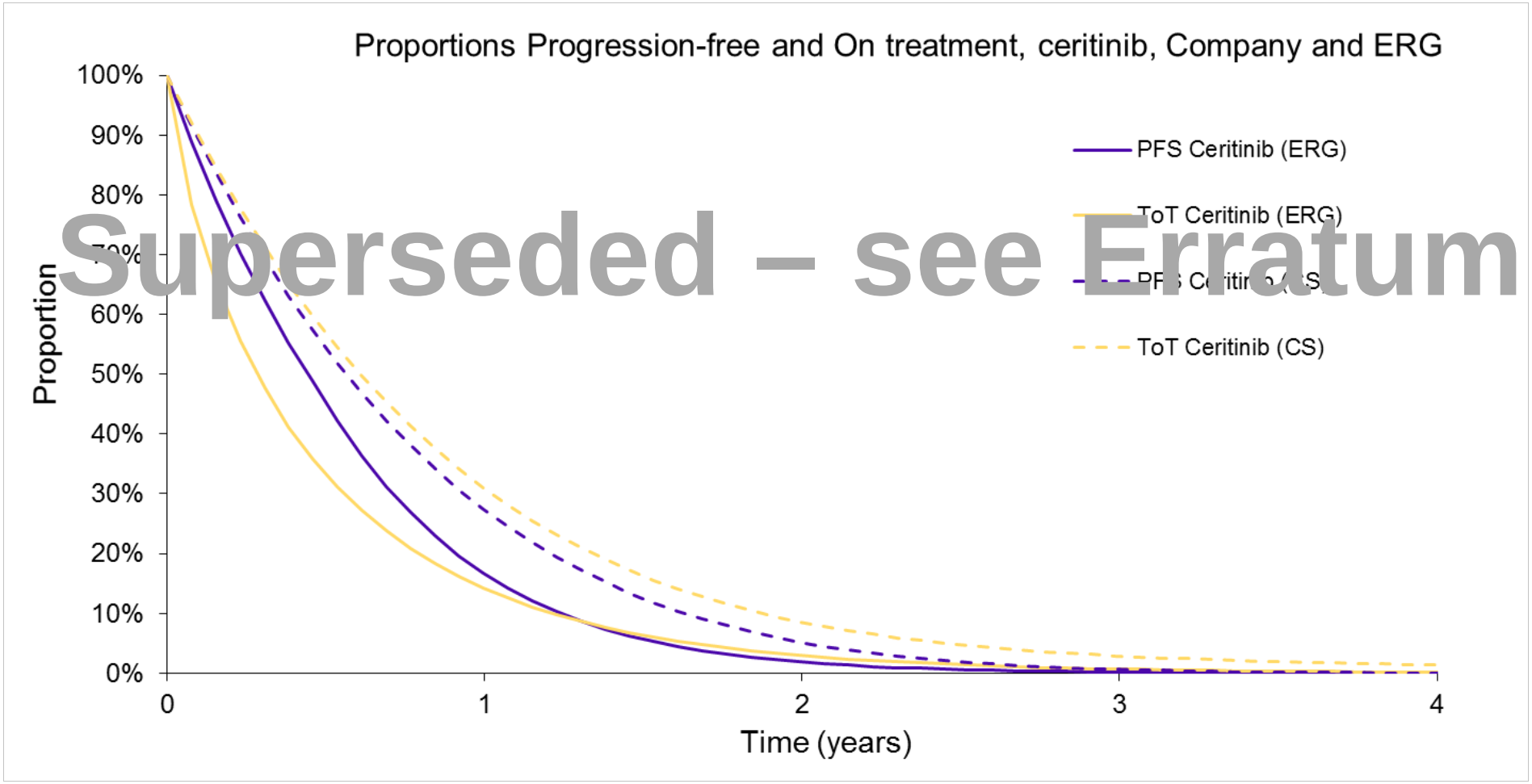
The overall effect of ERG base case changes 1, 2 and 3 is to reduce the long term estimate of time on ceritinib treatment.

Figure 24 Brigatinib TOT and PFS as a proportion of patients on treatments or progression-free, Company and ERG estimates



This graph illustrates the impact of the ERG approach on the estimate of TOT for brigatinib (green curves); and the contrast between the company estimate of brigatinib PFS (dashed orange) and the ERG estimate of brigatinib ToT (solid green).

Figure 25 Ceritinib TOT and PFS as a proportion of patients on treatments or progression-free, Company and ERG estimates



This graph illustrates the impact of the ERG approach on the estimate of TOT for ceritinib (yellow curves); and the contrast between the company estimate of ceritinib PFS (dashed purple) and the ERG estimate of ceritinib ToT (solid yellow).

4. The company assume no wastage in their base case, i.e. the NHS saves all costs associated with reduced dose intensity.(18) In the model this means the cost adjustment applied to treatment cost for any reduction from expected dose intensity is assumed to be fully realised. The company adjust by 0.889 for brigatinib and 0.8359 for ceritinib. The company justify this adjustment and the assumption of no wastage with the precedent of NICE TA395. The ERG have taken expert advice regarding drug wastage and checked the committee position in respect to the NICE TA395 of ceritinib after crizotinib.(78) Advice from senior oncology pharmacists and clinicians:
    - Unused tablets resultant from patients discontinuing treatment due to death, progression or tolerability issues are not recovered: the NHS burdens the full cost. This type of loss is inter-patient and not relevant to the adjustment factor described above.
    - Any tablets issued to patients that have left the hospital are not reused, as the pharmacy/hospital cannot guarantee the conditions in which they have been stored. Patients are seen prior to each cycle so they should only be issued a month's worth at a time.
    - All 28 tablets dispensed for a treatment course would be used, and that any course subsequently started gets a new prescription.
    - Patients are asked at clinic how many tablets they have left, so only what they actually need is prescribed to minimise wastage.

    Advice to Committee B during the appraisal of ceritinib in TA395:

    - For a short term reduction in dose, people would continue to have a 30 day supply of their usual dose of ceritinib and unused tablets would be wasted.
    - For long term dose reductions the lower dose would be prescribed and tablets are unlikely to be wasted.
    - People who stop ceritinib because of adverse reactions cannot return unused tablets to the NHS.

    Considering the mixed expert advice collected (above), the ERG base case adopts the pragmatic assumption that the NHS will pay for some unused tablets, because the difference between the observed trial dose and expected dose is likely a mix of short-term dose adjustment or treatment interruptions (unrecovered drug), and long term dose reduction, for which an altered drug prescription would be made both in practice and in trial. In coming to a reasonable estimate for a revised adjustment of the CS base case, the ERG also considered brigatinib dosing statistics reported in the final ALTA CSR (N=110).(36) This information does not provide a complete

picture allowing the differentiation of short and long term dose modifications/interruptions, but it is discernible that that most brigatinib dose interruptions are short-lived, and therefore some wastage is likely.
Aligned with this inference, TA395 Committee B agreed that on average in clinical practice the NHS would not pay for the full dose, but it was likely to pay for more than 82.8%, because of wastage. The committee concluded that the dose intensity in the model should be lower than 100% but higher than the estimate of 82.8% used by the company (the figure of 90% was later adopted).
In this is an appraisal of two ALK inhibitors with different toxicity profiles, the ERG prefer the assumption in respect to wastage that for each strategy half the difference between observed and expected dose should be used in the base case (brigatinib = [redacted]%, ceritinib = 91.80%). Note that the observed relative MDI reported in the ALTA CSR was preferred to that estimate provided in the CS.

- Given this change, the base case ICER changes from £54,311 to £55,843 (and with the PFS data source change (1), the PFS distribution change (2), and the TOT change (3) = £88,256)

5. The company assume there is no administration cost for either oral drug. In a scenario analysis they explore this using HRG currency code SB11Z; Deliver exclusively oral chemotherapy (unit cost = £170.75). The ERG consulted with a senior NHS pharmacist receiving advice that that the administration cost is that of home delivery, typically outsourced for oral chemotherapy. For the NHS Peninsula Purchasing Alliance this delivery is charged at £42.50 per item, monthly in this case. The ERG base case adopts this estimate.

    - Given this change, the base case ICER changes from £54,311 to £55,906 (and with the PFS data source change (1), the PFS distribution change (2), the TOT change (3), and the wastage change (4) = £90,032)

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

The ERG base case was different to the company base case in five aspects of simulation. All five changes could be implemented using existing functionality within the company model. Table 52 presents the ERG ICER, the individual impact each of the five changes has on the company base case, and their cumulative impact i.e. the ERG base case ICER.

Table 52 Summary derivation of ERG base case

	Cost per QALY gained (ICER)	*Individual impact of change*	*%*	*Cumulative impact of change*	*Cumulative %*
Company model base case (Sept 2017 data cut)	£54,311				
*ERG code and implementation corrections**	£54,404	£93	0.2%		
ERG base case (including all revisions) (1+2+3+4+5)	**£90,032**	£35,721	65.8%		
Alternative A. ERG BC excl. PAS arrangements (1+3+4+5)	£91,524	£37,213	68.5%		
Impact of revisions on company base case:					
(1) ASCEND-5 used in preference to Study 101 for PFS estimate	£60,274	£5,963	11.0%	£60,274	11.0%
(2) Gamma distribution for PFS extrapolations	£58,869	£4,558	8.4%	£64,686	19.1%
(3) ToT baseline from ALTA observations of ToT (using Gamma)	£77,706	£23,395	43.1%	£83,360	53.5%
(4) NHS partly recover cost of wastage	£55,843	£2,412	4.4%	£88,256	62.5%
(5) Administration / home delivery included	£55,906	£1,595	2.9%	£90,032	65.8%

*The ERG found a minor error in an isolated area of coding of the company model for time on treatment beyond progression; correcting for this had minimal impact on the company base case estimate. This error was not relevant to the ERG base case since it did not utilise this code.

Table 53 Summary ERG base case results

Technology	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Brigatinib	£146,945	3.49	2.46				
Ceritinib	£42,452	1.91	1.30	£104,493	1.58	1.1606	£90,032

Table 54 ICER results for alternative scenarios of main assumptions

Scenario	ICER	Difference from ERG base case ICER
Brigatinib OS data – pooled data for OS and PFS		
Gamma	£81,416	-9.57%
Weibull	£82,737	-8.10%
Gompertz (Company/ERG base case)	£90,032	0.00%
Exponential	£77,335	-14.10%
Brigatinib PFS INV data – pooled data for OS and PFS		
Gamma (ERG base case)	£90,032	0.00%
Weibull	£90,503	0.52%
Gompertz (Company base case)	£91,524	1.66%
Exponential	£88,205	-2.03%
Brigatinib PFS IRC data – ALTA data for OS and PFS		
Gamma	£89,114	-1.02%
Weibull	£89,625	-0.45%
Gompertz	£90,652	0.69%
Exponential	£86,967	-3.40%
ToT scenarios		
Extrapolated ToT (Gamma) curve fitted to ALTA data for Brigatinib, with PFS HR applied for Ceritinib (ERG base case)	£90,032	0.00%
Extrapolated ToT (Gamma) curve fitted to ALTA data and capped by PFS for Brigatinib, with the PFS HR applied for Ceritinib	£71,210	-20.91%
Treatment until progression for Brigatinib and Ceritinib	£69,323	-23.00%
Treatment until 1.53 months post progression for Brigatinib, and 3.2 months post progression for Ceritinib	£62,487	-30.59%
Treatment until 1.53 months post progression for Brigatinib and Ceritinib (Company base case)	£69,267	-23.06%
Relative efficacy OS		
Meta-analysis (RE) ALTA - MAIC	£80,111	-11.02%
Meta-analysis (RE) ALTA - Naïve ITC	£91,492	1.62%
Meta-analysis (RE) pooled data - Naïve ITC	£91,135	1.23%
Meta-analysis (RE) pooled data - MAIC full (Company/ERG base case)	£90,032	0.00%
Relative efficacy PFS		
MAIC full – pooled ALTA and Study 101 - ASCEND-2 (Company base case)	£81,999	-8.92%
MAIC full - ALTA - ASCEND-2	£83,729	-7.00%
MAIC full - ALTA - ASCEND-5	£97,014	7.76%
Meta-analysis (RE) ALTA - Naïve ITC	£86,268	-4.18%
Meta-analysis (RE) ALTA - MAIC full (ERG base case)	£90,032	0.00%
Long-term treatment effect		

Scenario	ICER	Difference from ERG base case ICER
No treatment benefit discontinuation (Company/ERG base case)	£90,032	0.00%
Treatment benefit discontinues at 5-years	£110,959	23.24%
Treatment benefit discontinues at 10-years	£91,849	2.02%
Cost inputs		
Include cost of used drug only	£86,142	-4.32%
No administration / home delivery costs	£87,249	-3.09%
HRQL inputs		
Nafees et al. (2008) for progressed disease	£91,202	1.30%
Utilities from Chouaid et al. (2013)	£95,375	5.94%
Utilities from Nafees et al. (2008)	£108,939	21.00%
Time horizon		
5-year time horizon	£110,994	23.28%
10-year time horizon	£92,094	2.29%

Abbreviations: HRQL, health-related quality of life; ICER, incremental cost-effectiveness ratio; IRC, independent review committee; MAIC, matching-adjusted indirect comparison; NHS, National Health Service; ORR, overall response rate; OS, overall survival; PFS, progression free survival; QALY, quality adjusted life year; RE, random effects; ToT, time on treatment

Source: Adapted from CS Addendum, p32, Table 16 (Takeda Ltd)

These results with the application of Patient Access Scheme arrangements are presented in detail in Appendix 2.

6 End of life

The four NICE End of Life criteria are as follows;(84)

- that the treatment is indicated for patients with a short life expectancy, normally less than 24 months;
- there is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment.
- the estimates of the extension to life are robust and can be shown or reasonably inferred from either progression-free survival or overall survival (taking account of trials in which crossover has occurred and been accounted for in the effectiveness review)
- the assumptions used in the reference case economic modelling are plausible, objective and robust

Table 55 presents company estimates of mean and median survival. Life expectancy is represented by survival on the comparator ceritinib; life extension is represented by the difference in survival.

Table 55 Survival estimates on ceritinib and brigatinib (months)

Company			
	Ceritinib (life expectancy)	Brigatinib	Increment (life extension)
Mean (months)	24.34	46.83	22.49
Median (months)	14.9[1] - 18.1[2]	34.1[3]	16.0 – 19.2

1=ASCEND-2; 2 = ASCEND-5; 3 = ALTA

ERG opinion:

- The company claim that the first EoL criterion is satisfied given that median survival on ceritinib is less than 24 months. However, the NICE EoL criteria refer to the mean rather than median estimates of survival. Strictly speaking the first EoL criterion is not satisfied, as the modelled mean life expectancy on the comparator treatment (24.34 months, or 2.03 undiscounted life-years) is slightly greater than 24 months. Also, the company have chosen the statistical distribution, the Gompertz which gives the

shortest life expectancy for the comparator. Therefore, the base case 24.34 months could be an underestimate of the true mean survival on ceritinib.

- The third EoL criterion refers to the estimate of extension to life as being “robust”. There is no doubt that the data used to estimate the extension to life is not robust, given that it derives from four small single arm trials, and that there is lack of randomisation. However, despite this, it is likely that the extension to life is at least three months.
- There is considerable uncertainty around the extrapolation of survival beyond short follow-up periods as is the case here. Median survivals reported within the included ASCEND trials were below 2 years and this should be considered.

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40. Bazhenova L, Gettinger S, Langer C, Salgia R, Gold K, Rosell R. Brigatinib (BRG) in patients (pts) with ALK+ non-small cell lung cancer (NSCLC): Updates from a phase 1/2 trial. American Society of Clinical Oncology; 2-6 June 2017; Chicago, IL.2017.

41. ARIAD Pharmaceuticals I, . Clinical Study Report AP26113-11-101 (31 May 2016 Data Cut): A Phase 1/2 Study of the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-Tumor Activity of the Oral ALK/EGFR Inhibitor AP26113. 2016 21 December 2016.

42. ARIAD Pharmaceuticals Inc. AP26113-11-101 Clinical Study Report: Section14 (May 2016). 2016.

43. U.S. National Library of Medicine. A Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-Tumor Activity of the Oral Anaplastic Lymphoma Kinase (ALK)/Epidermal Growth Factor Receptor (EGFR) Inhibitor Brigatinib (AP26113) [Available from: https://www.clinicaltrials.gov/ct2/show/NCT01449461?cond=NCT01449461.&rank=1.

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50. U.S. National Library of Medicine. LDK378 Versus Chemotherapy in ALK Rearranged (ALK Positive) Patients Previously Treated With Chemotherapy (Platinum Doublet) and Crizotinib [Available from: https://www.clinicaltrials.gov/ct2/show/NCT01828112?term=NCT01828112&rank=1.

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67. Carlson JJ, Wong WB, Canestaro W. The cost-effectiveness of alectinib in anaplastic lymphoma kinase-positive (ALK+) advanced NSCLC previously treated with crizotinib. Abstract. Journal of Clinical Oncology 2016;34(no pagination).

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75. Zhou Z-Y, Hurry M, Zhang J, Fan L, Zhang C, Xie J. Cost-Effectiveness Of Ceritinib In Previously Treated Patients With Crizotinib In Anaplastic Lymphoma Kinase-Positive (Alk+) Non–Small Cell Lung Cancer In Canada. Value in Health 2015;18(7):A455-A6.

76. submission ECe. Brigatinib for treating ALK-positive advanced non-small-cell lung cancer after crizotinib (ID1328). Document B2018.

77. Latimer N. NICE DSU Technical Support Document 14: Undertaking survival analysis for economic evaluation alongside clinical trials - extrapolation with patient-level data. 2011.

78. National Institue for Health and Care Excellence (NICE). Committee Discussion: Ceritinib for previously treated anaplastic lymphoma kinase positive non-small-cell lung cancer. 2016.

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80. Chouaid C, Agulnik J, Goker E, Herder GJ, Lester JF, Vansteenkiste J, et al. Health-related quality of life and utility in patients with advanced non-small-cell lung cancer: a prospective cross-sectional patient survey in a real-world setting. Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer. 2013;8(8):997-1003.

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Appendix 1. Company result with Patient Access Scheme

This appendix is supplied as a separate confidential document entitled ‘Brigatinib for treating ALK-positive non-small-cell lung cancer after crizotinib [ID1328] Appendix 1 Company results with Patient Access Schemes CONFIDENTIAL.’ [ID1328 Brigatinib for ALK+ NSCLC ERG confidential appendix 1 [cPAS].docx]

Appendix 2. ERG result with Patient Access Schemes

This appendix is supplied as a separate confidential document entitled ‘Brigatinib for treating ALK-positive non-small-cell lung cancer after crizotinib [ID1328] Appendix 2 ERG results with Patient Access Schemes CONFIDENTIAL.’ [ID1328 Brigatinib for ALK+ NSCLC ERG confidential appendix 2 ERG BC [cPAS].docx]

Appendix 3. Publications excluded at full text screening

Table 56. Publications excluded based on screening of full text documents (Stage I)

No.	Reference	Exclusion reason
1.	Chemotherapy in addition to supportive care improves survival in advanced non-small-cell lung cancer: a systematic review and meta-analysis of individual patient data from 16 randomized controlled trials (Structured abstract)2008; 26(28):[4617-25 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/cldare/articles/DARE-12009101173/frame.html.	Wrong population
2.	Chemotherapy and supportive care versus supportive care alone for advanced non-small cell lung cancer2010; (5). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007309.pub2/abstract.	Wrong outcomes
3.	Association between time to progression and subsequent survival in ceritinib-treated patients with advanced ALK-positive non-small-cell lung cancer2016. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/213/CN-01193213/frame.html.	Pooled data not from systematic review/meta-analysis
4.	Abraham J. Activity of crizotinib in patients with non-small cell lung cancer. Community Oncology. 2010;7(10):443.	Ineligible publication
5.	Abraham J. Alectinib provides a new option for ALK-positive NSCLC patients after progression on crizotinib. Journal of Community and Supportive Oncology. 2016;14(6):241-3.	Wrong study design
6.	Aix SP, Iglesias L, Nunez JA, Zugazagoitia J, Blazquez M, Cesar M, et al. Doublet combination of platinum with pemetrexed for advanced non-small-cell lung cancer: A retrospective analysis of a single institution. Journal of Thoracic Oncology. 2013;8:S583-S4.	Wrong population
7.	Akamatsu H, Mori K, Kikuchi T, Ueda H, Akamatsu K, Nakanishi M, et al. Overall response rate as a surrogate of progression-free survival with molecular targeted agents: A meta-analysis of phase III trials in advanced non-small cell lung cancer. Journal of Clinical Oncology Conference. 2015;33(15 SUPPL. 1).	Wrong outcomes
8.	Alam M, Binko J, Delahoy P, Tracey L. Real world experience from crizotinib in patients with alk positive advanced NSCLC, from a compassionate use program run in Australia and New Zealand. Asia-Pacific Journal of Clinical Oncology. 2015;11:166-7.	Abstract with insufficient information
9.	Anonymous. Results of a global phase II study with crizotinib in advanced ALK-positive non-small cell lung cancer (NSCLC). Clinical Advances in Hematology and Oncology. 2012;10(11):5.	Ineligible publication
10.	Anonymous. Erratum: Ceritinib for the treatment of late-Stage (Metastatic) non-small cell lung cancer (Clinical Cancer Research (2015) 21 (670-4)). Clinical Cancer Research. 2015;21(10):2412.	Ineligible publication
11.	Anonymous. Brigatinib Achieves Whole-Body and Intracranial Responses. Cancer Discovery. 2017;7(7):OF8.	Ineligible publication
12.	Anonymous. Brigatinib Effective in ALK+ NSCLC. Cancer Discovery. 2017;7(1):4-5.	Wrong study design
13.	Asai N, Yamaguchi E, Kubo A. Successful crizotinib rechallenge after crizotinib-induced interstitial lung disease in patients with advanced non-small-cell lung cancer. Clinical Lung Cancer. 2014;15(3):e33-5.	Wrong study design
14.	Asao T, Honma Y, Suina K, Muraki K, Shukuya T, Ohashi R, et al. Efficacy and toxicity of crizotinib for patients with ALK-positive advanced nsclc. Annals of Oncology. 2013;24:ix95.	<10 eligible patients
15.	Azevedo S, Bei L, Cunha J, Oliveira C, Rodrigues A, Pousa I, et al. Anaplastic lymphoma kinase fusion oncogene positive non-small cell lung cancer-the experience of an institution. Journal of Thoracic Oncology. 2017;12 (1 Supplement 1):S1179.	Outcomes for eligible subgroup not reported
16.	Badawy AA, Bae S, Grant SC. Treatment beyond second line chemotherapy outside of a clinical trial is appropriate for selected NSCLC patients. Journal of Thoracic Oncology. 2015;2):S654.	Wrong population
17.	Baggstrom MQ, Stinchcombe TE, Fried DB, Poole C, Hensing TA, Socinski MA. Third-generation chemotherapy agents in the treatment of advanced non-small cell lung cancer: A meta-analysis. Journal of Thoracic Oncology. 2007;2(9):845-53.	Wrong study design
18.	Bala S, Gundeti S, Linga V, Maddali L, Digumarti R, Uppin S. Clinicopathological features and outcomes in advanced nonsmall cell lung cancer with tailored therapy. Indian Journal of Medical and Paediatric Oncology. 2016;37(4):242-50.	Wrong population
19.	Bazhenova L, Gettinger S, Langer C, Salgia R, Gold K, Rosell R, et al. Brigatinib (BRG) in patients (Pts) with anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) in a phase 1/2 trial. Annals of Oncology Conference: 41st European Society for Medical Oncology Congress, ESMO. 2016;27(no pagination).	Abstract with insufficient information

No.	Reference	Exclusion reason
21.	Bazhenova L, Hodgson JG, Langer CJ, Simon GR, Gettinger SN, Ignatius Ou SH, et al. Activity of brigatinib (BRG) in crizotinib (CRZ)-resistant ALK+ NSCLC patients (pts) according to ALK plasma mutation status. Journal of Clinical Oncology Conference. 2017;35(15 Supplement 1).	Pooled data not from systematic review/meta-analysis
22.	Belani CP, Brodowicz T, Ciuleanu TE, Krzakowski M, Yang SH, Franke F, et al. Quality of life in patients with advanced non-small-cell lung cancer given maintenance treatment with pemetrexed versus placebo (H3E-MC-JMEN): results from a randomised, double-blind, phase 3 study2012; 13(3):[292-9 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/188/CN-00814188/frame.html.	Wrong population
23.	Belani CP, Wu YL, Chen YM, Kim JH, Yang SH, Zhang L, et al. Efficacy and safety of pemetrexed maintenance therapy versus best supportive care in patients from east asia with advanced, nonsquamous non-small cell lung cancer: An exploratory subgroup analysis of a global, randomized, phase 3 clinical trial. []. Journal of Thoracic Oncology. 2011;07.	Wrong population
24.	Belani CP, Wu YL, Chen YM, Kim JH, Yang SH, Zhang L, et al. Efficacy and safety of pemetrexed maintenance therapy versus best supportive care in patients from East Asia with advanced, nonsquamous non-small cell lung cancer: an exploratory subgroup analysis of a global, randomized, phase 3 clinical trial2012; 7(3):[567-73 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/977/CN-00842977/frame.html.	Wrong population
25.	Bendaly E, Dalal A, Culver K, Galebach P, Bocharova I, Foster R, et al. Treatment patterns and early outcomes of ALK+ non-small cell lung cancer patients receiving ceritinib: A chart review study. Journal of Thoracic Oncology. 2017;12 (1 Supplement 1):S1175-S6.	Outcomes for eligible subgroup not reported
26.	Bendaly E, Dalal A, Culver K, Galebach PJ, Bocharova I, Foster R, et al. PS01.70: Ceritinib Dosing Patterns and Outcomes of Patients with ALK+ NSCLC in a Real-World Practice in the United States: Topic: Medical Oncology. Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer. 2016;11(11S):S314-S5.	Abstract with insufficient information
27.	Bendaly E, Dalal AA, Culver K, Galebach P, Bocharova I, Foster R, et al. Monitoring for and Characterizing Crizotinib Progression: A Chart Review of ALK-Positive Non-Small Cell Lung Cancer Patients. Advances in Therapy. 2017;34(7):1673-85.	Abstract with insufficient information
28.	Berge EM, Lu X, Maxson D, Baron AE, Gadgeel SM, Solomon BJ, et al. Clinical benefit from pemetrexed before and after crizotinib exposure and from crizotinib before and after pemetrexed exposure in patients with anaplastic lymphoma kinase-positive non-small-cell lung cancer. Clinical Lung Cancer. 2013;14(6):636-43.	Wrong population
29.	Blackhall F, Hirsh V, Kim DW, Besse B, Nokihara H, Han JY, et al. Impact of crizotinib on patient-reported general health status compared with single-agent chemotherapy in a phase III study of advanced ALK-positive non-small cell lung cancer (NSCLC). European Journal of Cancer. 2013;49:S799-S800.	Wrong population
30.	Blackhall F, Hirsh V, Kim DW, Besse B, Nokihara H, Han JY, et al. Impact of crizotinib on patient-reported symptoms and global quality of life (QoL) compared with chemotherapy in a phase III study of advanced alk-positive non-small cell lung cancer (NSCLC). European Journal of Cancer. 2013;49:S795.	Wrong population
31.	Blackhall F, Kim DW, Besse B, Nokihara H, Han JY, Wilner KD, et al. 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. Journal of Thoracic Oncology. 2014;9(11):1625-33.	Wrong population
32.	Blackhall F, Ross Camidge D, Shaw AT, Soria J-C, Solomon BJ, Mok T, et al. Final results of the large-scale multinational trial PROFILE 1005: efficacy and safety of crizotinib in previously treated patients with advanced/metastatic ALK-positive non-small-cell lung cancer. ESMO Open. 2017;2(3).	Outcomes for eligible subgroup not reported
33.	Blackhall F, Shaw AT, Janne PA, Kim DW, Wilner KD, Schnell P, et al. Crizotinib safety profile in elderly and non-elderly patients (pts) with advanced ALK+ non-small cell lung cancer (NSCLC). European Journal of Cancer. 2013;49:S821.	Wrong population
34.	Blumenthal GM, Karuri SW, Zhang H, Zhang L, Khozin S, Kazandjian D, et al. Overall response rate, progression-free survival, and overall survival with targeted and standard therapies in advanced non-small-cell lung cancer: US Food and Drug Administration trial-level and patient-level analyses. Journal of Clinical Oncology. 2015;33(9):1008-14.	Relevant SLR handsearched
35.	Bonaventura M, Higginbottom K, Meyers A, Ilacqua J, Morimoto Y. Treatment patterns of ALK+ non-small cell lung cancer in Western Europe2016; 19(7):[A765 p.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/831/CN-01250831/frame.html.	Wrong outcomes
36.	Bos M, Gardizi M, Heukamp L, Nogova L, Merkelbach-Bruhse S, Konig K, et al. Overall survival of ALK translocation positive NSCLC patients treated with and without crizotinib. A retrospective analysis within the Network Genomic Medicine. Onkologie. 2013;36:26.	Outcomes for eligible subgroup not reported
37.	Bos M, Gardizi M, Heukamp LC, Schildhaus HU, Merkelbach-Bruse S, Nogova L, et al. A retrospective analysis of overall survival of ALK translocation-and of EGFR mutation positive NSCLC patients treated with and without personalized therapy. Oncology Research and Treatment. 2014;37:91.	Abstract with insufficient information

No.	Reference	Exclusion reason
38.	Brodowicz T, Niepel D, Booth E, Hernandez RK, Braileanu G, Cawkwell M, et al. Treatment patterns and clinical practices of advanced (Stage IV) Non-Small Cell Lung Cancer (NSCLC) in Europe - A structured literature review. Journal of Thoracic Oncology. 2017;12 (1 Supplement 1):S676.	Wrong study design
39.	Brosnan EM, Weickhardt AJ, Lu X, Maxon DA, Baron AE, Chonchol M, et al. Drug-induced reduction in estimated glomerular filtration rate in patients with ALK-positive non-small cell lung cancer treated with the ALK inhibitor crizotinib. Cancer. 2014;120(5):664-74.	Wrong outcomes
40.	Browning ET, Weickhardt AJ, Camidge DR. Response to crizotinib rechallenge after initial progression and intervening chemotherapy in ALK lung cancer. Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer. 2013;8(3):e21.	Wrong study design
41.	Cadranel J, Cortot A, Lena H, Mennecier B, Do P, Dansin E, et al. Ceritinib following crizotinib in ALK-positive (+) advanced NSCLC patients (PTS): Results from the French temporary authorization for use (ATU) experience. European Journal of Cancer. 2015;51:S616-S7.	Abstract with insufficient information
42.	Cadranel J, Park K, Arrieta O, Pless M, Bendaly E, Patel D, et al. Characteristics, treatment patterns, and survival among ALK+ non-small cell lung cancer (NSCLC) patients treated with crizotinib: A chart review study. Lung Cancer. 2016;98:9-14.	Outcomes for eligible subgroup not reported
43.	Calderón M, Bardach A, Pichon-Riviere A, Augustovski F, García Martí S, Alcaraz A, et al. Ceritinib for the treatment of ALK-positive metastatic non-small cell lung cancer (Structured abstract)2015; (4). Available from: http://onlinelibrary.wiley.com/o/cochrane/clhta/articles/HTA-32015001163/frame.html.	Abstract with insufficient information
44.	Camidge DR, Bazhenova L, Salgia R, Langer CJ, Gold KA, Rosell R, et al. Safety and efficacy of brigatinib (AP26113) in advanced malignancies, including ALK+ non-small cell lung cancer (NSCLC). Journal of Clinical Oncology Conference. 2015;33(15 SUPPL. 1).	Outcomes for eligible subgroup not reported
45.	Camidge DR, Bazhenova L, Salgia R, Weiss GJ, Langer CJ, Shaw AT, et al. Updated results of a first-in-human dose-finding study of the ALK/EGFR inhibitor AP26113 in patients with advanced malignancies. Journal of Thoracic Oncology. 2013;8:S296-S7.	Outcomes for eligible subgroup not reported
46.	Camidge DR, Bazhenova L, Salgia R, Weiss GJ, Langer CJ, Shaw AT, et al. First-in-human dose-finding study of the ALK/EGFR inhibitor AP26113 in patients with advanced malignancies: Updated results. Journal of Clinical Oncology Conference. 2013;31(15 SUPPL. 1).	Abstract with insufficient information
47.	Camidge DR, Bazhenova L, Salgia R, Weiss GJ, Langer CJ, Shaw AT, et al. Updated results of a first-in-human dose-finding study of the ALK/EGFR inhibitor AP26113 in patients with advanced malignancies. European Journal of Cancer. 2013;49:S795.	Outcomes for eligible subgroup not reported
48.	Camidge DR, Bazhenova LA, Salgia R, Langer CJ, Gold K, Rosell R, et al. Assessment of Brigatinib (AP26113) CNS activity in patients (Pts) with ALK+ NSCLC and intracranial metastases in a Phase 1/2 Study. European Journal of Cancer. 2015;51:S616.	Abstract with insufficient information
49.	Camps C, Felip E, Garcia-Campelo R, Trigo JM, Garrido P. SEOM clinical guidelines for the treatment of non-small cell lung cancer (NSCLC) 2013. Clinical and Translational Oncology. 2013;15(12):977-84.	Wrong study design
50.	Carnio S, Rapetti SG, Capelletto E, Vavala T, Levra MG, Gobbini E, et al. Treatment with crizotinib in patients with IV Stage non-small cell lung cancer (NSCLC) with ALK translocation: A single institution experience. Journal of Thoracic Oncology. 2013;8:S1207-S8.	Abstract with insufficient information
51.	Carrato A, Vergnenegre A, Thomas M, McBride K, Medina J, Cruciani G. Clinical management patterns and treatment outcomes in patients with non-small cell lung cancer (NSCLC) across Europe: EPICLIN-Lung study. Current Medical Research and Opinion. 2014;30(3):447-61.	Outcomes for eligible subgroup not reported
52.	Cha YJ, Kim HR, Shim HS. Clinical outcomes in ALK-rearranged lung adenocarcinomas according to ALK fusion variants. Journal of Translational Medicine. 2016;14(1):296.	Outcomes for eligible subgroup not reported
53.	Chaigneau A, Durand L, Lallart A, Laghouati S, Demirdjian S, Pinel S. Safety and efficacy profile of Ceritinib (LDK378) in ALK-Rearranged non-small-cell lung cancer (NSCLC). International Journal of Clinical Pharmacy. 2015;37 (1):211.	<10 eligible patients
54.	Chen G, Chen X, Zhang Y, Yan F, Fang W, Yang Y, et al. A large, single-center, real-world study of clinicopathological characteristics and treatment in advanced ALK-positive non-small-cell lung cancer. Cancer Medicine. 2017;6(5):953-61.	Wrong population
55.	Chen J, Jiang C, Wang S. LDK378: A promising anaplastic lymphoma kinase (ALK) inhibitor. Journal of Medicinal Chemistry. 2013;56(14):5673-4.	Ineligible publication
56.	Chiari R, Metro G, Iacono D, Bellezza G, Rebonato A, Dubini A, et al. Clinical impact of sequential treatment with ALK-TKIs in patients with advanced ALK-positive non-small cell lung cancer: Results of a multicenter analysis. Lung Cancer. 2015;90(2):255-60.	Outcomes for eligible subgroup not reported

No.	Reference	Exclusion reason
57.	Chow LQ, Barlesi F, Bertino EM, Kim DW, Van Den Bent MJ, Wakelee H, et al. Ceritinib in patients (PTS) with anaplastic lymphoma kinase (ALK)-rearranged (ALK+) non-small cell lung cancer (NSCLC) metastatic to the brain and/or leptomeninges: The phase II ascend-7 study. Annals of Oncology. 2015;26:i42.	Abstract with insufficient information
58.	Chow LQ, Barlesi F, Bertino EM, Kim DW, Van Den Bent MJ, Wakelee HA, et al. Ceritinib in ALK+ NSCLC metastatic to brain and/or leptomeninges: The ASCEND-7 study. Journal of Thoracic Oncology. 2015;2):S550-S1.	Abstract with insufficient information
59.	Christ MM. Non-small cell lung cancer (NSCLC): Alectinib for patients with ALK-positive lung cancer Alectinib fur Patienten mit ALK-positivem Lungenkrebs. Arzneimitteltherapie. 2017;35(6):240-1.	Ineligible publication
60.	Christopoulos P, Elsayed M, Ristau J, Bozorgmehr F, Heussel CP, Herth F, et al. Treatment and prognosis of ALK+ NSCLC in the routine clinical setting: A single-center experience. Oncology Research and Treatment. 2017;40 (Supplement 3):172-3.	Abstract with insufficient information
61.	Chun SG, Iyengar P, Gerber DE, Hogan RN, Timmerman RD. Optic neuropathy and blindness associated with crizotinib for non-small-cell lung cancer with EML4-ALK translocation. Journal of Clinical Oncology. 2015;33(5):e25-6.	Ineligible publication
62.	Cooper MR, Chim H, Chan H, Durand C. Ceritinib: a new tyrosine kinase inhibitor for non-small-cell lung cancer. Annals of Pharmacotherapy. 2015;49(1):107-12.	Wrong study design
63.	Corral J, Robles C, Mediano MD, Gastaldo AS, De La Pena MG, Alonso M. Third-line therapy and beyond for patients with advanced/metastatic non-small cell lung cancer (NSCLC). Journal of Thoracic Oncology. 2013;8:S999-S1000.	Wrong population
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No.	Reference	Exclusion reason
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No.	Reference	Exclusion reason
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94.	Gainor JF, Shaw AT. J-ALEX: Alectinib versus crizotinib in ALK-positive lung cancer. The Lancet. 2017.	Wrong population
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117.	Hida T, Nokihara H, Kondo M, Kim YH, Azuma K, Seto T, et al. Alectinib versus crizotinib in patients with ALK-positive non-small-cell lung cancer (J-ALEX): an open-label, randomised phase 3 trial2017; (no pagination). Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/054/CN-01374054/frame.html.	Wrong population
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128.	Ito K, Saiki H, Sakaguchi T, Hayashi K, Nishii Y, Watanabe F, et al. Background of patients (pts) with ALK rearranged (ALK+) non-small-cell lung cancer (NSCLC), and efficacy and safety of ALK inhibitors (ALK-Is) in actual clinical practice: Multicenter retrospective study. Annals of Oncology. 2015;26:ix140.	Abstract with insufficient information
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No.	Reference	Exclusion reason
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139.	Kazandjian D, Blumenthal GM, Chen HY, He K, Patel M, Justice R, et al. FDA approval summary: crizotinib for the treatment of metastatic non-small cell lung cancer with anaplastic lymphoma kinase rearrangements. Oncologist. 2014;19(10):e5-11.	Ineligible publication
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142.	Kim D, Mehra R, Tan DSW, Felip E, Chow LQM, Camidge DR, et al. Efficacy and safety of ceritinib in patients with advanced anaplastic lymphoma kinase (ALK)-rearranged (ALK+) non-small cell lung cancer (NSCLC): An update of ASCEND-1. International Journal of Radiation Oncology Biology Physics. 2014;1):S33-S4.	Phase I
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147.	Kim Y, Hida T, Nokihara H, Kondo M, Azuma K, Seto T, et al. 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-S9.	Wrong population
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149.	Kolek V, Pesek M, Skrickova J, Grygarkova I, Roubec J, Koubkova L, et al. Czech experience with crizotinib in the personalized treatment of NSCLC. Journal of Thoracic Oncology. 2015;2):S412.	Abstract with insufficient information

No.	Reference	Exclusion reason
150.	Kozuki T, Nishio M, Kiura K, Seto T, Nakagawa K, Maemondo M, et al. Updates on PFS and safety results of a Phase I/II study (AF-001JP) of alectinib in ALK-rearranged advanced NSCLC. Annals of Oncology. 2015;26:vii73.	Wrong population
151.	Kroeze SG, Fritz C, Hoyer M, Lo SS, Ricardi U, Sahgal A, et al. Toxicity of concurrent stereotactic radiotherapy and targeted therapy or immunotherapy: A systematic review. Cancer Treatment Reviews. 2017;53:25-37.	Outcomes for eligible subgroup not reported
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154.	Larkins E, Blumenthal GM, Chen H, He K, Agarwal R, Gieser G, et al. FDA Approval: Alectinib for the Treatment of Metastatic, ALK-Positive Non-Small Cell Lung Cancer Following Crizotinib. Clinical Cancer Research. 2016;22(21):5171-6.	Ineligible publication
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No.	Reference	Exclusion reason
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235.	Thomas M, Schuler M, Potzner M, Szczudlo T, Sutradhar S, Yovine A, et al. Experience from the ASCEND-1 trial: Ceritinib in patients (Pts) with ALK-rearranged (ALK+) Non-Small Cell Lung Cancer (NSCLC) and brain metastases. Oncology Research and Treatment. 2015;38:270.	Outcomes for eligible subgroup not reported
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247.	Wendling P. Alectinib active in ALK-positive, crizotinib-refractory NSCLC. Oncology Report. 2013(NOV):4-5.	Phase I
248.	Wilner K, Usari T, Polli A, Kim E. Comparison of cardiovascular effects of crizotinib and chemotherapy in patients (pts) with ALK-positive (+) advanced non-small cell lung cancer (NSCLC). Journal of Thoracic Oncology. 2016;1):S133.	Outcomes for eligible subgroup not reported
249.	Wolf J, Schneider CP, Potzner M, Cazorla Arratia P, Shen J, Branle F, et al. The phase II ASCEND-7 (CLDK378A2205) trial: Ceritinib in patients (pts) with ALK-rearranged (ALK+) Non-Small Cell Lung Cancer (NSCLC) metastatic to the brain and/or leptomeninges. Oncology Research and Treatment. 2015;38:138.	Abstract with insufficient information
250.	Wu X, Li J. Therapeutic effects of crizotinib in EML4-ALK-positive patients with non-small-cell lung cancer. [Chinese]. Nan Fang Yi Ke Da Xue Xue Bao = Journal of Southern Medical University. 2015;35(5):753-7.	Wrong population
251.	Xing P, Wang S, Hao X, Zhang T, Li J. Clinical data from the real world: efficacy of Crizotinib in Chinese patients with advanced ALK-rearranged non-small cell lung cancer and brain metastases. Oncotarget. 2016;7(51):84666-74.	Wrong population
252.	Yamamoto N, Nokihara H, Han JY, Hida T, Riely GJ, Baldini E, et al. Crizotinib vs. Pemetrexed or docetaxel in advanced ALK+ non-small cell lung cancer: Subgroup analysis in profile 1007. Annals of Oncology. 2013;24:ix43.	Wrong population
253.	Yanagitani N, Nishizawa H, Katayama R, Kobayashi H, Gyotoku H, Uenami T, et al. Patterns of relapse and prognosis after crizotinib therapy failure in ALK+ nonsmall cell lung cancer. Journal of Thoracic Oncology. 2013;8:S1188.	Abstract with insufficient information
254.	Yang J, Lei Y, Zhang X, Zhou Q, Yan HH, Chen HJ, et al. First-line versus second or further-line crizotinib for trial patients with advanced non-small-cell lung cancer harboring ALK rearrangements. Journal of Clinical Oncology Conference. 2015;33(15 SUPPL. 1).	Pooled data not from systematic review/meta-analysis
255.	Yang JC, Ou SI, De Petris L, Gadgeel S, Gandhi L, Kim DW, et al. Pooled Systemic Efficacy and Safety Data from the Pivotal Phase II Studies (NP28673 and NP28761) of Alectinib in ALK-positive Non-Small-Cell Lung Cancer. Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer. 2017:05.	Pooled data not from systematic review/meta-analysis
256.	Yang JCH, Ou SH, De Petris L, Gadgeel S, Gandhi L, Kim DW, et al. Pooled efficacy and safety data from two phase II studies (NP28673 and NP28761) of alectinib in ALK+ non-small-cell lung cancer (NSCLC). Journal of Thoracic Oncology. 2017;12 (1 Supplement 1):S1170-S1.	Pooled data not from systematic review/meta-analysis
257.	Yang JCH, Ou SHI, De Petris L, Gadgeel S, Gandhi L, Kim DW, et al. Pooled Systemic Efficacy and Safety Data from the Pivotal Phase II Studies (NP28673 and NP28761) of Alectinib in ALK-positive Non-Small Cell Lung Cancer. Journal of thoracic oncology. 2017;12(10):1552-60.	Pooled data not from systematic review/meta-analysis
258.	Yang JCH, Ou SHI, De Petris L, Gadgeel SM, Gandhi L, Kim DW, et al. Efficacy and safety of alectinib in ALK+ non-small-cell lung cancer (NSCLC): Pooled data from two pivotal phase II studies (NP28673 and NP28761). Journal of Clinical Oncology Conference. 2016;34(no pagination).	Wrong population
259.	Yoneda KY, Scranton JR, Cadogan MA, Tassell V, Nadanaciva S, Wilner KD, et al. Interstitial Lung Disease Associated With Crizotinib in Patients With Advanced Non-Small Cell Lung Cancer: Independent Review of Four PROFILE Trials. Clinical Lung Cancer. 2017:14.	Wrong population

No.	Reference	Exclusion reason
260.	Yoshida T, Oya Y, Shimizu J, Tanaka K, Horio Y, Hida T, et al. Impact of alectinib on survival after crizotinib failure in ALK-positive NSCLC patients. Journal of Clinical Oncology Conference. 2015;33(15 SUPPL. 1).	Abstract with insufficient information
261.	Yoshida T, Oya Y, Tanaka K, Shimizu J, Horio Y, Hida T, et al. Differential crizotinib response duration among ALK fusion variants in ALK-positive NSCLC. Annals of Oncology. 2015;26:ix139.	Abstract with insufficient information
262.	Yoshida T, Oya Y, Tanaka K, Shimizu J, Horio Y, Kuroda H, et al. Differential Crizotinib Response Duration Among ALK Fusion Variants in ALK-Positive Non-Small-Cell Lung Cancer. Journal of Clinical Oncology. 2016;34(28):3383-9.	Wrong population
263.	Yoshida T, Oya Y, Tanaka K, Shimizu J, Horio Y, Kuroda H, et al. Clinical impact of crizotinib on central nervous system progression in ALK-positive non-small lung cancer. Lung Cancer. 2016;97:43-7.	<10 eligible patients
264.	Yoshioka H, Nishio M, Kiura K, Seto T, Nakagawa K, Maemondo M, et al. Phase I/II study of alectinib (CH5424802/RO5424802) in patients with alk-rearranged non-small cell lung cancer (NSCLC): Updated results from the AF-001JP trial. [Japanese]. Japanese Journal of Lung Cancer. 2015;54(7):892-7.	Wrong population
265.	Yuan D, Wei S, Lu Y, Zhang Y, Miao X, Zhan P, et al. Single-agent maintenance therapy in non-small cell lung cancer: A systematic review and meta-analysis. Chinese Medical Journal. 2012;125(17):3143-9.	Wrong population
266.	Zhang J, Zhou Z, Cai X, Signorovitch J. Comparative efficacy of treatments for previously treated advanced or metastatic non-small cell lung cancer (NSCLC): A network meta-analysis. Value in Health. 2015;18 (7):A436-A7.	Abstract with insufficient information
267.	Zhang L, Jiang T, Li X, Wang Y, Zhao C, Zhao S, et al. Clinical features of Bim deletion polymorphism and its relation with crizotinib primary resistance in Chinese patients with ALK/ROS1 fusion-positive non-small cell lung cancer. Cancer. 2017;123(15):2927-35.	Outcomes for eligible subgroup not reported
268.	Zhao J, Zhang K, Zhang L, Wang H. [Clinical Efficacy of Crizotinib in Advanced ALK Positive Non-small Cell Lung Cancer]2015; 18(10):[616-20 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/346/CN-01169346/frame.html.	Wrong population
269.	Zhong C, Liu H, Jiang L, Zhang W, Yao F. Chemotherapy plus best supportive care versus best supportive care in patients with non-small cell lung cancer: a meta-analysis of randomized controlled trials (Structured abstract)2013; 8(3):[e58466 p.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/cldare/articles/DARE-12013018219/frame.html.	Wrong population
270.	Zhou Q, Yang J, Zhang X, Chen H, Su J, Tu HY, et al. Overall survival in patients with advanced non-small cell lung cancer harboring concomitant EGFR mutations and ALK rearrangements: A cohort study. Journal of Clinical Oncology Conference. 2014;32(15 SUPPL. 1).	Abstract with insufficient information
271.	Zhu Q, Hu H, Jiang F, Guo CY, Yang XW, Liu X, et al. Meta-analysis of incidence and risk of severe adverse events and fatal adverse events with crizotinib monotherapy in patients with ALK-positive NSCLC. Oncotarget. 2017:17.	Relevant SLR handsearched
272.	Zhu Q, Hu H, Weng DS, Zhang XF, Chen CL, Zhou ZQ, et al. Pooled safety analyses of ALK-TKI inhibitor in ALK-positive NSCLC. BMC Cancer. 2017;17(1):412.	Relevant SLR handsearched

Source: CS Appendix, p37-53, Table 10 (Takeda Ltd)

Table 57 Publications excluded based on screening of full text documents (Stage II)

No.	Reference	Reason for exclusion
1.	Afanasjeva J, Hui RL, Spence MM, Chang J, Schottinger JE, Millares M, et al. Identifying Subsequent Therapies in Patients with Advanced Non-Small Cell Lung Cancer and Factors Associated with Overall Survival. Pharmacotherapy. 2016;36(10):1065-74.	<10 patients
2.	Bala S, Gundeti S, Linga V, Maddali L, Digumarti R, Uppin S. Clinicopathological features and outcomes in advanced nonsmall cell lung cancer with tailored therapy. Indian Journal of Medical and Paediatric Oncology. 2016;37(4):242-50.	<10 patients
3.	Barlesi F, Mazieres J, Merlio JP, Debieuvre D, Mosser J, Lena H, et al. Routine molecular profiling of patients with advanced non-small-cell lung cancer: Results of a 1-year nationwide programme of the French Cooperative Thoracic Intergroup (IFCT). The Lancet. 2016;387(10026):1415-26.	<10 patients
4.	Berge EM, Lu X, Maxson D, Baron AE, Gadgeel SM, Solomon BJ, et al. Clinical benefit from pemetrexed before and after crizotinib exposure and from crizotinib before and after pemetrexed exposure in patients with anaplastic lymphoma kinase-positive non-small-cell lung cancer. Clinical Lung Cancer. 2013;14(6):636-43.	<10 patients

No.	Reference	Reason for exclusion
5.	Blackhall F, Kim DW, Besse B, Nokihara H, Han JY, Wilner KD, et al. 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.	<10 patients
6.	Blackhall F, Kim DW, Besse B, Nokihara H, Han JY, Wilner KD, et al. 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 cancer2014; 9(11):[1625-33 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/600/CN-01068600/frame.html.	<10 patients
7.	Browning ET, Weickhardt AJ, Camidge DR. Response to crizotinib rechallenge after initial progression and intervening chemotherapy in ALK lung cancer. Journal of thoracic oncology. 2013;8(3):e21-e2.	<10 patients
8.	Cui S, Zhao Y, Dong L, Gu A, Xiong L, Qian J, et al. Is there a progression-free survival benefit of first-line crizotinib versus standard chemotherapy and second-line crizotinib in ALK-positive advanced lung adenocarcinoma? A retrospective study of Chinese patients. Cancer Medicine. 2016;5(6):1013-21.	<10 patients
9.	de Castria Tiago B, da Silva Edina MK, Gois Aecio FT, Riera R. Cisplatin versus carboplatin in combination with third-generation drugs for advanced non-small cell lung cancer2013; (8). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD009256.pub2/abstract.	Outcomes not reported for eligible subgroup
10.	De Marinis F, Ardizzoni A, Fontanini G, Grossi F, Cappuzzo F, Novello S, et al. Management of italian patients with advanced non-small-cell lung cancer after second-line treatment: Results of the longitudinal phase of the life observational study. Clinical Lung Cancer. 2014;15(5):338-45.e1.	Outcomes not reported for eligible subgroup
11.	Ellis PM, Blais N, Soulieres D, Ionescu DN, Kashyap M, Liu G, et al. A systematic review and Canadian consensus recommendations on the use of biomarkers in the treatment of non-small cell lung cancer. Journal of thoracic oncology. 2011;6(8):1379-91.	Outcomes not reported for eligible subgroup
12.	Gandhi L, Drappatz J, Ramaiya NH, Otterson GA. High-dose pemetrexed in combination with high-dose crizotinib for the treatment of refractory CNS metastases in ALK-rearranged non-small-cell lung cancer. Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer. 2013;8(1):e3-5.	Outcomes not reported for eligible subgroup
13.	Gobbini E, Galetta D, Tiseo M, Graziano P, Rossi A, Bria E, et al. Molecular profiling in Italian patients with advanced non-small-cell lung cancer: An observational prospective study. Lung Cancer. 2017;111:30-7.	Wrong patient population
14.	Gobbini E, Gregorc V, Galetta D, Riccardi F, Bordi P, Scotti V, et al. Molecular profiling in advanced non-small-cell lung cancer: Preliminary data of an Italian observational prospective study. Journal of thoracic oncology. 2017;12 (1 Supplement 1):S973-S4.	Wrong patient population
15.	Gomez DR, Blumenschein GR, Lee JJ, Hernandez M, Ye R, Camidge DR, et al. Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study2016; 17(12):[1672-82 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/465/CN-01300465/frame.html.	Wrong patient population
16.	Guerin A, Sasane M, Wakelee H, Zhang J, Culver K, Dea K, et al. Treatment, overall survival, and costs in patients with ALK -positive non-small-cell lung cancer after crizotinib monotherapy. Current Medical Research and Opinion. 2015;31(8):1587-97.	Wrong patient population
17.	Harputluoglu H, Kaplan N, Dikilitas M, Yagar Y. Factors affecting survival in non-small cell lung cancer patients with brain metastasis Beyin Metastazi Olan Kucuk Hucre Disi Akciger Kanser Hastalarinda Sagkalimi Etkileyen Faktorler. UHOD - Uluslararasi Hematoloji-Onkoloji Dergisi. 2016;26(4):199-205.	Wrong patient population
18.	Harrison JP, Goncalves T, Kim H. Systemic treatments in advanced non-small cell lung cancer (NSCLC): A systematic review. Asia-Pacific Journal of Clinical Oncology. 2014;10:158.	Wrong patient population
19.	Kayaniyil S, Hurry M, Wilson J, Wheatley-Price P, Melosky B, Rothenstein J, et al. Treatment patterns and survival in patients with ALK-positive non-small-cell lung cancer: A Canadian retrospective study. Current Oncology. 2016;23(6):e589-e97.	Wrong patient population
20.	Kim YH, Hirabayashi M, Togashi Y, Hirano K, Tomii K, Masago K, et al. Phase II study of carboplatin and pemetrexed in advanced non-squamous, non-small-cell lung cancer: Kyoto thoracic oncology research group trial 0902. Cancer Chemotherapy and Pharmacology. 2012;70(2):271-6.	Wrong patient population
21.	Lim SH, Yoh KA, Lee JS, Ahn MJ, Kim YJ, Kim SH, et al. Characteristics and outcomes of ALK+ non-small cell lung cancer patients in Korea. Asia-Pacific Journal of Clinical Oncology. 2017;13(5):e239-e45.	Wrong patient population

No.	Reference	Reason for exclusion
22.	Pandey AV, Phillip DS, Noronha V, Joshi A, Janu A, Jambekar N, et al. Maintenance pemetrexed in nonsmall cell lung carcinoma: Outcome analysis from a tertiary care center. Indian Journal of Medical and Paediatric Oncology. 2015;36(4):238-42.	Wrong patient population
23.	Park J, Yamaura H, Yatabe Y, Hosoda W, Kondo C, Shimizu J, et al. Anaplastic lymphoma kinase gene rearrangements in patients with advanced-Stage non-small-cell lung cancer: CT characteristics and response to chemotherapy. Cancer Medicine. 2014;3(1):118-23.	Wrong patient population
24.	Park S, Park TS, Choi CM, Lee DH, Kim SW, Lee JS, et al. Survival Benefit of Pemetrexed in Lung Adenocarcinoma Patients With Anaplastic Lymphoma Kinase Gene Rearrangements. Clinical Lung Cancer. 2015;16(5):e83-9.	Wrong patient population
25.	Shaw AT, Varghese AM, Solomon BJ, Costa DB, Novello S, Mino-Kenudson M, et al. Pemetrexed-based chemotherapy in patients with advanced, ALK-positive non-small cell lung cancer. Annals of oncology. 2013;24(1):59-66.	Wrong patient population
26.	Tufman AL, Edelmann M, Gamarra F, Reu S, Borgmeier A, Schrodl K, et al. Preselection based on clinical characteristics in German non-small-cell lung cancer patients screened for EML4-ALK translocation. Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer. 2014;9(1):109-13.	Wrong publication type
27.	Wang F, Mishina S, Takai S, Le TK, Ochi K, Funato K, et al. Systemic Treatment Patterns With Advanced or Recurrent Non-small Cell Lung Cancer in Japan: A Retrospective Hospital Administrative Database Study. Clinical Therapeutics. 2017;39(6):1146-60.	Wrong study design
28.	Zhang J, Zhou Z, Cai X, Signorovitch J. Comparative efficacy of treatments for previously treated advanced or metastatic non-small cell lung cancer (NSCLC): A network meta-analysis. Value in Health. 2015;18 (7):A436-A7.	Wrong study design
29.	Zhao J, Zhang K, Zhang L, Wang H. Clinical Efficacy of Crizotinib in Advanced ALK Positive Non-small Cell Lung Cancer2015; 18(10):[616-20 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/346/CN-01169346/frame.html http://www.lungca.org/index.php?journal=01&page=article&op=download&path%5B%5D=10.3779%2Fj.issn.1009-3419.2015.10.03&path%5B%5D=5195.	Wrong study design

Source: CS Appendix, p53-55, Table 11 (Takeda Ltd)

Appendix 4. Economic studies included in review

Table 58 Summary of data extracted from studies included in the economic SLR

Study	Year	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
CADTH, Zykadia for NSCLC Re-submission (62)	2017	AUC model with three health states: progression free, post-progression and death. Canadian perspective Efficacy data were derived from ASCEND-5 and the published literature.	ALK+ locally advanced or metastatic NSCLC who have progressed on or who were intolerant to crizotinib	Ceritinib vs. chemotherapy Submitted incremental QALYs by health state: Progression free = 0.24 Progressed disease = 0.35 EGP estimates Progression free = 0.24 Progressed disease = 0.23	Ceritinib vs. chemotherapy Submitted incremental costs = $70,293 EGP estimates = $75,766 - $98,829	Ceritinib vs. chemotherapy Submitted ICER = $118,676 EGP estimates = $159,750 - $208,377 depending on whether treatment is until progression or until discontinuation
CADTH, Zykadia for NSCLC Original submission(63)	2015	AUC model with three health states: progression free, post-progression and death. Canadian perspective Unclear where efficacy data obtained from	ALK+ locally advanced or metastatic NSCLC	Incremental QALYs vs pemetrexed = 0.44	Incremental costs vs pemetrexed = $34,906	Ceritinib vs pemetrexed = $80,100 EGP's best estimate = $196,335 - $211,759 Ceritinib vs. historical control = $104,436 EGP's best estimate = $164,503 - $166,201 Ceritinib vs. BSC = $149,117 EGP's best estimate = $219,353 - $222,335 Ceritinib vs. docetaxel = $149,780 EGP's best estimate = $241,396 - $244,906

Study	Year	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
CADTH, Alecensaro for NSCLC (with CNS metastases)(64)	2017	AUC model with three health states: progression free, post-progression and death. Canadian perspective Efficacy data were obtained from a pooled subset of NP28761 and NP28673 and the published literature.	ALK+ locally advanced or metastatic NSCLC patients who have progressed on or are intolerant to crizotinib and have CNS metastases	Submitted incremental QALYs by health state: Progression free = 0.762 Progressed disease = 0.674	Submitted incremental costs = $156,501	Submitted ICER = $108,958 EGP estimates = $67,993 - $417,128
Carlson et al.(65)	2017	AUC model with three health states: progression free, post-progression and death. US perspective Efficacy data were derived from NP28761 and NP28673 for alectinib and ASCEND-1 and ASCEND-2 for ceritinib	ALK+ locally advanced or metastatic NSCLC who have progressed on or who are intolerant to crizotinib	Total QALYs Alectinib = 1.42 Ceritinib = 0.98 Incremental = 0.44	Total costs (USD $) Alectinib = $255,413 Ceritinib = $241,545 Incremental = $13,868	ICER per QALY gained = $31,180 ICER per LYG = $19,313
Saramago et al.(66)	2017	State transition Markov model Portuguese societal perspective	ALK+ NSCLC	NR	NR	ICER per QALY gained = €46,691 ICER per LYG = €29,326

Study	Year	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Carlson *et al*.(67)	2016	AUC model with three health states: progression free, post-progression and death. US payer perspective Efficacy data were derived from NP28761 and NP28673 for alectinib and ASCEND-1 and ASCEND-2 for ceritinib	ALK+ locally advanced or metastatic NSCLC who have progressed on or who are intolerant to crizotinib	Total QALYs Alectinib = 1.42 Ceritinib = 0.98 Incremental = 0.44	Total costs (USD $) Alectinib = $255,430 Ceritinib = $241,627 Incremental = $13,803	ICER per QALY gained = $31,034 ICER per LYG = $19,223
Hurry *et al*.(68)	2016	AUC partitioned survival model with three health states: stable, progressive and death Canadian healthcare perspective Efficacy data from ASCEND-1 and ASCEND-2 for ceritinib and from published clinical trials in NSCLC population and a Canadian retrospective chart study for comparators	ALK+ NSCLC	Total QALYs Ceritinib = 0.86 BSC = 0.33 Pemetrexed = 0.86 Historical control = 0.17 Incremental ceritinib vs. BSC = 0.53 Pemetrexed = 0.44 Historical controls = 0.69	Total costs (CAD $) Ceritinib = $89,740 BSC = $10,686 Pemetrexed = $89,740 Historical control = $17,658 Incremental ceritinib vs. BSC = $79,055 Pemetrexed = $34,906 Historical control = $72,083	ICER per QALY gained ceritinib vs. BSC = $149,117 Pemetrexed = $80,100 Historical control = $104,436 ICER per LYG ceritinib vs. BSC = $80,818 Pemetrexed = $40,748 Historical control = $55,202

Study	Year	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
National Institute for Health and Care Excellence (NICE) TA395 (ceritinib) (26)	2016	AUC partitioned survival model with three health states: progression free, progressed disease and death UK NHS perspective Efficacy data from ASCEND-1 and ASCEND-2 for ceritinib and from published clinical trials in NSCLC for comparator	ALK+ advanced or metastatic NSCLC who have progressed on or who are intolerant to crizotinib	Total QALYs Ceritinib = 1.08 BSC = 0.25 Incremental = 0.83	Total costs Ceritinib = £59,155 BSC = £7,203 Incremental = £51,952	ICER per QALY gained (without PAS) = £62,456 Updated ICER (without PAS) = £86,364
SMC No. (1097/15) (ceritinib) (69)	2015	AUC partitioned survival model with three health states: progression free, progressed disease and death Efficacy data from ASCEND-1 and ASCEND-2 for ceritinib and from published clinical trials in NSCLC for comparator	ALK+ advanced or metastatic NSCLC who have progressed on or who are intolerant to crizotinib	NR	NR	ICER per QALY (with PAS) = £50,908

Study	Year	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
NICE TA406 (crizotinib) (61)	2016	AUC partitioned survival model with three health states: progression free, progressed disease and death UK NHS perspective Efficacy data from PROFILE 1014 for crizotinib and chemotherapy.	Untreated ALK+ advanced NSCLC	Marked CiC	Total costs Crizotinib = £79,884 Pemetrexed + cisplatin/carboplatin = £21,480 Incremental = £58,404	ICER per QALY gained marked CiC Updated ICER per QALY = £47,291
Scottish Medicines Consortium (SMC) No. (1152/16) (crizotinib) (70)	2016	Markov model with three health states: progression-free, progressed disease and death Efficacy data from PROFILE 1014 for crizotinib and chemotherapy.	Untreated ALK+ advanced NSCLC	NR	NR	ICER per QALY gained (with PAS) = £48,355
NICE TA422 (crizotinib) (71)	2016	AUC partitioned survival model with three health states: progression free, progressed disease and death UK NHS perspective Efficacy data from PROFILE 1007 for crizotinib	Previously treated ALK+ advanced NSCLC	Total QALYs Crizotinib = CiC Chemotherapy = 0.84	Total costs Crizotinib = CiC Chemotherapy = £8,015	ICER per QALY gained marked CiC The most plausible ICER for crizotinib compared with docetaxel being less than £50,000 per QALY gained including the revised PAS

Study	Year	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Scottish Medicines Consortium (SMC) SMC No. (865/13) and re-submission(72)	2013	Markov model with three health states: disease before progression, disease after progression and dead Efficacy data from PROFILE 1005 and PROFILE 1007 for crizotinib	Previously treated ALK+ advanced NSCLC	Total QALYs Crizotinib = 1.95 Docetaxel = 0.98 BSC = 0.59 Incremental crizotinib vs. docetaxel = 0.97 Incremental crizotinib vs. BSC = 1.36	Incremental cost crizotinib vs. docetaxel = £40,954 Incremental cost crizotinib vs. BSC = £49,806	ICER per QALY gained crizotinib vs. docetaxel = £42,295 ICER per QALY gained crizotinib vs. BSC = £36,691
Balu *et al*. (2015)(73)	2015	AUC partitioned survival model Mexican perspective Efficacy data from ASCEND-1 for ceritinib and naïve indirect comparisons	ALK+ NSCLC	Total QALYs Ceritinib = 2.49 Crizotinib = 1.62 Pemetrexed = 0.64 Docetaxel monotherapy = 0.68 Paclitaxel = 0.74	Costs in Mexican Pesos	ICER ceritinib vs. crizotinib = MXN 375,458 ICER ceritinib vs. paclitaxel = MSN 610,125 NB: does not specify if ICER per QALY or per LYG
Zhou et al.(74)	(2015 a)	AUC partitioned survival model with three health states: stable disease, progressive disease and death UK NHS and PSS perspective Efficacy data were obtained from ASCEND-1, ASCEND-2 and ASCEND-3 for ceritinib and from indirect comparisons for comparators	ALK+ advanced or metastatic NSCLC	Total QALYs Ceritinib = 0.94 BSC = 0.17 Docetaxel = 0.36 Pemetrexed = 0.39 Incremental ceritinib vs. BSC = 0.76 Docetaxel = 0.58 Pemetrexed = 0.54	Total costs Ceritinib = £44,043 BSC = £5,165 Docetaxel = £9,153 Pemetrexed = £20,597 Incremental ceritinib vs. BSC = £38,878 Docetaxel = £34,890 Pemetrexed = £23,447	ICER per QALY gained ceritinib vs. BSC = £50,997 Docetaxel = £60,556 Pemetrexed = £43,221 ICER per LYG ceritinib vs. BSC = £26,403 Docetaxel = £32,086 Pemetrexed = £21,562

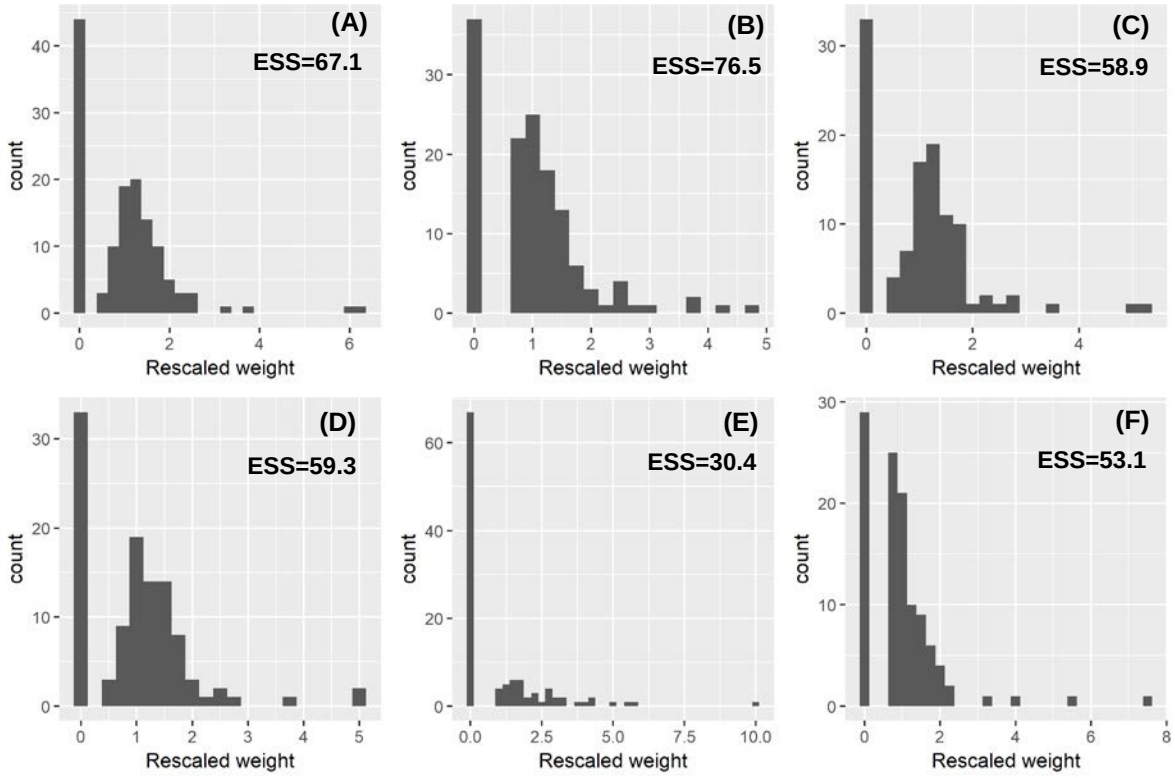
Study	Year	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Zhou et al.(75)	(2015 b)	AUC partitioned survival model with three health states: stable disease, progressive disease and death Canadian perspective Efficacy data were obtained from ASCEND-1 and ASCEND-2 for ceritinib and from PROFILE 1007 and published literature for comparators.	ALK+ advanced or metastatic NSCLC previously treated with crizotinib	Total QALYs Ceritinib = 0.86 BSC = 0.33 Pemetrexed = 0.43 Historical controls = 0.17 Incremental ceritinib vs. BSC = 0.53 Pemetrexed = 0.44 Historical controls = 0.69	Total costs (CAD $) Ceritinib = $89,740 BSC = $10,686 Pemetrexed = $54,834 Historical control = $17,658 Incremental ceritinib vs. BSC = $79,055 Pemetrexed = $32,569 Historical control = $72,082	ICER per QALY gained ceritinib vs. BSC = $149,117 Pemetrexed = $80,100 Historical controls = $104,436 ICER per LYG ceritinib vs. BSC = $80,818 Pemetrexed = $40,748 Historical control = $55,202

Abbreviations: ALK, anaplastic lymphoma positive; AUC, area under the curve; BSC, best supportive care; CADTH, Canadian Agency for Drugs and Technologies in Health; CiC, commercial in confidence; EGP, Economic Guidance Panel; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NSCLC, non-small-cell lung cancer; PSS, Personal Social Services; QALYs, quality-adjusted life years; SMC, Scottish Medicines Consortium; UK, United Kingdom

Source: Takeda submission. Section B, page 83-90

Appendix 5. Weight re-scaling from MAIC analyses

Figure 26. Histogram of rescaled weights from MAIC analyses



Notes: (A) Pooled ALTA/Study 101 vs ASCEND-2 MAIC [reduced]*; (B) Pooled ALTA/Study 101 vs ASCEND-5 MAIC [reduced]*; (C) ALTA vs ASCEND-2 MAIC [full]; (D) ALTA vs ASCEND-2 MAIC [reduced]; (E) ALTA vs ASCEND-5 MAIC [full]; (F) ALTA vs ASCEND-5 MAIC [reduced]; *MAIC [full] analysis defaults to MAIC [reduced] analysis due to lack of covariate data available in Study 101.

Source: CS Appendix, p76, Figure 11 (Takeda Ltd)

It should be noted that updated versions of these rescaled weight graphs for the September 2017 ALTA data cut were not provided in the CS Addendum (revision document), so those from the original CS are shown above (February 2017 ALTA data cut).

Appendix 6. Heterogeneity in Cox regression

Figure 27. Comparison of confidence intervals from Cox regression in R dependent on whether heterogeneity is taken account of in sampling probabilities (by use of sandwich estimators).

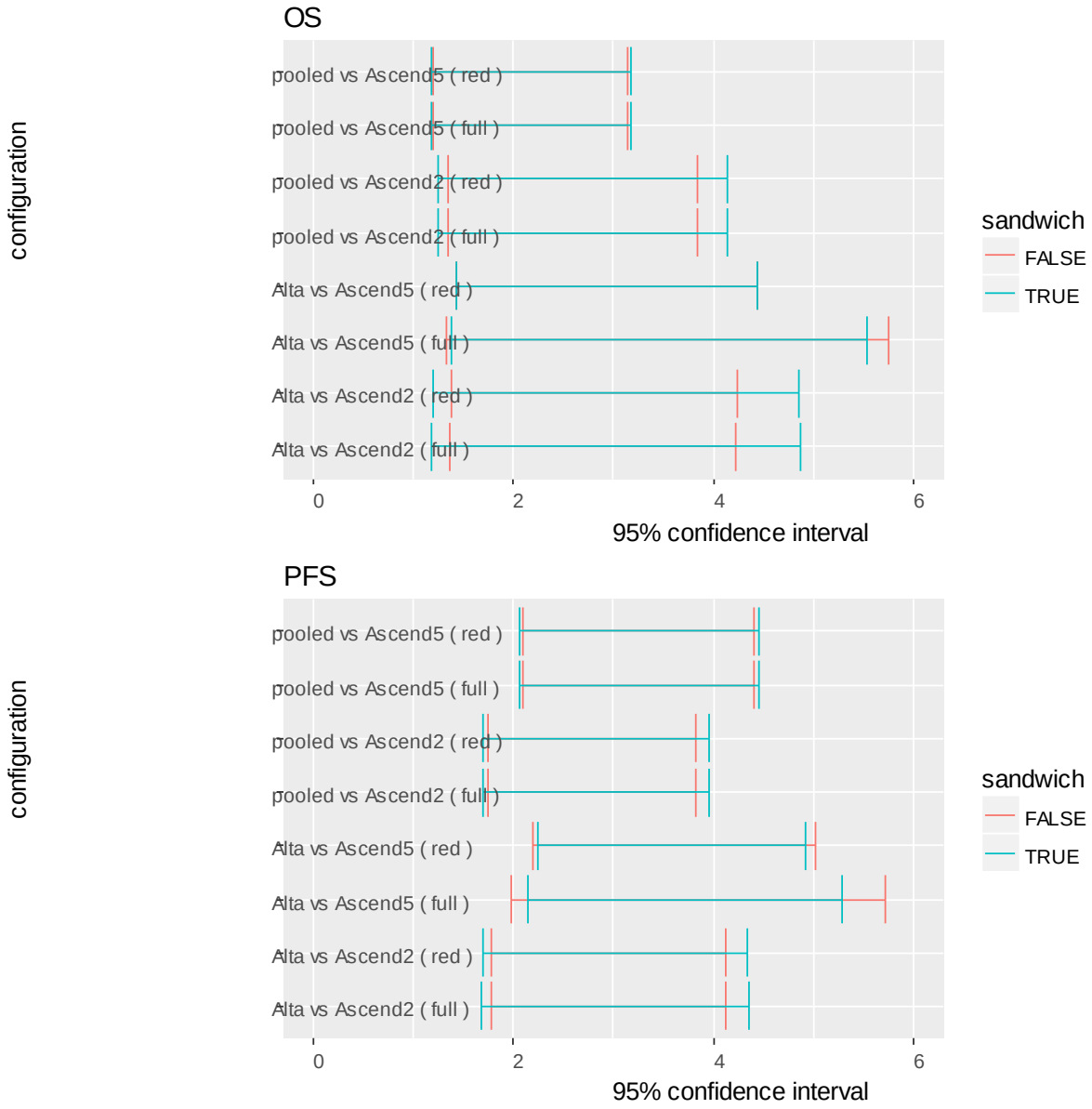


Figure 28. Comparison of confidence intervals under estimation with coxph() in R 3.5 versus stcox() in Stata 14.