Single Technology Appraisal

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

Committee Papers

HIGHLY CONFIDENTIAL

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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The final scope and final matrix are available to view on the NICE website.

1. **Pre-Meeting Briefing (PMB)**

2. **Company submission** from Takeda

3. **Clarification letters**
   - NICE request to the company for clarification on their submission
   - Company response to NICE's request for clarification

   The company addendum to the clarification response contains updated information from a newer data-cut (superseding some of the results in the original submission).

4. **Patient group, professional group and NHS organisation submission** from:
   - Roy Castle Lung Cancer Foundation
   - British Thoracic Oncology Group
   - British Thoracic Society
   - NHS England

5. **Expert personal perspectives** from:
   - Dr Yvonne Summers, Consultant Medical Oncologist – clinical expert, nominated by Takeda
   - Karen Clayton, Macmillan Lung CNS – patient expert, nominated by National Lung Cancer Forum for Nurses (NLCFN)

6. **Evidence Review Group report** prepared by Peninsula Technology Assessment Group (PenTAG)

7. **Evidence Review Group report – factual accuracy check**

8. **Evidence Review Group report – erratum**

9. **Evidence Review Group report – addendum**

Pre-meeting briefing

Brigatinib for treating ALK-positive advanced non-small-cell lung cancer after crizotinib (ID1328)

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

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

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

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

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

Abbreviations

ACP	The Association of Cancer Physicians
ALK	Anaplastic lymphoma kinase
ALK+	Anaplastic lymphoma kinase positive
BSC	Best supportive care
BTOG	The British Thoracic Oncology Group
EoL	End of life
HRQoL	Health related quality of life
INV	Investigator assessed
IRC	Independent review committee assessed
ITC	Indirect treatment comparison
MAIC	Matching-adjusted indirect comparison
NCRI	National Cancer Research Institute
NSCLC	Non small cell lung cancer
OS	Overall survival
PFS	Progression free survival
QALY	Quality-adjusted life years
RCP	Royal College of Physicians
RCR	Royal College of Radiologists
TKI	Tyrosine kinase inhibitor
ToT	Time on treatment
WCLC	World Conference on Lung Cancer

Key issues – clinical effectiveness

- **All studies were single-arm studies**
- **ITC analyses:** How reliable are the results from the ITC analyses?
  - Which is more relevant: ITC (Study 101) or ITC (ACEND-5)?
- **Overall survival extrapolation:** Is the selection of statistical distribution reasonable for OS?
  - Is Gompertz an appropriate choice of distribution?
  - Is the impact on end of life designation justifiable?
- **Progression-free survival extrapolation:** Is the selection of statistical distribution reasonable for PFS?
  - In combination with the distribution selected for OS, is the impact on end of life designation justifiable?

Key issues – cost effectiveness

- **Time on treatment:** Is treatment continued following disease progression?
  - For how long is treatment given following progression?
- **Treatment benefit beyond progression:** Is a treatment benefit beyond progression experienced in this patient population?
  - How long is the treatment benefit sustained from treatment initiation?
- **Costs**: Should the model account for drug wastage? Should the model account for drug administration costs?
- **Utilities:** Is a utility estimate of 0.643 for progressed disease applicable to patients receiving treatment at 2nd line?
  - Should the disease impact on CNS be taken into account?
- **End of life criteria:** Does brigatinib meet the end of life criteria?
- **Innovation:** Is brigatinib innovative? Are any benefits not captured in the model?

Non-small cell lung cancer (NSCLC)
Disease background

- Lung cancer → approx. 36,000 people diagnosed in England in 2016
- NSCLC = estimated 88.5% of lung cancer cases in England in 2016
- NSCLC highly heterogeneous with different driver mutations (including anaplastic lymphoma kinase (ALK) gene rearrangement)
- ALK+ status = ~3.8% advanced* NSCLC population
- Majority ALK+ NSCLC = adenocarcinomas
- People with ALK+ NSCLC tend to be younger & without smoking history → likely to be diagnosed later, with more progressed disease (brain metastases)
- Crizotinib = oral TKI recommended for untreated (TA406) & previously treated (TA422) ALK+ NSCLC
  - But acquired resistance, suboptimal target inhibition & poor CNS penetration → ~70% people treated with crizotinib experience brain metastases

**Updated post committee meeting to correct for factual inaccuracy*

Patient perspective

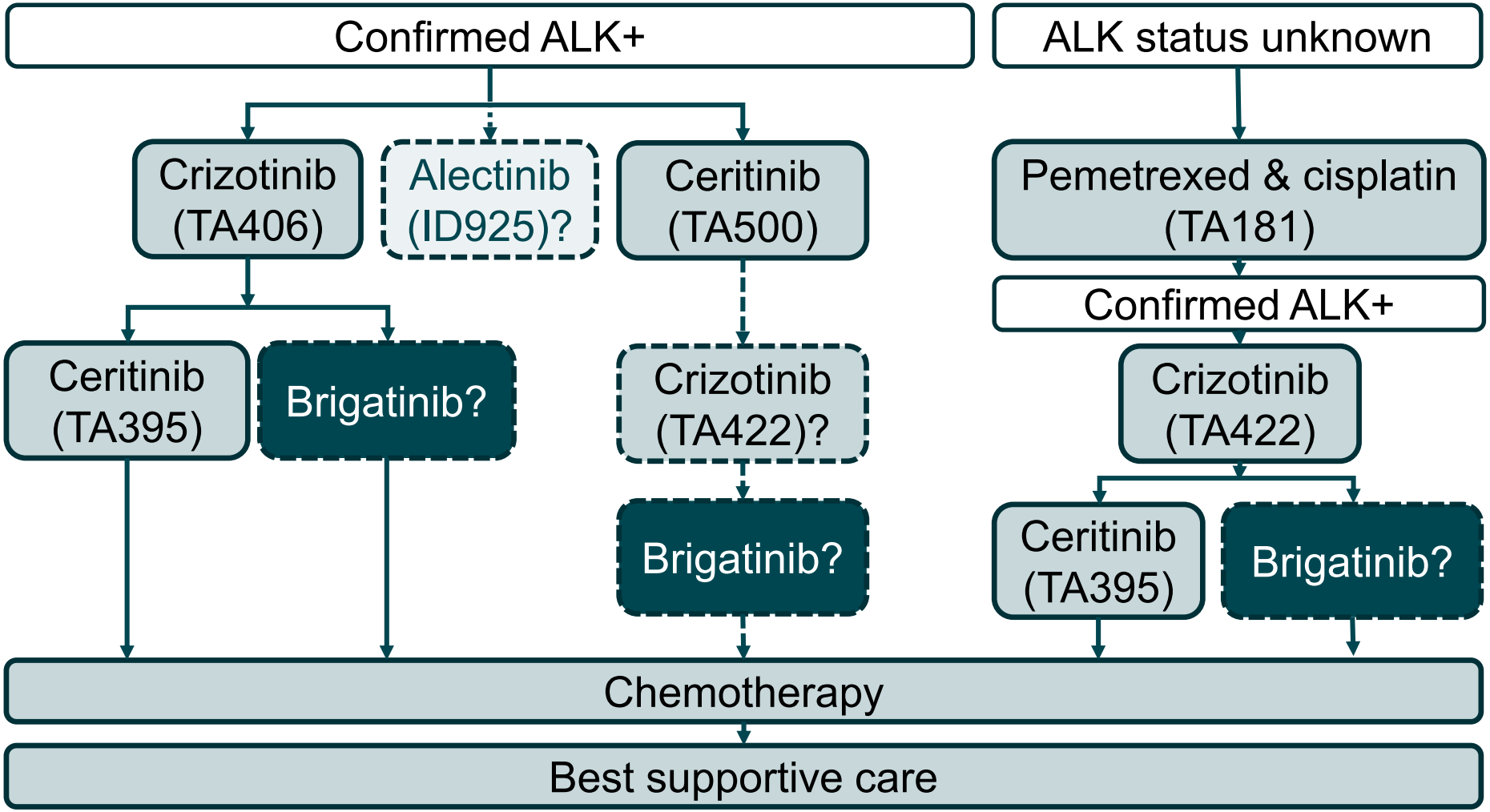
- **Submissions: Roy Castle Lung Cancer Foundation & National Lung Cancer Forum for Nurses**
- ALK+ NSCLC is a debilitating disease → patients worry about poor outcomes
- Carers advise that supporting a patient with NSCLC is stressful → patient's symptoms are apparent and debilitating
- Improved QoL, symptom management & small extension in duration of life = 'of considerable significance to the individual and their family'
- End of life therapies are of 'crucial importance to patients and relatives'
- Anecdotal patient experience of brigatinib = generally well tolerated & common side effects that are easily managed clinically
- Oral therapy eases administration
- Older people and people having a learning disability may benefit more from brigatinib

Clinician perspectives

- **Submissions: Consultant Medical Oncologist (The Christie), British Thoracic Society & Joint response from BTOG/NCRI/RCP/RCR/ACP**
- Unmet clinical need due to acquired resistance to available ALK inhibitors
- Poor prognosis → *'urgent need'* for more treatment options
- If approved, brigatinib would be second line ALK-TKI *'treatment of choice'*
- Expect brigatinib to ↑ OS, HRQoL & tolerability (vs crizotinib & ceritinib)
- Improved tolerability compared to ceritinib → ↓ need for dose reduction & therefore ↓ wastage
- Brigatinib's protective activity in CNS may not be adequately captured by standard QoL measures
- Innovative treatment → Effectiveness in CNS, improved tolerability & potential suppression of resistance
- First line crizotinib usage likely to ↓ over time (alectinib/ceritinib more efficacious) → ↓ population progressing on crizotinib suitable for brigatinib will ↓
- UK audit data available - will be presented at conference (WCLC, Sept 2018)

Current treatment for ALK+ NSCLC

based on current NICE guidance



*Alectinib = ongoing appraisal (expected publication August 2018)

Brigatinib (Alunbrig)
Takeda

Mechanism of action	Tyrosine kinase inhibitor (TKI)
Anticipated marketing authorisation	Indicated as monotherapy for the treatment of adult patients with ALK+ advanced NSCLC previously treated with crizotinib
Administration	Oral
Dose	90mg once daily for first 7 days, then 180mg once daily
Duration of treatment	Continue as long as clinical benefit is observed
Cost (list price)	£4,900 per 28 tablet pack (28 day supply) Cost of average treatment course = £93,680* An application for a patient access scheme has been submitted to Department of Health. This provides a simple discount to list price.

**Updated post committee meeting to correct for factual inaccuracy*

Decision problem

	Scope	Company
Population	People with ALK+ advanced NSCLC previously treated with crizotinib	Trial inclusion = ≥18 years → 'Adults'
Intervention	Brigatinib	✓
Comparators	Ceritinib	✓
Outcomes	• Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health-related quality of life	✓

ERG comment: Satisfied that the company addressed the decision problem

Clinical evidence for brigatinib

- No head-to-head trial data of brigatinib vs ceritinib
- Single arm trials within scope: ALTA & Study 101 subgroup
- Study 101 = phase 1 dose escalation + phase 2 extension with multiple cohorts → 1 cohort of 25 patients within scope (hereafter = Study 101)

	ALTA	Study 101
Design	Single arm, open-label, phase 2	
Intervention	Brigatinib 180mg once daily (7 day of 90mg once daily)	
Comparator	Brigatinib 90mg once daily	-
Population	Adults with locally advanced or metastatic ALK+ NSCLC, previously treated with crizotinib	
1◦ outcome	ORR (investigator, RECIST)	
2◦ outcomes	PFS, OS, CNS response (PFS, ORR), duration of response	
	HRQoL, Adverse effects, ORR (IRC), time to response	-

Key baseline characteristics

Brigatinib trials

		ALTA: 180mg n=110	ALTA: 90mg n=112	Study 101 n=25
Locations, number of sites		USA: 15, Canada: 1, Europe: 38 (inc. UK:1), Australia: 6, Asia: 11		USA & Spain:9
Age	Median (range)	56.5 (20-81)	50.5 (18-82)	57.0 (32-73)
Gender	Male, n (%)	46 (41.8)	50 (44.6)	14 (56.0)
Race	Asian, n (%) Non-Asian, n (%) Other, n (%)	30 (27.3) 76 (69.1) 4 (3.6)	39 (34.8) 72 (64.3) 1 (0.9)	3 (12.0) 20 (80.0) 2 (8.0)
ECOG PS	0 or 1, n (%) 2, n (%)	101 (91.8) 9 (8.2)	105 (93.8) 7 (6.3)	25 (100) 0 (0)
Brain metastases, n (%)		74 (67.3)	80 (71.4)	18 (72.0)
Prior brain radiotherapy, n (%)		46 (41.8)	50 (44.6)	7 (28.0)
Prior therapy	Crizotinib, n (%) Pltnm chemo, n (%) Any chemo, n (%)	110 (100) 80 (72.7) 81 (73.6)	112 (100) NR 83 (74.1)	25 (100) NR 17 (68.0)

NR = not reported

Key clinical effectiveness results - brigatinib

Months (95% CI)	ALTA: 180mg	ALTA: 90mg	Study 101
Median follow-up	24.3 months	19.6 months	Not reported
Median OS	34.1 (27.7, NR)	29.5 (18.2, NR)	NR (1.4, 24.3)
Investigator-assessed outcomes:			
ORR (%)*	56.4 (45.2, 67.0)	45.5 (34.8, 56.5)	76 (54.9, 90.6)
Median PFS	15.6 (11.1, 21.0)	9.2 (7.4, 11.1)	16.3 (9.2, NE)
Median DOR	13.8 (10.2, 19.3)	12.0 (9.2, 17.7)	26.1 (7.9, 26.1)
IRC-assessed outcomes:			
ORR (%)	56.4 (46.6, 65.8)	50.9 (41.3, 60.5)	-
Median PFS	16.7 (11.6, 21.4)	9.2 (7.4, 12.8)	-
Median DOR	15.7 (12.8, 21.8)	16.4 (7.4, 24.9)	-

*97.5% CI for ALTA ORR (investigator), NR = not reached, NE = not estimable

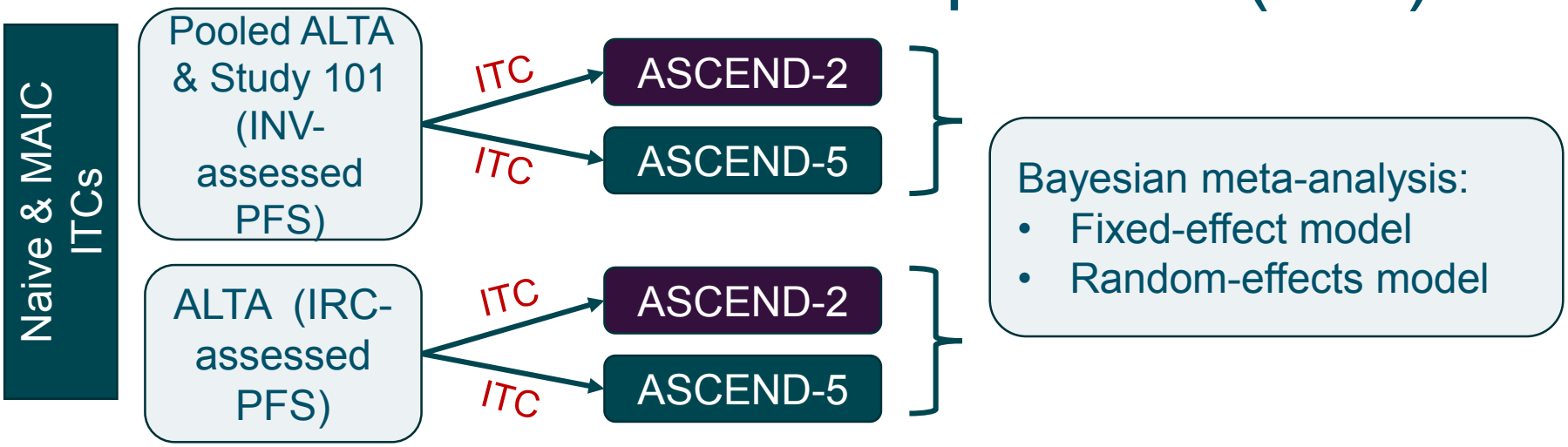
ERG comment: Company could have calculated median Study 101 follow-up & median overall survival from individual patient data

Clinical evidence for ceritinib

- No head-to-head trial data of brigatinib vs ceritinib
- Estimate efficacy using unanchored indirect treatment comparisons (ITCs)
- ASCEND-2 & ASCEND-5 trials used to represent ceritinib evidence

	ASCEND-2 (n=140)	ASCEND-5 (n=231)
Design	Single-arm	RCT
Intervention	Ceritinib 750mg daily	
Comparator	-	Docetaxel or pemetrexed
Population	ALK+ NSCLC who received prior treatment with ≥1 previous platinum-based chemotherapy regimen and previous crizotinib	
1◦ outcome	ORR (investigator assessed)	PFS (IRC-assessed)
2◦ outcomes	OS, ORR (ASC-5), PFS (ASC-2), DCR, DOR, TTR, Intracranial response, safety, QoL/patient reported outcomes	
	(Outcomes investigator assessed)	(Outcomes IRC assessed)

Indirect treatment comparison (ITC)

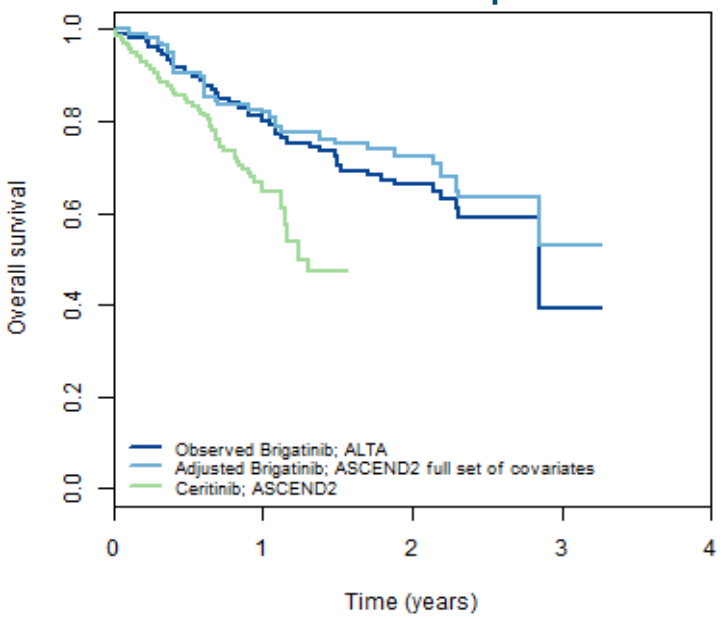


- ITCs of brigatinib data (from ALTA and pooled ALTA & Study 101) compared to ceritinib data (from ASCEND-2 and ASCEND-5)
- Results of ITCs meta-analysed to estimate clinical effectiveness
- Naive ITC = Data treated as 'head-to-head' trials, no adjustment for differences in study populations
- Unanchored MAIC = Individual patient data (IPD) used to 'weight' the data according to a set of identified prognostic covariates → adjusts for imbalances in study populations
- MAIC analyses conducted for 'full' and 'reduced' set of covariates

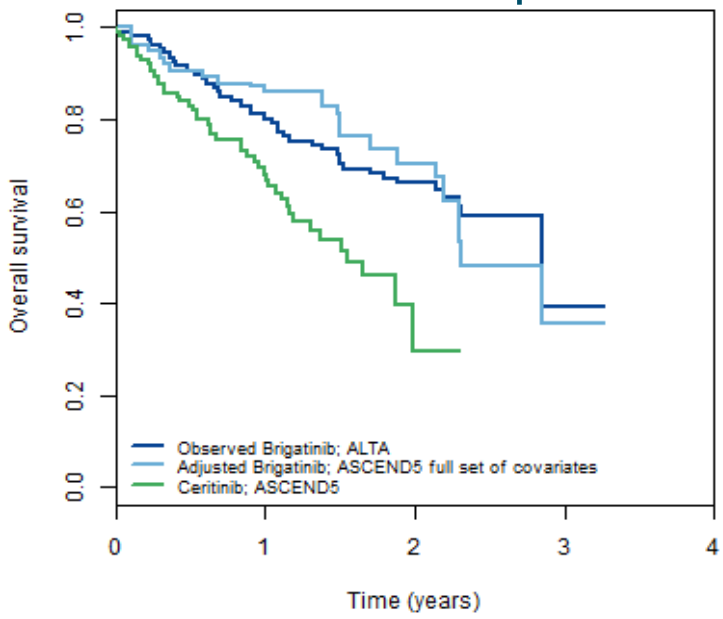
ERG comment: the ITC analysis is broadly appropriate. Considerably consistent results are produced using each analytical strategy to meta-analyse the ITC analyses

Overall survival ITC results

ASCEND-2 vs pooled



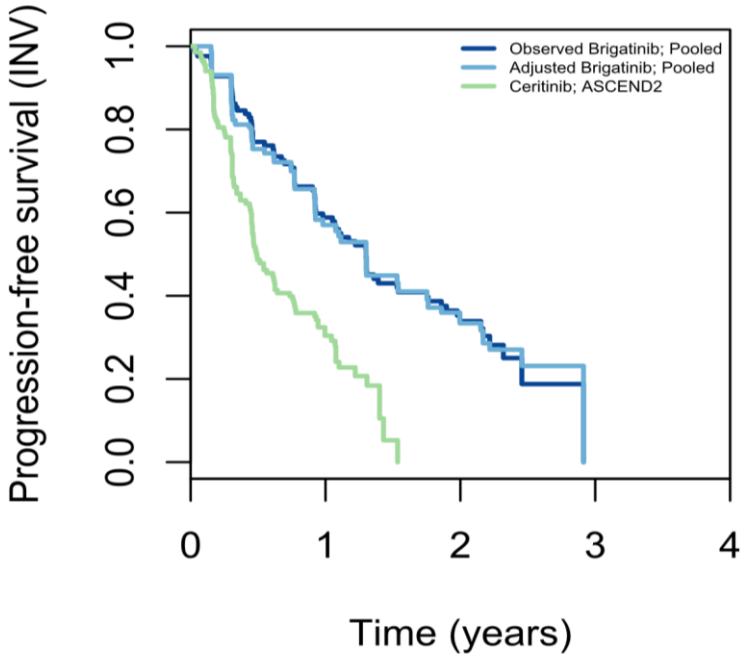
ASCEND-5 vs pooled



Ceritinib vs brigatinib, HR (95% CI)		Ceritinib				
		ASCEND-2 (Naive)	ASCEND-5 (Naive)	ASCEND-2 (adjusted)*	ASCEND-5 (adjusted)*	Meta-analysis (Random)*
Brigatinib	vs ALTA	2.12 (1.34, 3.35)	2.07 (1.32, 3.26)	2.44 (1.39, 4.29)	2.64 (1.34, 5.22)	2.51 (1.43, 4.60)
Brigatinib	vs pooled	2.15 (1.39, 3.31)	2.06 (1.35, 3.16)	2.31 (1.37, 3.89)	2.00 (1.23, 3.23)	2.14 (1.29, 3.54)

**adjusted results are for the 'full' set of adjustment covariates*

Progression-free survival ITC results



ASCEND-2 vs pooled

Ceritinib vs brigatinib, HR (95% CI)		Ceritinib				
		ASCEND-2 (Naive)	ASCEND-5 (Naive)	ASCEND-2 (adjusted)*	ASCEND-5 (adjusted)*	Meta-analysis (Random)*
Brigatinib	vs ALTA	2.61 (1.84, 3.70)	3.52 (2.43, 5.10)	2.77 (1.81, 4.23)	5.19 (2.79, 9.65)	3.50 (2.06, 6.26)
	vs pooled	2.59 (1.87, 3.59)	NA	2.62 (1.77, 3.88)	NA	NA

**adjusted results are for the 'full' set of adjustment covariates*

Adverse events in ALTA, ASCEND-2 & -5

- Study 101 sample n=25 → lack of adverse event data

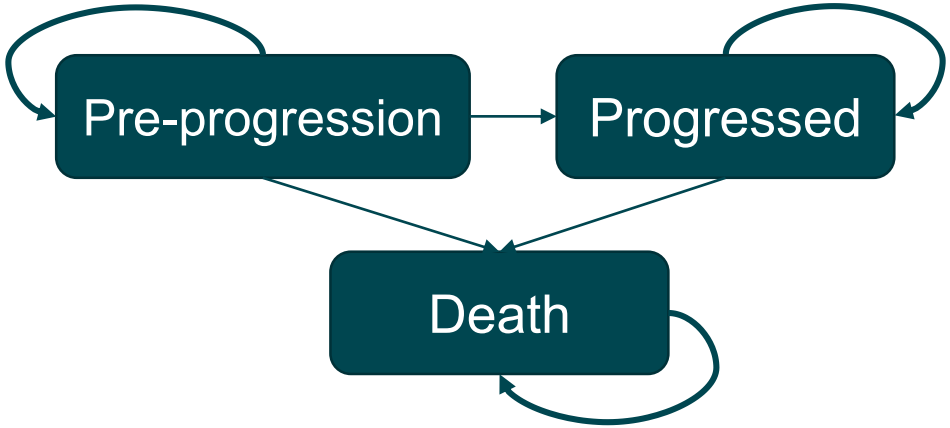
Event, n (%)		ALTA: 180mg n=110	ASCEND-2 n=140	ASCEND-5 n=115
Median follow-up		24.3	11.3	16.6
Serious AEs		56 (50.9)	57 (40.7)	49 (42.6)
Treatment emergent AEs		110 (100.0)	135 (96.4)	110 (95.6)
≥ Grade 3		72 (65.5)	100 (71.4)	104 (90.4)
Dose reduction		33 (30.0)	76 (54.3)	70 (61)
Discontinuation		12 (10.9)	11 (7.9)	6 (5.0%)
AEs of special interest	Cough	NR	30 (21.4)	16 (14)
	Dysponea	NR	29 (20.7)	20 (17.4)
	Pneumonia	NR	10 (7.1)	NR
	Nausea	52 (47.3)	114 (81.4)	76 (66.1)
	Diarrhoea	48 (43.6)	112 (80.0)	83 (72.2)
	Vomiting	33 (30.0)	88 (62.9)	60 (52.2)

NR = not reported

ERG comment on clinical evidence

- Largest risk of bias for trials is lack of comparator (although ASC-5 is RCT, treated as single-arm data source as comparator outside of scope)
- Reasonable to assume proportional hazards in ITCs
- Unanchored MAIC appropriate (as no common comparator)
- Could be bias from covariates not adjusted for in MAICs, but can compare results from multiple analyses → consistency in results
- **Results show brigatinib significantly ↑ OS, PFS & ORR regardless of ITC/meta-analysis method used**
- Separate ITCs of brigatinib data vs ASC-2 & -5, then both comparisons meta-analysed → **potential for double counting of brigatinib patients**
- Could have used MAIC to pool ALTA & Study 101
- Bayesian prior 'relatively generic'; more specific option available based on pharmacological data
- **Brigatinib better tolerated than ceritinib (naïve comparison) for common adverse events (but had slightly more serious adverse events)**

Company's model



Model design	Area-under-the-curve model with 3 health states
Time horizon	14.03 years (5- and 10-year horizon explored)
Cycle length	28 days
Half cycle correction	Yes
Discount rate	3.5%
Perspective	NHS and PSS

Treatment beyond progression

- The company assume an additional duration of treatment beyond progression of 1.53 months for brigatinib and ceritinib
  - calculated by the difference in median ToT and median PFS observed in ALTA (17.15 months – 15.62 months)

ERG comment:

- 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 ERG reject the company's method in favour of estimating ToT directly from the ToT observation in the ALTA trial
- ERG preference is to extrapolate the observed ToT for brigatinib in ALTA using the gamma distribution and apply the PFS HR as a best approximation to estimate time on ceritinib treatment. The difference between median duration of exposure to ceritinib and median PFS is calculated
  - ERG estimate is 3.2 months

Treatment benefit beyond stopping treatment

- The company assumes a continued treatment benefit associated with OS and PFS for brigatinib and ceritinib
  - extrapolated curves presented for OS and PFS INV used for the duration of the model time horizon (14.03 years)
- NICE clinical expert submission: would not anticipate significant benefit beyond discontinuation, but in those who may discontinue for reasons other than progressed disease it maybe a month or two
- 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

ERG comment:

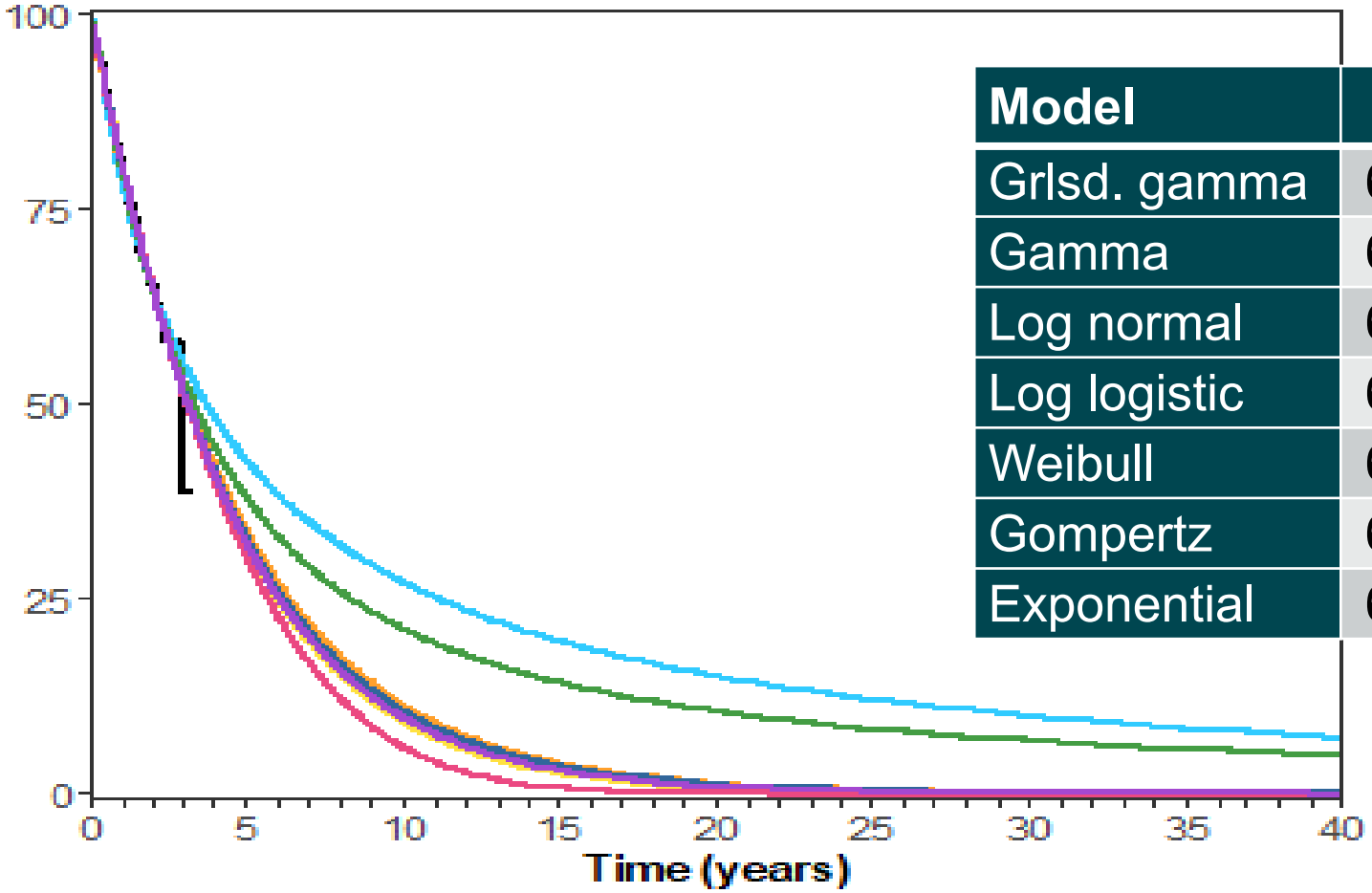
- The ERG adopt the assumption that treatment benefits for both drugs extend beyond the end of treatment = no treatment benefit discontinuation
  - The ERG note there is limited evidence for a strong position either way, other than expert clinical opinion, which the ERG found to be mixed

Clinical parameters in the company base case model

	Brigatinib	Ceritinib
Median outcomes (months)	**Model result**	
Overall survival	37.72	18.40
Progression-free survival (investigator)	16.56	7.36
Time on treatment	17.48	7.36
Mean outcomes (months)	**Model result**	
Overall survival	46.83	24.34
Progression-free survival (investigator)	19.27	8.84
Time on treatment	20.81	10.37

Overall survival extrapolations for brigatinib (1)

Based on Kaplan-Meier data from pooled ALTA & Study 101 (n=135)



Model	AIC	BIC
Grlsd. 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

Overall survival extrapolations for brigatinib (2)

	3-years	5-years	10-years	20-years
Company clinician's opinion, avg (range)	50.00% (35 to 65%)	28.50% (17.5 to 50%)	5.83% (<5% to 7.5%)	0.00% (0 to <5%)
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%

Company base-case OS extrapolation = Gompertz

ERG comment: accuracy of the extrapolation of OS is very uncertain. Conclusions made on the results based on a time-horizon of 14.03 years should be treated with caution

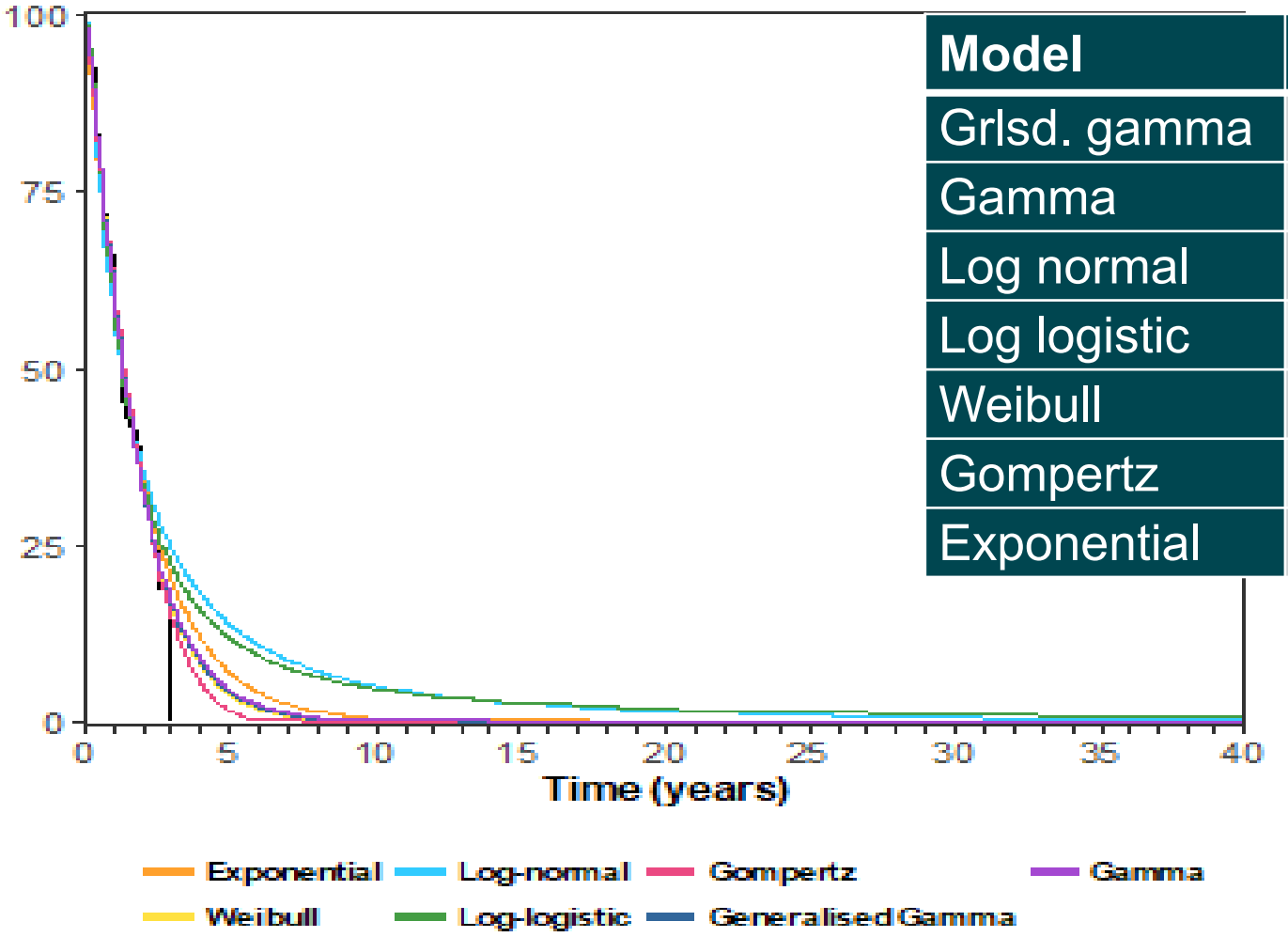
Overall survival extrapolations for brigatinib (3)

	Predicted mean over trial period (months)	Predicted mean over lifetime (months)	Median from pooled data (months)	Mean from pooled data (months)
Generalised gamma	21.79	53.12	34.1	27.5
Gamma	21.80	51.75		
Log-normal	21.53	82.21		
Log-logistic	21.72	71.56		
Weibull	21.81	50.95		
Gompertz	21.79	46.83		
Exponential	21.69	54.19		

ERG comment: Gompertz gives the lowest predicted mean survival over a lifetime, 46.83 months. This has implications for EoL criteria designation

Progression-free survival extrapolations for brigatinib (1)

Based on investigator assessed PFS data from pooled ALTA & Study 101 (n=135)



Model	AIC	BIC
Grlsd. 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

Progression-free survival extrapolations for brigatinib (2)

	Predicted median	Predicted mean (trial period)	Predicted mean (lifetime)	Median (pooled data)	Mean (pooled data)
Grlisd. gamma	16.56	14.00	20.50	15.61	17.62
Gamma	15.64	13.98	20.75		
Log-normal	15.64	13.61	28.98		
Log-logistic	15.64	13.84	27.70		
Weibull	16.56	14.03	20.30		
Gompertz	16.56	14.05	19.27		
Exponential	15.64	13.63	22.15		

Company base-case PFS extrapolation = Gompertz

ERG comment: the selection of Gompertz is not justified. It may seem acceptable given the conservative selection of Gompertz for OS but it has a secondary effect → produces lowest estimate of OS for ceritinib → impacts on life expectancy criterion of EoL designation

Utility values used in the model

- Utility estimates for pre-progression collected in ALTA trial using EORTC QLQ-C30 and mapped to EQ-5D-3L using a published mapping algorithm
- Post-progression estimates identified from literature searching

Health state	Mean value
Progression free (whether on brigatinib or ceritinib)	0.793*
Progressed disease (whether on brigatinib or ceritinib)	0.643*
Age	-0.002
Adverse events (grade 3/4)	-0.0678

* 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

ERG comment:

- The estimate of progression state mean utility of 0.643 included in the company model is higher than two included studies; Chouaid (0.46) and Nafees (0.473). Noted that these studies are of the general NSCLC population → possible higher disease burden.
- Higher utility estimate may underestimate the ICER → superior OS cumulate more QALYs

Costs and health care resource use

- Unit costs identified from standard sources
- Resource use was identified from literature searching

Cost breakdown of health state cost (discounted)	Brigatinib, £	Ceritinib, £	Increment (brigatinib vs ceritinib), £
Treatment (list prices)	93,680	42,052	51,628
Concomitant medications	1,231	627	604
Resource use – pre-progression	6,863	3,373	3,489
Resource use – post-progression	13,079	7,956	5,123
Terminal care	1,490	1,594	-104
Adverse events	2,687	2,331	356
Total costs	**119,029**	**57,932**	**61,097**

ERG comment on economic evaluation (1)

- The model structure is consistent with those used in other ALK= lung cancer NICE appraisals
- Length of ToT uses PFS from ALTA as a proxy rather than directly observed data & could have been modelled independently using a parametric distribution
- Population, intervention, comparator & outcomes used in the model match the NICE scope
- MAIC has a small impact on the relative OS treatment effect → 1% decrease in the ICER & little impact on relative PFS treatment effect → <1% impact on the ICER
- **OS extrapolation is very uncertain as trials underlying the model have short follow-up and extrapolation periods are long → conclusions on the results should be treated with caution**
- **Gompertz for PFS extrapolation is not justified** → it has a secondary effect for EoL designation

ERG comment on economic evaluation (2)

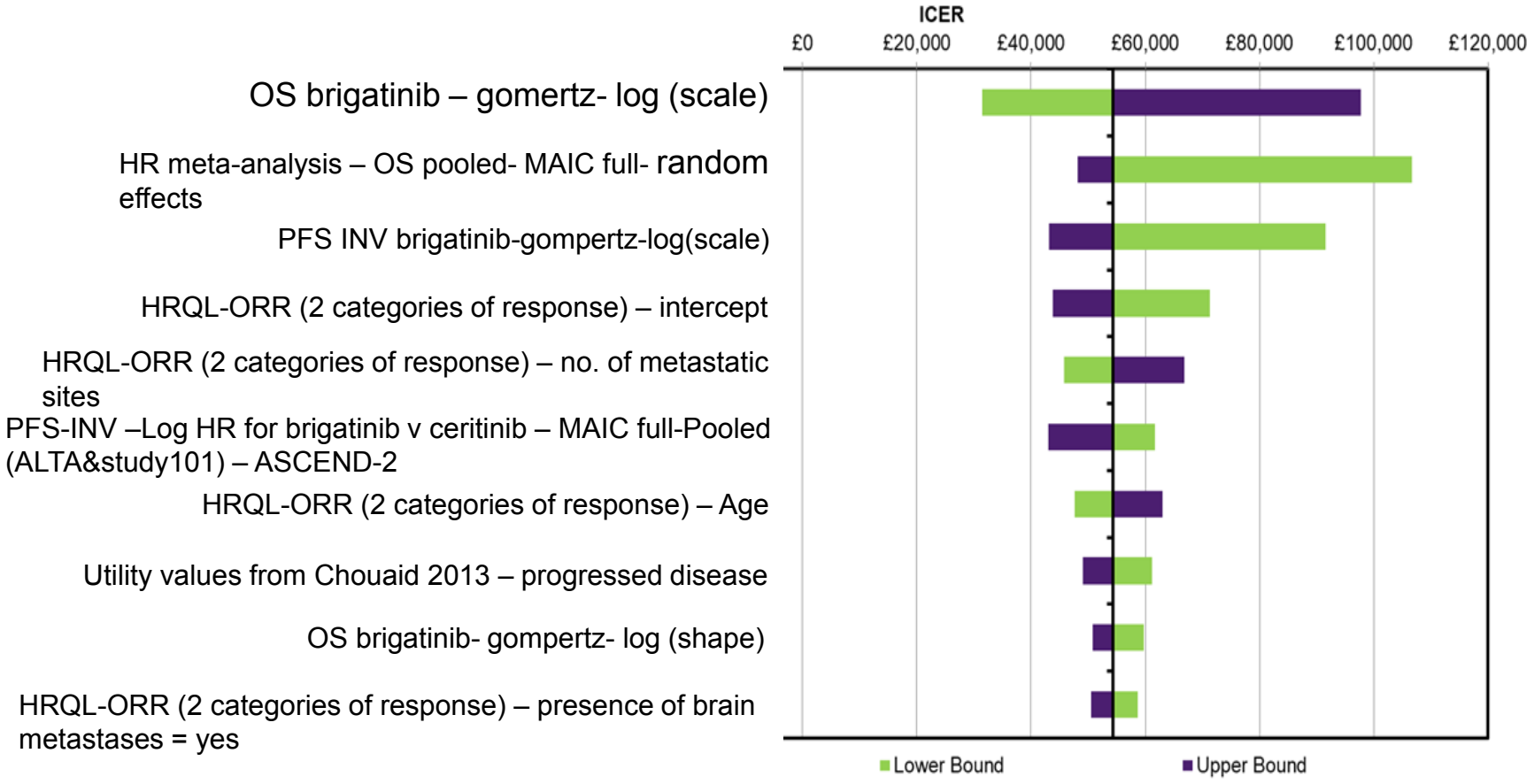
- **Little evidence for continuation of treatment benefit beyond progression but ERG consider it plausible that the benefit is carried through the model's lifetime horizon**
- Background mortality has not been adjusted for & omission not explained
- Algorithm for mapping EORTC-QLQ-C30 results to EQ5D values was not described, justified or explored in sensitivity analyses
- Utility value for progression free health state is reasonable but estimate of progression increment is higher than value in identified studies → could underestimate the ICER
- **The ICER may be under estimated because of the method used to estimate ToT and the mean dose intensity of brigatinib being too low**
  - All other cost estimates are reasonable

Company deterministic base case results
List price vs. list price

- Brigatinib and ceritinib have confidential discounts
- All results including intervention and comparator discounts are confidential and are presented in a confidential appendix for committee members
- Analyses of brigatinib list price versus ceritinib list price presented for information
- Total life years gained for brigatinib = 3.49 and for ceritinib = 1.91

	Total costs, £	Total QALYs	Δ costs, £	Δ QALYs	ICER £/QALY
Brigatinib	119,029	2.45			
Ceritinib	57,932	1.32	61,097	1.12	54,311

Company deterministic sensitivity analysis results (using list prices)

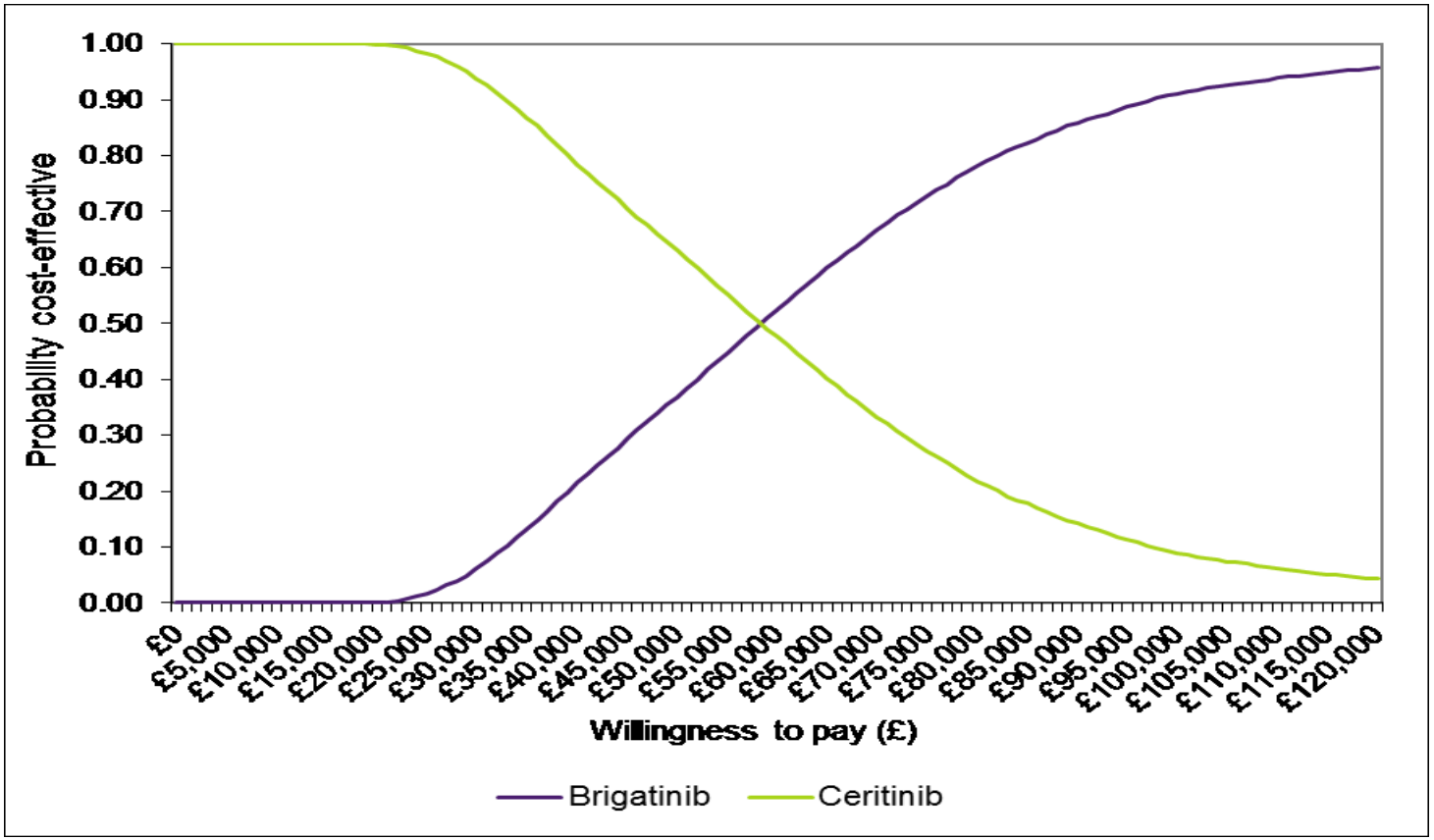


The company base case ICER is most sensitive to:

- OS and PFS estimates for brigatinib AND OS and PFS HRs applied to ceritinib

Company probabilistic base case results
List price vs. list price

	Probabilistic Δ costs, £	Probabilistic Δ QALYs	Probabilistic ICER £/QALY
Brigatinib vs. ceritinib	67,540	1.30	51,882



Company scenario analyses

- The company provided 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
- The ICER was sensitive to:
  - selection of trial data
  - selection of distribution for PFS and OS extrapolation
  - method for estimates of time on treatment

Company scenario analysis

Trial data and selection of distribution for OS

Brigatinib outcomes	Base case ICER £/QALY	ICER £/QALY range using other distributions
OS – pooled data		
Gompertz (base case)	54,311	35,649 to 54,311
OS – ALTA data	-	34,252 to 47,361
PFS – pooled INV data		
Gompertz (base case)	54,311	54,311 to 80,511
PFS – ALTA INV data	-	46,220 to 69,697
PFS – ALTA IRC data	-	49,552 to 76,808

Company scenario analysis
Methods for estimating time on treatment

ToT scenarios	ICER £/QALY	ICER change (% from company BC)
Company base case	54,311	-
ToT beyond progression: Brigatinib: 1.53 months & Ceritinib:1.6 months	54,053	-0.48%
Brigatinib: extrapolated ToT curves* and Ceritinib: PFS HR applied to brigatinib ToT	77,706	43.08%
Brigatinib extrapolated ToT curves** and Ceritinib: PFS HR applied to brigatinib ToT	55,624	2.42%
Brigatinib extrapolated ToT curves* and ceritinib ToT equal to brigatinib's ToT*	23,797	-56.18%
Brigatinib extrapolated ToT curves** & ceritinib ToT equal to brigatinib's ToT**	51,076	-5.96%

* uncapped, ** capped for PFS

Company scenario analysis
Exploration of treatment benefit discontinuation

Duration of treatment benefit from treatment initiation*	ICER £/QALY
OS- Gompertz distribution	
2 years	105,434
3 years	91,210
4 years	79,282
5 years	70,573
10 years	55,793
Source: Company submission addendum. Section B4.1.2 (page 35)	

**Gompertz distribution used for estimating OS in the company base case*

ERG exploratory analyses*

- The company's model included the functionality to run each of the ERG exploratory analyses
- The ERG did not agree with some important model assumptions or their justification:
  - data sources used for the simulation of PFS should include the ASCEND-5 rather than Study 101 → size and quality of ASCEND-5 deemed superior
  - extrapolation of PFS to full time horizon – ERG prefers gamma instead of Gompertz → best statistical fit to observed data for time on treatment and the second best for PFS
  - IPD data from ALTA can be used to estimate of time on treatment for both drugs → ERG suggests difference between median duration of exposure and median PFS in ACSEND-2 is 3.2 months (company calculates an additional 1.53 months from ALTA)
  - No drug wastage assumed by company → ERG prefer that for each strategy half the difference between observed and expected dose is used (based on expert advice & NICE TA395)
  - No administration cost for either oral drug is assumed by the company → the ERG preferred assumption is that a delivery is charge included at £42.50 per item for home delivery (based on consultation with a senior NHS pharmacist)

** Updated in committee slides*

ERG exploratory analyses*

Brigatinib vs ceritinib (list prices)

	ICER £/QALY	ICER change (% from company base case)
Company base case	54,311	-
ERG's code and implementation of minor corrections	54,404	0.2%
(1) ASCEND-5 used in preference to Study 101 for PFS estimate	60,274	11.0%
(2) Gamma distribution for PFS extrapolations	58,869	8.4%
(3) ToT baseline from ALTA observations of ToT (using Gamma)	77,706	43.1%
(4) NHS partly recover cost of wastage	55,843	4.4%
(5) Administration / home delivery included	55,906	2.9%
ERG base case (including all revisions) (1+2+3+4+5)	**90,032**	**65.8%**

** Updated in committee slides*

End of life considerations (1)

NICE criterion	Company assessment	ERG assessment
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Median survival on ceritinib is less than 24 months	• Life expectancy on the comparator treatment = 24.4 months • Gompertz distribution chosen by the company gives the shortest life expectancy for the comparator → could be an underestimate of true survival
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	Mean life expectancy (months): **Ceritinib = 24.34** **Brigatinib = 46.83** **Increment = 22.49** Median life expectancy (months): **Ceritinib = 14.9 to 18.1** **Brigatinib = 34.1** **Increment = 16 to 19.2**	The ERG estimate for life expectancy is the same as the company

End of life considerations (2)

NICE criterion	Company assessment	ERG assessment
The estimates of the extension to life are robust and can be shown or reasonably inferred from either progression-free survival or overall survival	Not discussed	• Doubt that the data used to estimate life extension is robust • Derived from 4 small single arm trials • However, suggest that it is likely that extension to life is at least 3 months
The assumptions used in the reference case economic modelling are plausible, objective and robust	Not discussed	• Considerable uncertainty surrounds the extrapolation of survival beyond the short follow-up • Median survivals reported within the included ASCEND trials were < 2 years and these should be considered

Equality and innovation

- No equality issues identified by the company or ERG
- **Company** considers brigatinib to be innovative:
  - addresses unmet clinical need → systematically and intra-cranially
  - offers meaningful extension of life with PFS improvement
  - relieves disease burden in a population whose general characteristics are of a type for which the benefits may not be fully captured in the QALY
  - offers clinicians and patients a post-crizotinib treatment that bids encouraging response rates, longer PFS and potential for meaningful extension to life beyond that of existing treatments
  - should be considered for End of Life treatment
- **Clinical groups:** Effectiveness in CNS, improved tolerability & potential suppression of resistance

Authors

- **Lucy Beggs and Emily Eaton Turner**
  Technical Lead
- **Chris Griffiths**
  Technical Adviser
- with input from the Lead Team (David Bowen, Rob Hodgson and Rebecca Harmston)

Single technology appraisal

Brigatinib for treating ALK-positive advanced non-small-cell lung cancer after crizotinib (ID1328)

Document B

Company evidence submission

6th April 2018

File name	Version	Contains confidential information	Date
		Yes/no	

Contents

Tables and figures

List of 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
CSR	Clinical study report
CTCAE	Common terminology criteria for adverse events
DLT	Dose limiting toxicity
DOR	Duration of response
DSU	Decision support unit
ECGs	Electrocardiograms
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EGFR	Epidermal growth factor receptor
EGP	Economic guidance panel
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30
EQ-5D	EuroQol 5-dimensions
ERG	Evidence review group

ESS	Effective sample size
FE	Fixed effect
HR	Hazard ratio
HRQL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IGF-1R	Insulin-like growth factor 1 receptor
INV	Investigator
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
NCI	National Cancer Institute (US)
NHS	National health service
NICE	National Institute for Health and Care Excellence
NR	Nor reached
NR	Not reported
NSCLC	Non-small cell lung cancer
OR	Odds ratio
ORR	Objective response rate/ Overall response rate
OS	Overall survival
PD	Progressive disease
PF	Prognostic factor
PFS	Progression-free survival
PK	Pharmacokinetics
PR	Partial response
PRISMA	Preferred reporting items for systematic review and meta-analysis
PS	Performance status
PSS	Personal social services

QALYs	Quality adjusted life years
QD	Once daily
QoL	Quality of Life
RCT	Randomised controlled trial
RE	Random effect
RECIST	Response Evaluation Criteria in Solid Tumours
RP2D	Recommended phase 2 dose
RT-PCR	Reverse transcriptase polymerase chain reaction
SAE	Serious adverse event
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

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

B.1.1 Decision problem

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

The decision problem for this technology appraisal as defined in the final NICE scope(1) is an evaluation of the clinical and cost-effectiveness of brigatinib (Alunbrig®), for the treatment of anaplastic lymphoma kinase positive (ALK+) advanced non-small cell lung cancer (NSCLC) after crizotinib.

Clinical evidence regarding brigatinib is from ALTA study which is a phase II, open-label, non-comparator trial examining the efficacy and safety of brigatinib in patients who had a diagnosis of ALK+ locally advanced or metastatic NSCLC and have experienced progression on crizotinib.(2) Supportive efficacy evidence comes from Study 101, a phase I/II, single arm, open-label, multi-cohort trial examining the efficacy and safety of brigatinib in ALK-rearranged NSCLC and other malignancies which includes a sub-group of patients eligible for the proposed indication.(3)

The final scope issued by NICE in February 2018 and the decision problem addressed in this submission is shown in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib	Adults with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib	Trials of brigatinib included patients of ≥18 years.
Intervention	Brigatinib	Brigatinib	None.
Comparator(s)	Ceritinib	Ceritinib	None.
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • adverse effects of treatment • health-related quality of life.	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • adverse effects of treatment • health-related quality of life.	None.

B.1.2 Description of the technology being appraised

Brand name: Alunbrig®

Generic name: Brigatinib

Therapeutic class: Anti-neoplastic agent

Pharmacological class: Tyrosine kinase inhibitor (TKI)

Brigatinib is a phosphine oxide-containing, potent, orally active, tyrosine kinase inhibitor (TKI),(4) developed for the treatment of anaplastic lymphoma kinase rearranged (ALK+), non-small cell lung cancer (NSCLC), a genetically defined subgroup. Brigatinib was designed for potent 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.(5)

The draft summary of product characteristics (SmPC) is included in Appendix C.

Table 2: Technology being appraised: Brigatinib for the treatment of ALK-positive non-small cell lung cancer, after crizotinib

UK approved name and brand name	Brigatinib (Alunbrig®)
Mechanism of action	Brigatinib is a tyrosine kinase inhibitor with in vitro activity at clinically achievable concentrations against multiple kinases including ALK, ROS1, insulin-like growth factor-1 receptor (IGF-1R), and FLT-3 as well as EGFR deletion and point mutations. Brigatinib inhibited autophosphorylation of ALK and ALK-mediated phosphorylation of the downstream signalling proteins STAT3, AKT, ERK1/2, and S6 in in vitro and in vivo assays. Brigatinib also inhibited the in vitro proliferation of cell lines expressing EML4-ALK and NPM-ALK fusion proteins and demonstrated dose-dependent inhibition of EML4-ALK-positive NSCLC xenograft growth in mice.(6) At clinically achievable concentrations (≤ 500 nM), brigatinib inhibited the in vitro viability of cells expressing EML4-ALK and 17 mutant forms associated with resistance to ALK inhibitors including crizotinib, as well as EGFR-Del (E746-A750), ROS1-L2026M, FLT3-F691L, and FLT3-D835Y. Brigatinib exhibited in vivo anti-tumour activity against 4 mutant forms of EML4-ALK, including G1202R and L1196M mutants identified in NSCLC tumours in patients who have progressed on crizotinib. Brigatinib also reduced tumour burden and prolonged survival in mice implanted intracranially with an ALK-driven tumour cell line. Brigatinib binds to and inhibits ALK kinase and ALK fusion proteins as well as EGFR and mutant forms. This leads to the inhibition of ALK kinase and EGFR kinase, disrupts their signalling pathways and eventually inhibits tumour cell growth in susceptible tumour cells.

Marketing authorisation/CE mark status	In February 2017, Takeda submitted the EU Marketing Authorisation Application for brigatinib with the target of receiving the opinion of the European Medicine Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) in July/August 2018, and full EMA approval in September/October 2018.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	It is anticipated that brigatinib will be indicated as monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib.(6) ALK positive NSCLC status should be known prior to initiation of brigatinib therapy. A validated ALK assay is necessary for the selection of ALK-positive NSCLC patients. Assessment for ALK positive NSCLC should be performed by laboratories with demonstrated proficiency in the specific technology being utilised.
Method of administration and dosage	The proposed recommended starting dose of brigatinib is 90 mg once daily for the first 7 days, then 180 mg once daily. Treatment should continue as long as clinical benefit is observed. If brigatinib is interrupted for 14 days or longer for reasons other than adverse reactions, treatment should be resumed at 90 mg once daily for 7 days before increasing to the previously tolerated dose. If a dose is missed or vomiting occurs after taking a dose, an additional dose should not be administered, and the next dose should be taken at the scheduled time.
Additional tests or investigations	NICE guidelines on lung cancer recommends that ALK status testing should be done for all people with non-squamous NSCLC at diagnosis, because the mutation is more common in this subgroup.(7) ALK status testing is done through fluorescence in situ hybridisation (FISH), immunohistochemistry, chromogenic in situ hybridisation and reverse transcription polymerase chain reaction (RT‑PCR). NICE also published a Medtech innovation briefing [MIB128] for HTG EdgeSeq ALKPlus Assay EU for ALK status testing in non-small-cell lung cancer in November 2017.(8) This proposed indication for brigatinib is in patients previously treated with crizotinib, therefore all patients would have undergone ALK status testing prior to initiation of crizotinib and there would be no requirement to repeat this.
List price and average cost of a course of treatment	£4,900 per 28-tablet pack
Patient access scheme (if applicable)	The price for brigatinib has not yet been agreed with the Department of Health. The proposed list price is: £4,900 for the recommended dose (180mg/day) for 1 pack of 28 tablets of 180mg/day or a starter pack (7x90mg + 21x180mg). Brigatinib will also be available via alternative pack strengths of 90mg 30mg. A confidential (commercial in confidence) [redacted] discount from list price reduces the net price a pack for all formulations. Relating to the starter pack (7x90mg + 21x180mg) and the full 180mg strength (28x180mg) i.e. recommended dose pack) the discount reduces the cost per month from £4,900 to [redacted]

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

B.1.3.1 Health condition

Lung cancer remains the leading cause of cancer death worldwide, with 36,761 cases diagnosed in England alone during 2016..(9) The most common type of lung cancer is non-small cell lung cancer (NSCLC), accounting for 88.5% of cases in England in 2016.(9) Chemotherapy is the traditional standard of care in advanced NSCLC but although these treatments have improved over recent years, limited benefits are seen, especially in patients receiving later-line chemotherapy, as response rates can be low, response duration short and survival poor. Furthermore, only a small percentage of patients derive benefit from later-line therapy, with most experiencing deteriorating quality of life and significant toxicities.(10)

Advances in genetic research have revealed that NSCLC is not a single disease, but highly heterogenous with many different driver mutations.(11) This has led to a major paradigm shift in the management of NSCLC. Whilst empirical chemotherapy with a platinum-doublet remains the gold standard for advanced NSCLC without a known driver mutation, targeted therapy for the major subtypes of oncogenic drivers are pushing the boundary to significantly improve patient outcomes and quality of life. These targeted therapies specifically challenge the action of molecules that help cancer cells grow, making them not only more effective but also less likely to harm a patients' normal cells leading to a preferable safety profile.

In a small proportion of people with NSCLC, the growth of cancer cells is caused in part by an anaplastic lymphoma kinase (ALK) gene rearrangement. This rearrangement is detected by means of a ALK biomarker test and ALK positive (ALK+) status is believed to be present in 3.8% of NSCLC patients,(12) although there is some doubt academically as to whether this estimate may still be too high. Tyrosine kinase inhibitors (TKIs), treat ALK+ NSCLC by blocking the action of the altered ALK gene to help shrink or slow cancer growth. Crizotinib was the first oral ALK inhibitor to be granted FDA approval in 2011, and later received NICE guidance for both untreated and pre-treated ALK-positive NSCLC in 2016 (TA406 (13) and TA422,(14) respectively). While the superiority of crizotinib to traditional chemotherapy has been well documented, studies have shown that patients may experience disease progression less than a year after starting treatment with their first ALK inhibitor.(15-17) For patients with ALK+ NSCLC, the most common sites of disease progression (or metastasis) include brain, liver and bone. Brain metastases can affect up to 70% of patients with ALK+ NSCLC who have been previously treated with crizotinib.(18) This intracranial progression is reported to be due to acquired resistance to crizotinib, suboptimal target inhibition (5) and inadequate penetration of crizotinib into the central nervous system (CNS).(19)

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

- Median age of estimated 49-52 years,(20) younger than that of the total NSCLC population (21) (71 years at diagnosis).(22)
- Not associated with smoking, as most patients have no or a light (<10 pack-years) smoking history.(23)
- Most ALK+ patients have advanced disease at the time of diagnosis.(21)

- Most ALK+ NSCLCs are adenocarcinomas, with few reports of squamous cell pathology.(21)
- Most ALK+ tumours (56%) show a solid growth pattern and a significant component of signet-ring cells (≥10%).(24)

In essence, due to the nature of this disease, ALK+ NSCLC patients tend to be younger with no/little smoking history, hence still working and often present late with advanced disease due to their low suspicion of disease. This, coupled with a high rate of progression to the CNS, results in a small but significant patient population who are relative young but in advanced disease states, suffering with considerable disease burden, particularly where brain metastases are present which infer considerable morbidities.(25)

Prior to the introduction of targeted therapy, the risk of experiencing lung cancer progression or recurrence within five years after diagnosis was more than doubled in ALK+ patients vs. ALK- patients.(26) ALK-targeted therapies have improved response rates and survival of patients considerably compared to traditional chemotherapy but there remains unmet need to improve progression free survival (PFS) in patients who progress on crizotinib when current approved target therapies at second line, such as Ceritinib only offer a range of median PFS between 5.4-7.2 months.(27, 28) Alectinib, showed a range of median PFS between 8.2-9.6 months, however Alectinib was not submitted for reimbursement review at second line. This submission will demonstrate the potent activity of brigatinib both systemically and intra-cranially, offering patients a post-crizotinib treatment that infers improved duration of PFS, alongside extended OS and potent intracranial efficacy.

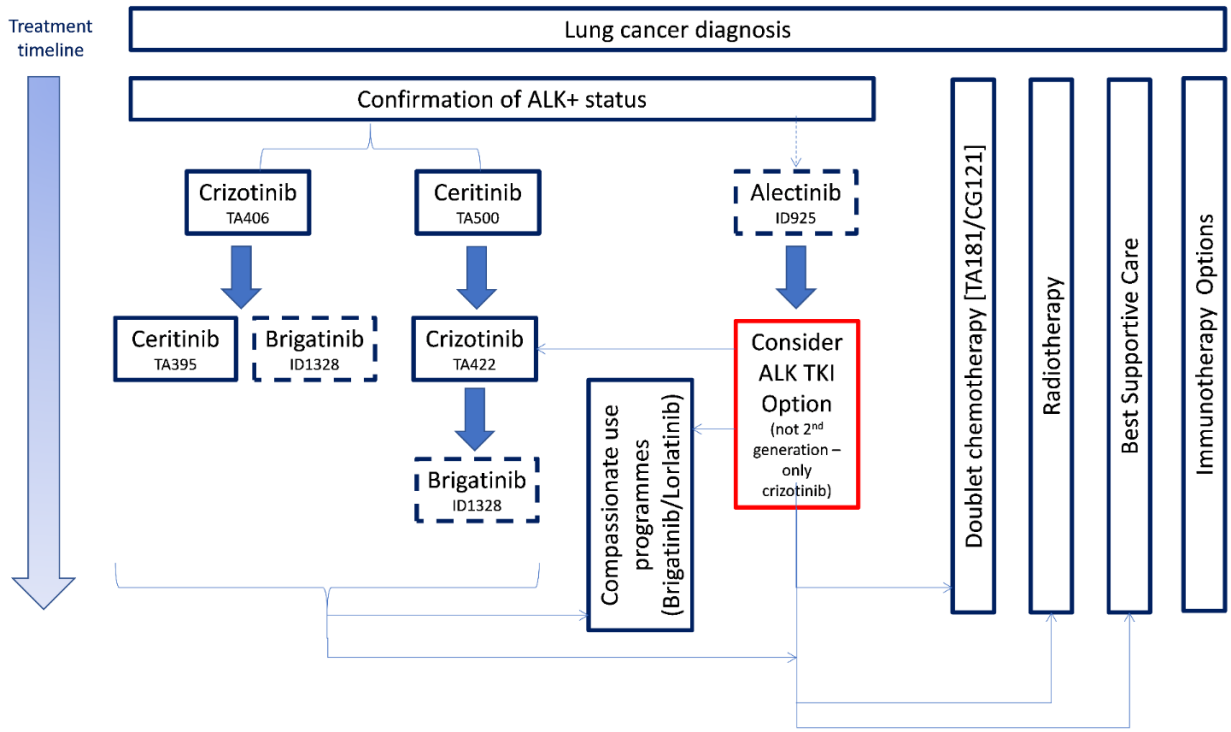
1.3.2 Position of the technology in the treatment pathway

NICE lung cancer treatment pathway flowcharts show that once diagnosis of NSCLC is confirmed, patients who are medically fit and suitable for treatment with curative intent may be offered surgery and/or radiotherapy in the first instance, but these are often only suitable where patients have presented early with a less-advanced disease stage and good performance status. It is also recommended that ALK status testing be done for all people with non-squamous histology at diagnosis, because the mutation is more common in this subgroup. On confirmation of ALK-status, those with the ALK rearrangement with untreated advanced or metastatic NSCLC who are suitable for systemic anticancer treatment have currently have two targeted first line TKI therapy options; ceritinib or crizotinib, and chemotherapy options remain in the pathway and are detailed as; pemetrexed or a generalised chemotherapy treatment, which should be a combination of a single third-generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus a platinum drug (either carboplatin or cisplatin). Expert clinical opinion sought by Takeda, suggests that currently in the UK, the proportion of ALK+ NSCLC patients that go on to receive crizotinib treatment after confirmation of ALK rearrangement is over 95%.(29) However, Takeda acknowledge that this figure is likely to be lower given the recent approval of ceritinib in untreated ALK+ NSCLC patients (TA 500),(30) and the availability of alectinib in compassionate use programs, alongside other in-trial medicinal products. In addition, the NLCA Report 2017 suggests that only 62% of patients with advanced disease (stage IIIB/IV) and good performance status (0 or 1) received systemic anti-cancer treatment a proportion

believed to be fairly consistent when compared to the previous report, and in line with clinician input.(9)

Subsequently, NICE pathways state that persons with previously treated advanced or metastatic ALK+ NSCLC have the same treatment options available to them in the second or subsequent line as they did in first line; namely chemotherapy, crizotinib and ceritinib. The National Lung Cancer Audit 2017 (9) stated that ALK-targeting therapies, namely crizotinib and ceritinib, were used in 1.2% of advanced NSCLC patients with a good performance status, during 2016, although the line of therapy was not specified. Brigatinib would sit alongside ceritinib and crizotinib 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, which is suggested to be the vast majority of current patients,(29) although this is likely to decrease over time due to the diminishing use of crizotinib in light of the changing treatment landscape. This would be a small and very specific population of patients, estimated to be approximately 46 patients (see section 3 of BIM).

Figure 1: Treatment flow for ALK+ NSCLC patients



B.1.4 Equality considerations

There are no major equality issues concerning the use of brigatinib.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) of the clinical evidence was performed, relating to the efficacy and safety of brigatinib and comparator interventions, for the treatment of ALK+ advanced NSCLC patients, previously treated with crizotinib. The comparator for this decision problem is ceritinib, as per the NICE final scope.(1)

The clinical SLR identified two trials of brigatinib and two trials of ceritinib that fall within the scope of this decision problem and were eligible for inclusion in the SLR. These were ALTA and Study 101 for brigatinib, with ASCEND-2 and ASCEND-5 identified for ceritinib.

Full methodology and results of the SLR, including PRISMA diagrams, used to identify and select clinical evidence relevant to the technology being appraised are discussed in Appendix D.

B.2.2 List of relevant clinical effectiveness evidence

The clinical SLR identified two single-arm, non-comparator trials of brigatinib that were considered relevant to the decision problem. One was a randomised, non-comparator, open-label trial of ALK+ NSCLC patients treated with two different brigatinib doses (ALTA trial, see Table 3); and the other a multi-cohort, open label, dosing trial which included a relevant subgroup of patients who were both ALK+ and previously treated with crizotinib (Study 101, see

Table **4**). No randomised controlled trials (RCTs) demonstrating the clinical effectiveness of brigatinib were identified in the clinical SLR.

Table 3: Clinical effectiveness evidence for brigatinib from the ALTA trial

<table>
<tr><td>Study</td><td colspan="5">ALTA (AP26113-13-201; NCT02094573)</td></tr>
<tr><td>Study design</td><td colspan="5">An open-label, multi-national, non-comparator phase II study</td></tr>
<tr><td>Population</td><td colspan="5">Adult patients with locally advanced or metastatic ALK+ NSCLC, previously treated with crizotinib</td></tr>
<tr><td>Intervention(s)</td><td colspan="5">• Brigatinib 90mg once daily (Arm A)
• Brigatinib 180mg once daily (with a 7-day lead-in at 90mg once daily) (Arm B)</td></tr>
<tr><td>Comparator(s)</td><td colspan="5">None.</td></tr>
<tr><td rowspan="2">Indicate if trial supports application for marketing authorisation</td><td>Yes</td><td>✓</td><td rowspan="2">Indicate if trial used in the economic model</td><td>Yes</td><td>✓</td></tr>
<tr><td>No</td><td></td><td>No</td><td></td></tr>
<tr><td>Rationale for use in the model</td><td colspan="5">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.</td></tr>
</table>

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.(2) 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.(31) 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.(32) ARIAD Pharmaceuticals Inc. AP26113-13-201 Clinical Study Report: Section14 (Feb 2017). 2017.(33) Takeda Pharmaceuticals Ltd. Brigatinib (ALUNBRIG™) Study AP26113-13-201 Clinical Data Update (21 February 2017 Data Extraction). 1st August 2017.(34) ARIAD Pharmaceuticals Ltd. Brigatinib (ALUNBRIG™) Study AP26113-13-201: Clinical Study Report Addendum I (29 September 2017 Data Extraction). 11 January 2018.(35)
* 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.	

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.(3) 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.(36) 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.(37) ARIAD Pharmaceuticals Inc. AP26113-11-101 Clinical Study Report: Section14 (May 2016). 2016.(38)				
* 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.					

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

The clinical effectiveness evidence base for brigatinib comes from two trials identified from the clinical SLR. These are the pivotal ALTA trial (see Section B.2.3.1.1 ***ALTA***) and Study 101 (see Section

B.***2.3.1.2 Study 101***.

B.2.3.1 Brigatinib clinical effectiveness evidence

B.2.3.1.1 ALTA

Rationale:

There continues to be a need to explore new treatment options for patients who have experienced failure of crizotinib due to resistance or intolerance. Chemotherapy is an approved treatment option for such patients, although it is not specifically approved for use in ALK+ NSCLC patients. Since design and commencement of the ALTA trial, new therapies such as ceritinib and alectinib (alectinib is not reimbursed in this indication in the UK at the present-time), have been introduced but there remains a need to improve response rates, provide greater durability of response, and to overcome resistance to crizotinib. Like all cancers, ALK+ NSCLC is a serious condition, and patients who have experienced failure of crizotinib likely have increased morbidity and mortality. Based on the preclinical activity profile of brigatinib in vitro and in vivo, and the clinical activity demonstrated in the phase 1/2 study (AP26113-11-101, known as Study 101), this phase 2 study (AP26113-13-201, known as ALTA), evaluated brigatinib using two dosing regimens.

The two recommended doses used in this study were selected based on results from the phase 1/2 study (Study 101), which suggested that while a dose of 90mg QD would provide adequate plasma drug concentration and antitumor activity, 180mg QD preceded by a 90-mg QD 7-day lead-in might result in greater penetration of the CNS and higher CNS response rates. A 90mg dose lead-in regimen dose also offers the prospect of improved tolerability.(3)

Trial design:

The phase II, open-label, randomised, multi-centre, international ALTA trial, was designed to evaluate brigatinib using two dosing regimens in patients with crizotinib-refractory, advanced, ALK+ NSCLC. The primary objective was to determine the efficacy of brigatinib, as evidenced by investigator-assessed objective response rates (ORR) per RECIST v1.1. Secondary objectives included additional efficacy assessments: IRC-confirmed ORR, overall survival (OS), progression-free survival (PFS), duration of response (DOR), time to response (TTR) and intra-cranial responses (IRC-assessed intra-cranial confirmed ORR and PFS in patients with active brain metastases; and assessments of safety, tolerability, and patients-reported symptoms of lung cancer and health-related quality of life (QoL) scores assessed with the European Organisation for Research and Treatment of cancer QoL questionnaire (EORTC QLQ C-30 v3.0), including mean transformed global health status/QoL score (question 29 and 30).(2)

Patients were stratified by baseline brain metastases (present vs. absent), and best investigator-assessed response to crizotinib (complete response [CR] or partial response [PR] vs. other or unknown) and were randomly assigned (1:1) to receive brigatinib 90mg once daily (arm A) or 180 mg once daily with a 7-day lead-in at 90mg (arm B). Treatment continued until disease progression requiring alternative systemic therapy, intolerable toxicity, or consent withdrawal. Patients on Arm A being treated at 90 mg QD who experienced progressive disease were allowed, at the discretion of the treating investigator, to escalate their dose to 180 mg QD. Patients in either arm who experienced disease progression could continue to be treated at the same dose, if in the opinion of the treating investigator they continued to experience clinical benefit. Dose interruptions or reductions were allowed to manage treatment-related adverse events (TRAEs), on the basis of investigator judgement.(2)

At screening, disease assessment (per RECIST v1.1) included chest and abdomen imaging by computed tomography or magnetic resonance imaging (MRI) with contrast. Contrast-enhanced brain MRI was required at screening and was repeated post-baseline for patients with central nervous system (CNS) metastases. A central independent review committee (IRC) reviewed on-study images. Disease was assessed every 8 weeks through to week 60, and then every 12 weeks until progression. Objective responses were confirmed ≥ 4 weeks after initial response.(2)

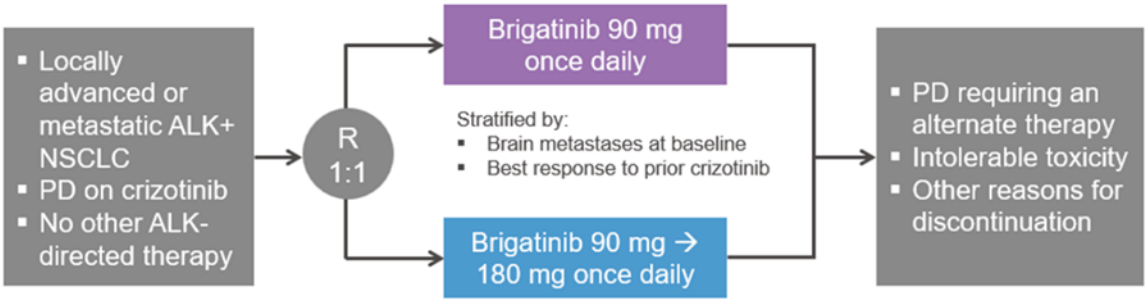
Visits were scheduled to occur on days 1 ,8, and 15 of the first 28-day cycle and then every 4 weeks, at treatment discontinuation, and then 30 days post-treatment. Follow-up for survival and subsequent therapy continued every 3 months after treatment discontinuation and is intended to continue for 2 years after the last patient enrolled.(32)

All AEs starting/worsening on or after the first dose of study drug and no later than 30 days after the last dose date were considered as treatment-emergent. AEs were graded with National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. The incidence rates of treatment emergent AEs, as well as the frequency of occurrence of overall toxicity categorized by maximum toxicity grades (severity), were described. In addition, treatment-emergent AEs were summarised by causal relationship to study drug (in the opinion of the investigator) and action taken on study drug, including dose modifications, interruptions and discontinuation. Serious treatment-emergent AEs, both overall and by causal relationship to study drug, were also summarized.(2, 32)

Data extraction from the ALTA trial occurred initially in February and May 2016, (2, 32) for investigator and IRC assessed outcomes, respectively. This was followed by a further data extraction point in February 2017 (31, 34) and finally updated most recently with a September 2017 data cut. This submission considers the main published data from May 2016 (2, 32) and the February 2017 updated data cut,(31, 34) the latter of which informs subsequent indirect treatment comparison (ITC) and the economic model. Efficacy data from the most recent September 2017 data extraction is also presented, although this was not made available in time for statistical analyses and inclusion in the economic model.

A visual overview of the ALTA trial design is show in **Figure 2**.

Figure 2: Study overview of the ALTA trial



Source: Takeda data on file

Eligibility criteria:

Key inclusion and exclusion criteria for the ALTA trial are presented in Table 5.

Table 5: ALTA trial: inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Patients who met all of the following criteria were eligible to enter the study: ≥18 years old Had histologically or cytologically confirmed locally advanced or metastatic NSCLC that was ALK+ Had progressive disease while on crizotinib, as assessed by the investigator Had at least 1 measurable lesion per RECIST v1.1 Had adequate organ and hematologic function Had ECOG performance status ≤2 Recovered from toxicities related to prior anticancer therapy Had a life expectancy ≥3 months	Patients who met any of the following criteria were not eligible to enter the study: Received any prior ALK inhibitor, other than crizotinib Received crizotinib within 3 days prior to the first dose of brigatinib Received cytotoxic chemotherapy or radiotherapy within 14 days Received monoclonal antibodies within 30 days History or presence of pulmonary interstitial disease or drug-related pneumonitis Symptomatic CNS brain metastases
Abbreviations: ALK+, anaplastic lymphoma kinase positive; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version.	

Settings and location:

Patients were enrolled into the ALTA trial between 4th June, 2014 and 21st September, 2015. As of 29 February 2016, 222 patients were enrolled into the study in 18 countries: 105 patients at 38 sites in 12 countries in Europe. This included one site in England; The Christie NHS Foundation Trust, Manchester.

Trial drugs and concomitant medications:

Patients were randomised on a 1:1 basis (stratified by the presence of brain metastases at baseline and the best investigator-assessed response to prior crizotinib), to receive either 90 mg QD continuously or 180 mg QD with a 7-day lead-in at 90 mg QD. Patients were to be dosed with brigatinib until they experienced disease progression or intolerable toxicity.(32)

Palliation and supportive care were permitted during the study for management of symptoms and underlying medical conditions that developed during the study. Concomitant medications for all ongoing medical history conditions or AEs were reported. A total of 96.3% of the treated population reported using at least one concomitant medication during the study (96.3% [105/109] in Arm A and 96.4% [106/110] in Arm B).(32) No other medication was permitted.

Brigatinib was self-administered by the patients, therefore to support treatment compliance patients were provided with a diary card or equivalent where the date of study drug administration was recorded, and instructions for completing the diary card were provided with the Study Reference Manual. Patients who forgot to take their dose should not have made up the missed dose. Any missing doses were recorded in an appropriate source record (e.g. clinic chart), patient diary card, and study drug administration eCRF. The investigator was responsible for ensuring that the patient diary card(s) were accounted for and noted in source documentation.(32)

Outcomes:

In the ALTA Study, the primary efficacy endpoint was confirmed ORR as assessed by the investigator as per RECIST v1.1. The ORR was defined as the proportion of patients who were confirmed to have achieved CR or PR after initiation of brigatinib. Confirmed ORR assessed by Independent Review Committee (IRC) was defined as the proportion of patients who were confirmed to have achieved CR or PR using RECIST v1.1 after initiation of brigatinib (a secondary objective).

Further secondary objectives included:

- To further characterise the efficacy of brigatinib in patients with ALK positive, locally advanced or metastatic NSCLC whose disease has progressed on therapy with crizotinib, as shown by: PFS, OS, IRC-assessed ORR, disease control rate, time to/duration of response, and time on treatment;
- To assess CNS response (IRC assessed intra-cranial confirmed ORR and PFS in patients with measurable and/or active brain metastases);
- To assess the safety in terms of adverse events experienced on treatment;
- To assess tolerability in terms of dose modifications;
- To assess patient-reported symptoms and health-related quality of life (HRQoL) with the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 (v3.0).(2)

B.2.3.1.2 Study 101

Rationale:

Brigatinib was developed to address the limitations of currently approved ALK inhibitors by maximising selective inhibition of ALK+ NSCLC cells through optimal binding to the ALK kinase domain and a broad activity against resistant ALK mutant cells. Brigatinib also had preclinical activity against ROS1 fusions and mutated epidermal growth factor receptor (EGFR), including the resistant EGFR-T790M mutant. Based on the promising preclinical inhibitory activity profile of brigatinib for ALK, as well as other potentially important targets of oncogenesis, this phase 1/2 study was conducted to evaluate the initial safety, tolerability, pharmacokinetics (PK) profile, and anti-tumour activity of brigatinib in patients with advanced malignancies.

The primary objective of the phase I portion of Study 101 was to determine the safety profile of orally administered brigatinib including identification of the maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs). This would then be used to determine the recommended phase II dose (RP2D) of orally administered brigatinib. The overall objective of the phase II portion of Study 101 was to describe the preliminary anti-tumour activity of brigatinib in NSCLC with ALK gene rearrangement or mutated epidermal growth factor receptor (EGFR), and other cancers with abnormal targets. In the phase 2 expansion stage, three oral once-daily regimens were assessed: 90 mg, 180 mg, and 180 mg with a 7 day lead-in at 90 mg. Patients were enrolled into five cohorts: ALK inhibitor-naive ALK-rearranged NSCLC (cohort 1), crizotinib-treated ALK-rearranged NSCLC (cohort 2), EGFRT790M-positive NSCLC and resistance to one previous EGFR tyrosine kinase inhibitor (cohort 3), other cancers with abnormalities in brigatinib targets (cohort 4), and crizotinib-naive or crizotinib-treated ALK-rearranged NSCLC with active, measurable, intracranial CNS metastases (cohort 5). From this multi-cohort, multi-dose trial design, only a proportion of patients that were diagnosed with ALK+ NSCLC and pre-treated with crizotinib, were within the scope of this submission.

Trial design:

This single-arm, open-label, phase I/II trial was carried out at nine centres in the USA and Spain. Phase I was a dose-escalation phase in patients with histologically confirmed advanced malignancies and was followed by an expansion phase (phase II) in five histologically and molecularly defined cohorts. Out of a total of 137 patients, 128 had a NSCLC diagnosis of which 79 had the confirmed ALK+ rearrangement and 71 had also received prior crizotinib. During phase II, three oral once-daily regimens were assessed: 90mg, 180mg and 180mg with a 7-day lead-in at 90mg. In total, 25 patients fell within the scope of this decision problem in being ALK-rearranged, pre-treated with crizotinib and were assigned to receive brigatinib at 180mg daily (with 7-day lead-in 90mg once daily), which is consistent with the proposed recommended dose. Only these 25 patients formed part of the analyses and will be considered in this submission going forward (see Figure 3).

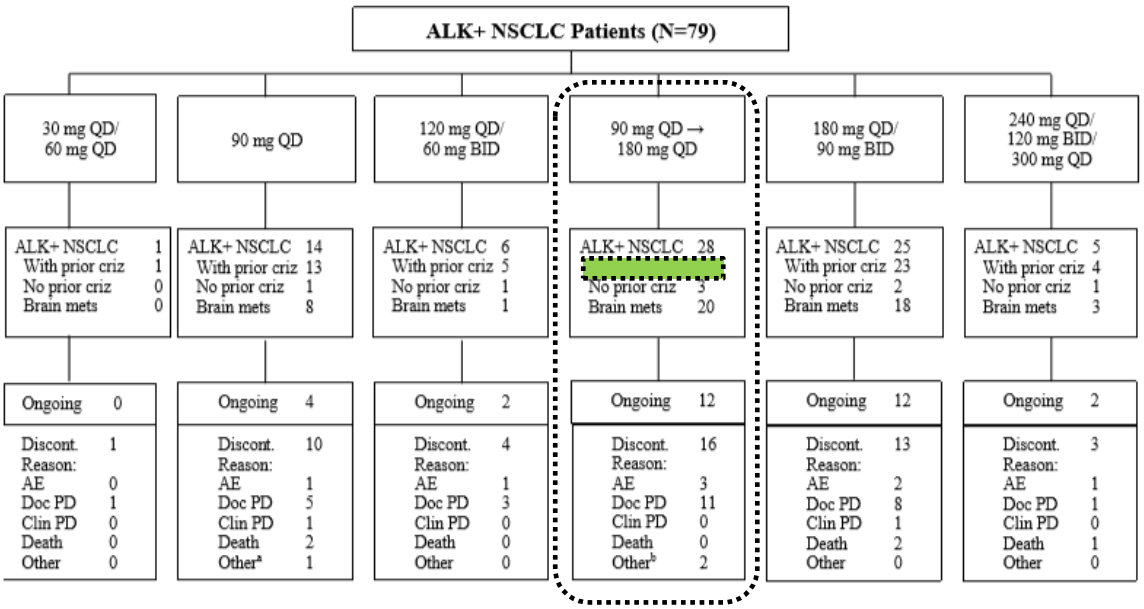
At screening, disease assessment included imaging of the chest, abdomen, pelvis and brain using appropriate radiological procedures (computed tomography [CT] scan, MRI scan) and physical examination (for palpable lesions). A contrast enhanced brain MRI was required for

all patients at baseline and for patients who have CNS metastases at follow-up visits. Target and non-target lesions were selected at study start and followed throughout the course of treatment for response assessment using RECIST version 1.1. Disease assessments were performed at screening and 8-week intervals.(3)

To evaluate the potential for brigatinib anti-tumour activity in the CNS, a post hoc, independent analysis of intracranial response was performed in ALK+ NSCLC patients with brain metastases at baseline. Contrast-enhanced brain MRI scans were analysed by neuro-radiologists in an independent central review. The reviewers were blinded to investigator assessment and systemic response.(3)

Safety assessments included physical and laboratory examinations, vital signs, and ECGs. Adverse events (AEs) were graded according to the National Cancer Institute (of the United States) Common Terminology Criteria for Adverse Events (NCI CTCAE v 4.0). Periodic meetings with study investigators were held to assess safety throughout the study.

Figure 3: ALK+ NSCLC patient disposition by collapsed dose groups from the phase II portion of Study 101



Source: CSR Study AP26113-11-101.(37)

Data were extracted for analyses for Study 101 initially in June 2015 and November 2015,(36) then later in May 2016. This submission considers results from the May 2016 data cut.(3, 32, 36)

Eligibility criteria:

For the phase II portion of Study 101 in the subgroup of patients considered (n=25), the eligibility criteria are given in Table 6.

Settings and location:

Nine academic hospitals or cancer centres in USA and Spain recruited the patient population in this trial.(3) Patients self-administered their oral dose of brigatinib, therefore not requiring an inpatient setting.

Table 6: Key eligibly criteria for patients entering the Study 101 of brigatinib

Inclusion criteria	Exclusion criteria
Patients who met **all** of the following criteria were eligible to enter the study: - ≥18 years old - Histologically or cytologically confirmed NSCLC - Confirmed ALK rearrangement - Resistant to crizotinib (and had not received any other prior ALK inhibitor therapy) - Measurable disease by (RECIST v1.1) - ECOG PS 0 or 1 - Minimum life expectancy of ≥ 3 months - Adequate renal and hepatic function - Adequate bone marrow function - Normal QT interval on screening ECG	Patients who met **any** of the following criteria were not eligible to enter the study: - Received an investigational agent ≤14 days prior to initiating brigatinib - Received systemic anticancer therapy or radiation therapy ≤14 days prior to initiating brigatinib - Received crizotinib less than 72 hours prior to brigatinib - Received any prior ALK-targeted agents, with the exception of crizotinib - Major surgery within 28 days - Brain metastases that were neurologically unstable or required anticonvulsants or an increasing dose of corticosteroids. Patients with previously treated brain metastases without evidence of disease or recurrence were allowed for Cohorts 1 to 4. Patients with evaluable but non-measurable, active brain lesions who otherwise met the criteria for Cohort 5 for CNS disease could be enrolled in other cohorts - Significant uncontrolled/active CV disease - Uncontrolled hypertension - History or presence of pulmonary interstitial disease or drug–related pneumonitis
Abbreviations: Abbreviations: ALK+, anaplastic lymphoma kinase positive; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version.	

Source: Gettinger et al. 2016;(3) CSR Study 101.(37)

Trial drugs and concomitant medications:

The brigatinib drug product was supplied as either tablets or capsules (tablets-only in the UK), and the patients in the relevant cohort received 90mg once daily for seven days, followed by 180mg once daily from then on.(37) Patients continued treatment until disease progression or intolerable toxicity, as established by the investigator; however, patients were permitted to continue treatment beyond progressive disease if they continued to receive

clinical benefit, according to the investigator. Dose interruptions and reductions were permitted to manage adverse events.

Palliation and supportive care were permitted during the study for management of symptoms and underlying medical conditions that developed during the study. Concomitant medications for all ongoing medical history conditions or AEs were reported. Nearly all (99.3% [136/137]) patients in the study reported using at least one concomitant medication during the study. No further medication was permitted.(37)

To support treatment compliance patients were provided a diary card where the date of study drug administration was recorded. Patients who forgot to take their dose did not make up the missed dose. Any missing doses were recorded in an appropriate source record, patient diary card, and study drug administration electronic case report form (eCRF). When possible, patients took the study drug under observation during scheduled study visits to the clinic. The investigator was responsible for ensuring that the patient diary card(s) were accounted for and noted in source documentation.

Outcomes:

Primary efficacy endpoint:

During the dose escalation component of this study, the primary endpoint was the recommended phase II dose (RP2D) of orally administered brigatinib. For the expansion cohorts, which made up phase II and included the subgroup of 25 patients relevant to this decision problem, the primary endpoint was the overall response rate, per investigator assessment (RECIST v1.1).

Secondary endpoints included:

- Progression-free survival (PFS);
- Overall survival (OS);
- Duration of response (DOR);
- CNS response (IRC-assessed intracranial ORR and PFS in patients with active brain metastases);
- Safety and tolerability.

B.2.3.2 Comparative summary of brigatinib trial methodology

Table 7 presents the comparative summary of methodology from the ALTA trial and Study 101. Both trials recruited patients from the same population; adult patients diagnosed with ALK+ NSCLC, previously treated with crizotinib. Eligibility criteria were very similar as were pre-defined outcomes, although Study 101 did originally recruit patients of ECOG PS 0 or 1, excluding patients with ECOG PS 2, unlike ALTA. Both were open-label and unblinded, although the ALTA trial utilised a blinded independent review committee (BIRC) to confirm efficacy outcomes.

Table 7: Comparison of trial methodology for ALTA and Study 101

Trial name	ALTA (2)	Study 101 (3, 37)
Location	71 cancer centres (USA n =15; Canada n =1; Europe n =38; Australia n = 6; Asia n = 11)	9 centres in USA and Spain
Trial design	Open-label, multi-national, non-comparator phase II study	Single-arm, open-label, phase I/II*** dosing trial
Eligibility criteria for participants: key inclusion criteria	≥ 18 years Locally advanced or metastatic ALK-positive NSCLC Disease progression on crizotinib ≥1 measurable lesion per RECIST (v1.1) ECOG PS ≤ 2 No prior ALK inhibitor (other than crizotinib) Prior crizotinib >3 days prior to first dose of brigatinib No chemotherapy* or radiotherapy within 14 days No monoclonal antibodies within 30 days	≥ 18 years Locally advanced or metastatic ALK-positive NSCLC Disease progression on crizotinib Measurable disease per RECIST (v1.1) ECOG PS ≤ 1 No prior ALK inhibitor (other than crizotinib) Prior crizotinib >3 days prior to first dose of brigatinib No chemotherapy* or radiotherapy within 14 days
Eligibility criteria for participants: key exclusion criteria	History/presence of pulmonary interstitial disease or drug-related pneumonitis Symptomatic CNS metastases	Brain metastases that were neurologically unstable or required anticonvulsants or an increasing dose of corticosteroids. Patients with previously treated brain Significant uncontrolled/active CV disease History or presence of pulmonary interstitial disease or drug–related pneumonitis
Patient numbers	N=222 (Arm A=112, Arm B=110)	N=25 (relevant sub-group)
Settings and locations	71 cancer centres (USA n =15; Canada n =1; Europe n =38; Australia n = 6; Asia n = 11)	9 academic hospitals or cancer centres in USA and Spain
Trial drugs **- Interventions**	Oral brigatinib 90mg once daily Oral brigatinib180mg once daily with 7 –day lead in of 90mg once daily	Oral brigatinib 180mg once daily with 7 –day lead in of 90mg once daily
Trial drugs **- Permitted and disallowed concomitant medication**	Permitted therapy: Palliation and supportive care were permitted during the study for underlying medical conditions and management of symptoms. Prohibited treatments: Other anticancer therapy; investigational drugs or devices; extensive surgery; medications associated with Torsades de Pointes.	Permitted therapy: Palliation and supportive care were permitted during the study for underlying medical conditions and management of symptoms. Prohibited treatments: Other anticancer therapy; investigational drugs or devices; extensive surgery; medications associated with Torsades de Pointes; herbal preparations; Medications know

Trial name	ALTA (2)	Study 101 (3, 37)
		to be potent inhibitors/inducers of P450 cytochromes.
Primary outcomes (including scoring method and timings of assessments)	Confirmed INV ORR per RECIST v1.1 Disease was assessed every 8 weeks through to week 60, and then every 12 weeks until progression. Objective responses were confirmed ≥ 4 weeks after initial response	Confirmed INV ORR per RECIST v1.1. Disease assessment was performed at screening and at 8-week intervals.
Other outcomes used in the economic model/specified in the scope	Confirmed IRC ORR per RECIST v1.1 Response rates (including DOR, and CNS response rates) PFS OS Safety and tolerability QOL	Response rates (including DOR, and CNS response rates) PFS OS Safety and tolerability- NR for subgroup of n=25 eligible patients QOL – NR in Study 101
* Any number of prior chemotherapy regimens were permitted ** N=137 in total, but only n=25 were ALK+, post-crizotinib and treated with proposed recommended dose *** Only the phase II portion of this trial was within the scope Abbreviations: ALK+, anaplastic lymphoma kinase positive; CNS, central nervous system; DOR, duration of response; ECOG, Eastern cooperative oncology group; INV, investigator-assessed; IRC, independent review committee assessed; NR, not reported; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression free survival; QOL, quality of life; RECIST (v1.1), Response Evaluation Criteria in Solid Tumours version 1.1.		

B.2.3.3 Baseline characteristics

ALK+ NSCLC patients in clinical trials have consistently been reported to have homogeneous characteristics being likely to be younger, with little/no smoking history and of non-squamous histology. The populations recruited for treatment with brigatinib in ALTA and Study 101 are reflective of these broad assumptions and similar in recruiting younger (median age <60 years),(2, 37, 38) mainly white (64-80% white) patients, with adenocarcinoma histology (95.5-98%), and with an ECOG of 0 or 1 (91-100%)(2, 37, 38) with a high proportion of never smokers. Further to this, more recent retrospective studies of real-world patient characteristics support that patient demographics in the real-world are consistent with those patients enrolled in these brigatinib trials.(12)

Table 8 presents the baseline characteristic of patients treated in the ALTA and Study 101 trials of brigatinib.

Table 8: Baseline characteristics for brigatinib-treated patients in ALTA and Study 101

Trial name	**ALTA Arm A (2, 32)**	**ALTA Arm B (2, 32)**	**Study 101 Relevant subgroup only (38)**
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)
ECOG PS (%) 0 1 0 or 1 2 3+ Missing	 34 (30.4) 71 (63.4) 105 (93.8) 7 (6.3) 0 (0) 0 (0)	 45 (40.9) 56 (50.9) 101 (91.8) 9 (8.2) 0 (0) 0 (0)	 10 (40.0) 15 (60.0) 25 (100) 0 (0) 0 (0) 0 (0)
Smoking status (%) Never Former Current Unknown	 71 (63.4) 40 (35.7) 0 (0) 1 (0.9)	 63 (57.3) 43 (39.1) 4 (3.6) 0 (0)	 NR
Histology (%) Adenocarcinoma Adenosquamous Large-cell carcinoma Squamous cell carcinoma Other	 107 (95.5)) 1 (0.9) 1 (0.9) 2 (1.8) 1 (0.9)	 108 (98.0) 0 (0) 1 (0.9) 1 (0.9) 0 (0)	 24 (96.0) 0 0 0 1 (4.0)
Prior therapy (%)			

Trial name	**ALTA Arm A (2, 32)**	**ALTA Arm B (2, 32)**	**Study 101 Relevant subgroup only (38)**
Crizotinib Platinum-based chemo Any chemo	112 (100) NR 83 (74.1)	110 (100) 80 (72.7) 81 (73.6)	25 (100) NR 17 (68.0
Prior radiotherapy to the brain (%)	50 (44.6)	46 (41.8)	7 (28.0)
Disease Stage at study entry IIIA IIIB IV Other	 0 (0) 3 (2.7) 109 (97.3) 0 (0)	 1 (0.9) 1 (0.9) 108 (98.2) 0 (0)	 NR
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.			

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

Table 9 describes the primary objectives, statistical methodology and data handling techniques used in ALTA and Study 101.

Table 9: Overview of the statistical approach in ALTA and Study 101

Trial number (acronym)	**ALTA (2, 32)**	**Study 101 (3, 37)**
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,	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.

Trial number (acronym)	**ALTA (2, 32)**	**Study 101 (3, 37)**
	but post-hoc HRs were estimated for PFS to support dose selection.	
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 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.	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 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.		

Participant flow through the relevant clinical trials

In the ALTA trial, 222 patients were enrolled and randomly assigned to a treatment arm: Arm A 90mg once daily; n=112, and Arm B 180mg with a 7-day lead-in at 90mg; n=110. Three patients in Arm A were never treated and are included in the intention-to-treat analyses, but not in the safety population (n=219). Appendix D (section D.1.2), shows the flow of participants through ALTA by means of a CONSORT diagram.

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

Guidance for quality analysis produced by the Centre for Reviews and Dissemination (CRD)(39) was used to inform the quality assessment of the brigatinib trials. As these were both non-RCTs, they were quality assessed using domains of the Cochrane risk of bias tool, adapted using criteria outlined by CRD guidance for quasi-experimental study designs. Trials were also quality-accessed in accordance with NICE guidelines (40) with summary results presented in **Table 10**. Detailed quality assessment overview table for brigatinib trials can be found in Appendix D (section D.1.3). In addition, the full consideration of risk of bias in each trial can be found in Appendix D (section D.1.1.12).

Both ALTA and Study 101 (n=25 subgroup), recruited patients that represent the eligible population for this intervention in that patients were diagnosed with advanced ALK+ NSCLC and had progressed on or were intolerant to crizotinib. Patients are consistent with those that are treated in clinical UK practice in terms of baseline demographics and the nature of their disease.

Selection bias was minimised with pre-specified eligibility criteria which was consistent across both trials. All participants recruited in the trials were accounted for with withdrawal reasons reported. Efficacy analyses were conducted in ITT populations and safety analyses in a safety population (treated). Both trials were unblinded although in ALTA, Independent Review Committee (IRC) assessment of responses were used to confirm investigator-assessed outcomes and the IRC was blinded to the dosage assignment (arm A or B), although not to the treatment since all patients received brigatinib.

The main evidence base for the clinical effectiveness of brigatinib comes from the pivotal ALTA trial.(2) Although ALTA was not an RCT, it was a fully randomised, robustly conducted study. Patients were stratified by baseline metastases and best investigator-assessed response to crizotinib for randomisation and although the trial was non-comparative, steps were taken to reduce the risk of bias by utilising an IRC to confirm efficacy endpoints. Overall, the findings from ALTA can be considered internally valid as steps were successfully taken to reduce the impact of confounding variables. Likewise, ALTA is also externally valid as findings were consistent with the pre-clinical activity of brigatinib and with the efficacy outcomes reported in the earlier phase I/II Study 101.(3)

The subgroup of 25 eligible patients from Study 101 provide supporting clinical effectiveness evidence for brigatinib. Due to the small sample size it is harder to assess quality, but the trial was well conducted and valid in overall terms.

Table 10: 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		

B.2.6 Clinical effectiveness results of the relevant trials

B.2.6.1 Summary of clinical effectiveness results

A summary of the key efficacy results reported in both ALTA and Study 101 is presented in Table 11. For ALTA, the data presented is that used in the ITC and economic model (February 2017),(34) in addition to the recent data update (September 2017 data extraction).(35) For Study 101, the May 2016 data extraction is included.(3, 36, 37) Full results for each study can be found in section B.2.6.2 and B.2.6.3.

Table 11: Efficacy summary from ALTA trial (ITT population, 21 February 2017 and 29 September 2017,) and Study 101 (n=25 patients from ITT population, 31 May 2016)

Trial	ALTA (31, 34, 35)								Study 101 (36-38)
Data extraction	September 2017				February 2017				May 2016
Assessment	INV		IRC		INV		IRC		INV
	Arm A	Arm B	Arm A	Arm B	Arm A	Arm B	Arm A	Arm B	N=25
Median duration of follow-up, months	19.6	24.3	19.6	24.3	16.8	18.6	16.8	18.6	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)	46 (35-57)*	55 (44-66)*	51 (41-61)	55 (45-64)	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)	12.0 (9.2-17.7)	13.8 (10.2-17.5)	13.8 (7.4-NR)	14.8 (12.6-NR)	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)	9.2 (7.4-11.1)	15.6 (11.1-19.4)	9.2 (7.4-12.8)	16.7 (11.6-NR)	16.3 (9.2-NE)
Median OS, months	29.5 (18.2-NR)	34.1 (27.7-NR)	---	---	NR (20.2-NR)	27.6 (27.6-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

B.2.6.2 Efficacy data from the ALTA trial of brigatinib

B.2.6.2.1 Overview

During the ALTA trial, brigatinib demonstrated robust efficacy and a predictable and manageable safety profile. Results from an interim data extraction of 31st May 2016 (investigator-assessment was to 29th February 2016), an updated data extraction of 21st February 2017 and the most recent of 29th September 2017 are included in this section. For the February 2017 data extraction, the median duration of follow-up was 17.9 months,(34) compared with a median duration of follow up of 7.97 months at the 31 May 2016 data extraction.(2) By the September 2017 data cut, the median duration of follow-up extended to 19.6 months in Arm A and 24.3 months in arm B.(35)

All 222 patients (N=112 in Arm A and N=110 in Arm B) enrolled in the study and are included in the Intent-to-Treat (ITT) population for efficacy analyses and the 219 (98.6%) patients who received study drug are included in the Treated Population for the safety analyses.

By February 2017, response rates remained like the earlier data cut and demonstrated that brigatinib showed high response rates in ALK+ patients whose disease had progressed on crizotinib and that these responses were durable. Data for PFS and OS had matured and remained consistent with the previous data cut. With more mature follow-up from the September 2017 data extraction, data are showing systemic and CNS efficacy that is consistent with and improved over the clinically meaningful efficacy observed at prior data cuts. This additional follow-up shows that responses are durable, with the magnitude of effect on ORR, DOR and PFS being clinically meaningful. The data is also mature, as evidenced by the duration of follow and the proportion of PFS events that have accrued. By the latest data extraction, the primary efficacy endpoint of investigator-assessed ORR was 56.4% (97.5% CI:45.2-67.0) in Arm B (the proposed recommended dose at 180mg with a 7day lead-in at 90mg), with a median IRC-assessed PFS extending to 16.7 months (95% CI: 11.6-21.4) and median OS of 34.1 months (95% CI: 27.7-not reached).(35)

Complete efficacy results are shown in sections B.2.6.2.2- B.2.6.2.6.

B.2.6.2.2 Response rates

In the ALTA study, the primary efficacy endpoint was confirmed ORR as assessed by the investigator (INV) per RECIST v1.1 (Table 12). The ORR was defined as the proportion of patients who were confirmed to have achieved complete response (CR) or partial response (PR) after initiation of brigatinib. Confirmed ORR assessed by Independent Review Committee (IRC) was defined as the proportion of patients who were confirmed to have achieved CR or PR using RECIST v1.1 after initiation of brigatinib. As secondary response endpoints, ALTA also investigated time to response, duration of response (Table 13) and intracranial responses (Table 14).

Intra-cranial response rates

In the ALTA trial, 153 patients had baseline brain metastases and 44 had measurable lesions. Of the patients with measurable lesions, 34 patients had at least 1 active brain metastasis at baseline identified by the investigator and for those with non-measurable lesions, there were 68 patients who had a least 1 active brain metastasis at baseline. An active brain metastasis is defined for this study as a lesion that has not previously been irradiated or had prior radiation treatment but then definitely progressed after being irradiated, as assessed by the investigator. All intracranial responses in patients with brain metastases were assessed by IRC (see Table 14, Figure 6, Figure 7,

Figure 8,

Figure **9**).

Overall response rates

Table 12: Objective response rates (as per INV or IRC assessment) from the ALTA trial, ITT population (Arm A, n=112; Arm B, n=110)

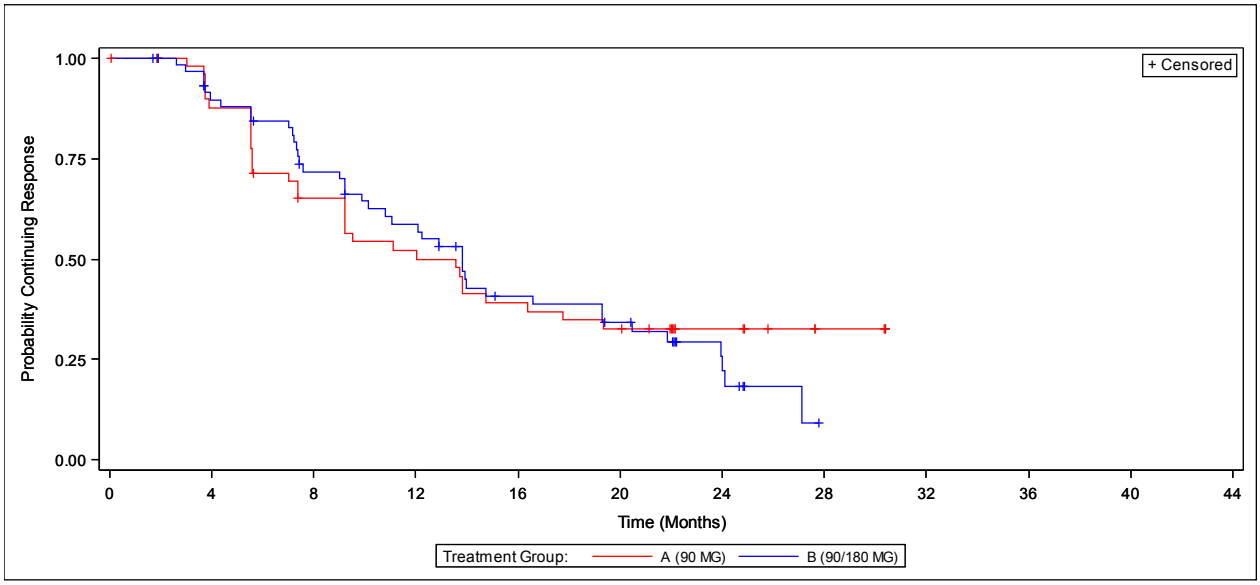
Trial name	ALTA											
Data cut	September 2017 (35)				February 2017 (34, 41)				May 2016 (2)			
	Arm A		Arm B		Arm A		Arm B		Arm A		Arm B	
Median months duration of follow-up (range)	19.6 (0.1-35.2)		24.3 (0.1-39.2)		16.8 (0.1-28.5)		18.6 (0.1-32.0)		7.8 (0.1-16.7)		8.3 (0.1-20.2)	
Assessment	INV	IRC	INV	IRC	INV	IRC	INV	IRC	INV	IRC	INV	IRC
Confirmed ORR, % (CI 95%)	45.5 (34.8-56.5)	50.9 (41.3-60.5)	56.4 (45.2-67.0)	56.4 (46.6-65.8)	46 (35-57)	51 (41-61)	55 (44-66)	55 (45-64)	45 (34-56)	48 (39-58)	54 (43-65)	53 (43-62)
Disease control rate % (CI 95%)	NR	NR	NR	NR	NR	NR	NR	NR	82 (74-89)	78 (69-85)	86 (79-92)	84 (75-90)
CR %	1.8	5.4	4.5	5.5	1.8	5.4	4.5	5.5	1	4	4	5
PR %	43.8	45.5	51.8	50.9	43.8	45.5	50.9	49.1	44	45	50	48
Abbreviations: Abbreviations: ORR; overall response rate; CR complete response; PR partial responses; SD stable disease; PD progressive disease; NR, not reported; CI, confidence interval. ** In ALTA 97.5% CI was used for investigator-assessed outcomes (primary endpoint)												

IRC- assessed time to response and duration of response

Table 13: Time to response and duration of response

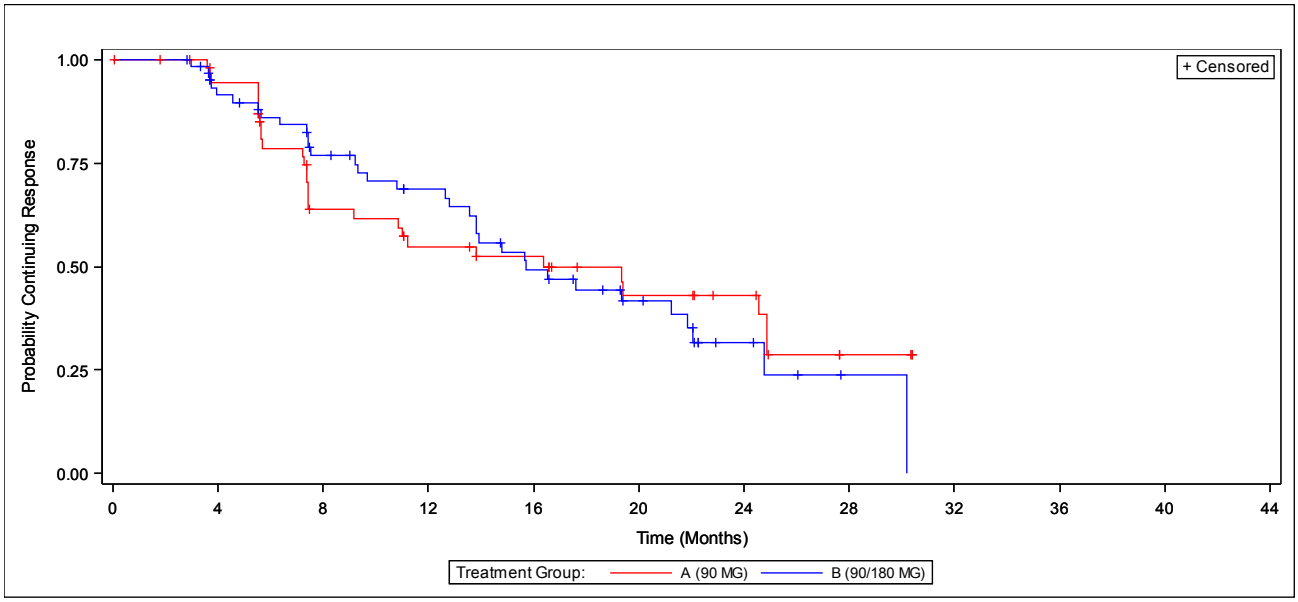
Trial name	ALTA											
Data cut	September 2017 (33, 35)				February 2017 (33, 34, 41)				May 2016 (2, 32)			
	Arm A		Arm B		Arm A		Arm B		Arm A		Arm B	
Median months duration of follow-up (range)	19.6 (0.1-35.2)		24.3 (0.1-39.2)		16.8 (0.1-28.5)		18.6 (0.1-32.0)		7.8 (0.1-16.7)		8.3 (0.1-20.2)	
Assessment	INV	IRC	INV	IRC	INV	IRC	INV	IRC	INV	IRC	INV	IRC
Analysis set, responders (N)	51	57	62	62	51	57	61	60	50	54	59	58
Median time to response, months (range)	1.8 (1.7-11.1)	1.8 (1.6-26.6)	1.9 (1.0-21.1)	1.9 (1.0-23.4)	1.8 (1.7-11.1)	1.8 (1.6-12.8)	1.9 (1.0-11.0)	1.9 (1.0-15.6)	1.8 (1.7-9.1)	1.8 (1.6-7.3)	1.9 (1.0-11.0)	1.9 (1.0-9.3)
Median duration of response, months (CI 95%)	12.0 (9.2-17.7)	16.4 (7.4-24.9)	13.8 (10.2-19.3)	15.7 (12.8-21.8)	12.0 (9.2-17.7)	13.8 (7.4-NR)	13.8 (10.2-17.5)	14.8 (12.6-NR)	13.8 (5.6-13.8)	13.8 (7.4-NR)	11.1 (9.2-13.8)	13.8 (9.3-NR)
Events (% of responders)	32 (62.7)	29 (50.9)	41 (66.1)	34 (54.8)	30 (60.0)	26 (45.6)	35 (57.4)	26 (43.3)	14 (28.0)	17 (31.5)	12 (20.3)	14 (24.1)
Abbreviations: CI, confidence interval; INV, investigator-assessed; IRC, independent review committee assessed; NR, not reached.												

Figure 4: Kaplan-Meier plot of duration of response for patients with an investigator-assessed confirmed response (CR or PR) (N=113) by treatment arm (September 2017)



Source: CSR Addendum for Study AP26113-11-201, September 2017 data extraction (TLF 14.2.1.9)(35)

Figure 5: Kaplan-Meier plot of IRC-assessed systemic duration of response, by treatment arm, in the population with IRC-confirmed response (N=119)



Source: CSR Addendum for Study AP26113-11-201, September 2017 data extraction (TLF 14.2.3.10)(35)

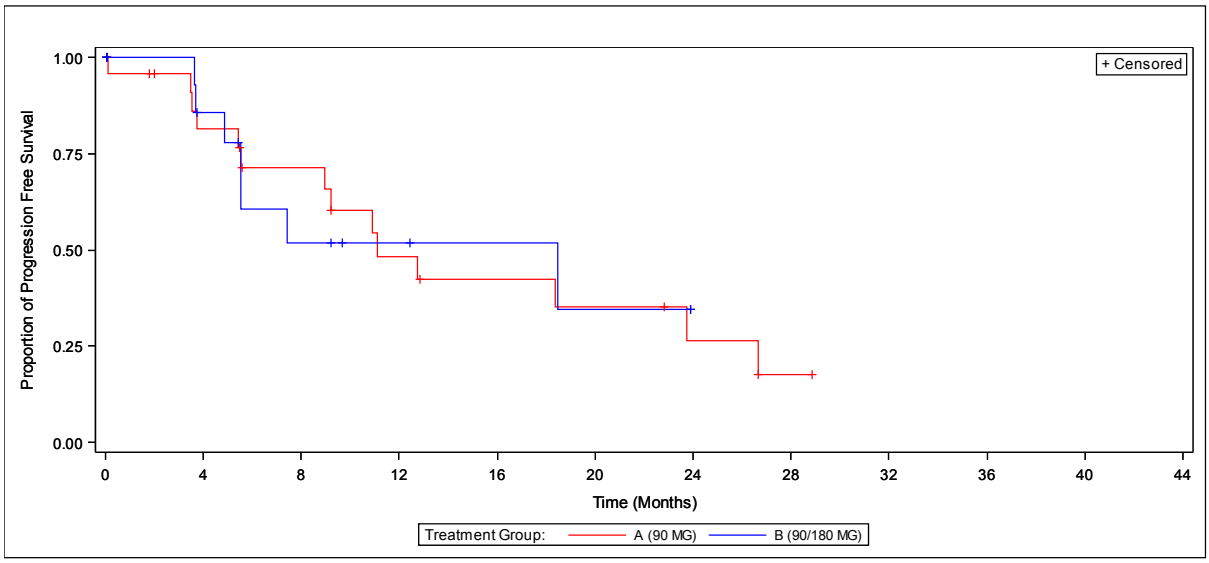
Table 14: Intracranial responses in patients with baseline brain metastases

Trial name	ALTA											
Data cut	September 2017 (35)				February 2017 (31, 34)				May 2016 (2)			
	Arm A		Arm B		Arm A		Arm B		Arm A		Arm B	
Patients included in analyses	Patients with measurable BM	Patients with measurable, active BM	Patients with measurable BM	Patients with measurable, active BM	Patients with measurable BM	Patients with measurable, active BM	Patients with measurable BM	Patients with measurable, active BM	Patients with measurable BM	Patients with measurable, active BM	Patients with measurable BM	Patients with measurable, active BM
Analyses group, n	26	19	18	15	26	19	18	15	26	19	18	15
Confirmed intracranial ORR, % (95% CI)	50.0	47.4	66.7	73.3	50.0 (29.9-70.1)	47.4 (24.4-71.1)	66.7 (41.0-86.7)	73.3 (44.9-92.2)	42 (23-63)	42 (20-67)	67 (41-87)	73 (45-92)
Median intracranial DOR/ months (95% CI)	9.4 (3.7-24.9)	9.4 (3.7-NR)	16.6 (3.7-NR)	16.6 (3.0-NR)	NR (3.7-NR))	9.4 (3.7-NR)	16.6 (3.7-16.6)	16.6 (3.0-NR)	NE	NR	5.6 (3.7-NR)	5.6 (3.0-NR))
Median intracranial PFS / months (95% CI)	11.1 (5.6-23.7)	---	18.5 (4.9-NR)	---	11.1 (5.6-NR))	11.1 (3.7-26.7)	18.5 (4.9-18.5)	7.4 (4.9-NR)	---	---	---	---
Intracranial disease control rate, % (CI 95%)	84.6	84.2	83.3	93.3	84.6 (65.1-95.6)	---	83.3 (58.6-96.4)	---	85 (65-96)	84 (60-97)	83 (59-96)	93 (68-100)

Abbreviations: BM, brain metastases; ORR, objective response rates; DOR, duration of response; PFS, progression free survival; CI, confidence interval; CNS, central nervous system; NE, not estimable; NR, not reached; QD, once daily; ---, not reported.

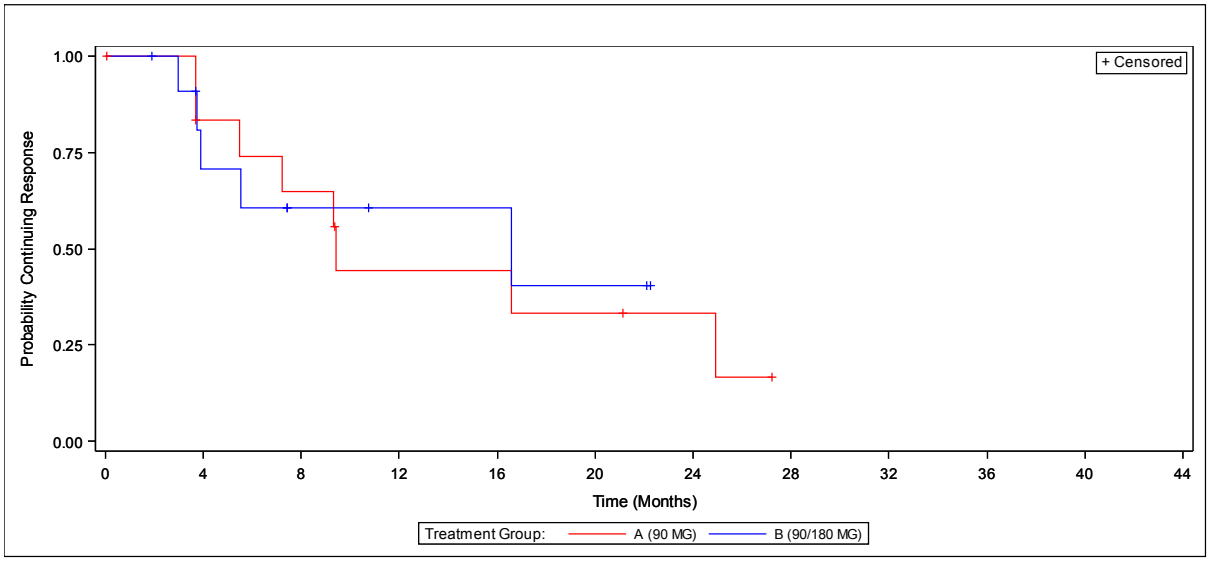
** Active BM were defined as lesions without prior radiotherapy or those with investigator-assessed progression after prior radiotherapy

Figure 6: Kaplan-Meier plot of IRC-assessed CNS progression free survival in patients with measurable brain metastases at baseline (n=44)



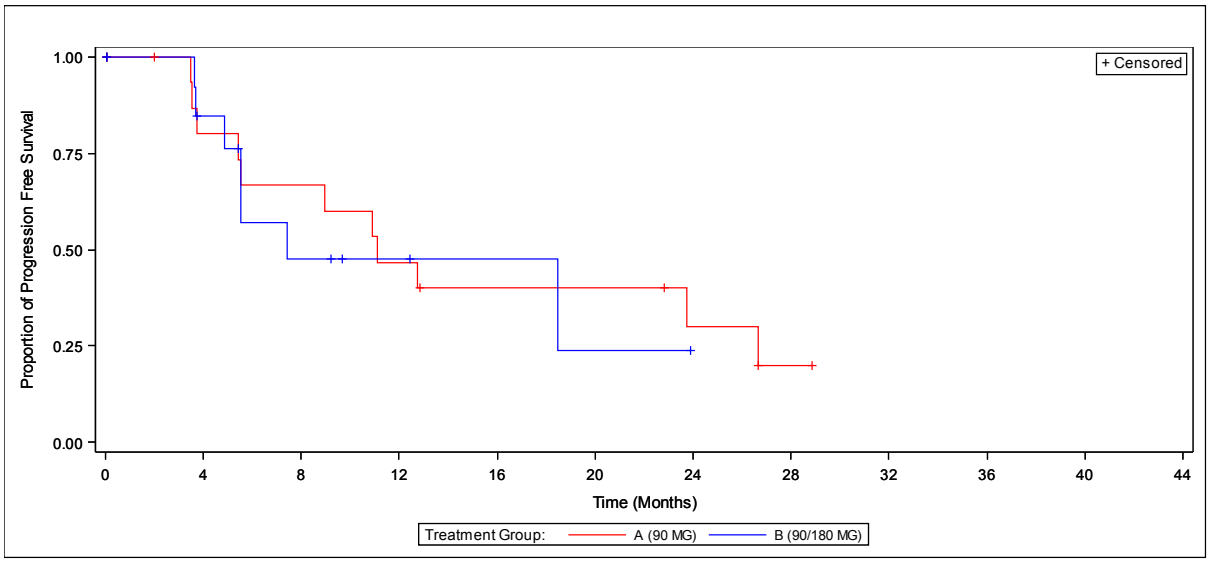
Source: CSR Addendum for Study AP26113-11-201, September 2017 data extraction (TLF 14.2.4.7)(35)

Figure 7: Kaplan-Meier plot of IRC-assessed CNS duration of response in patients with measurable baseline metastases and a confirmed CNS response (n=25)



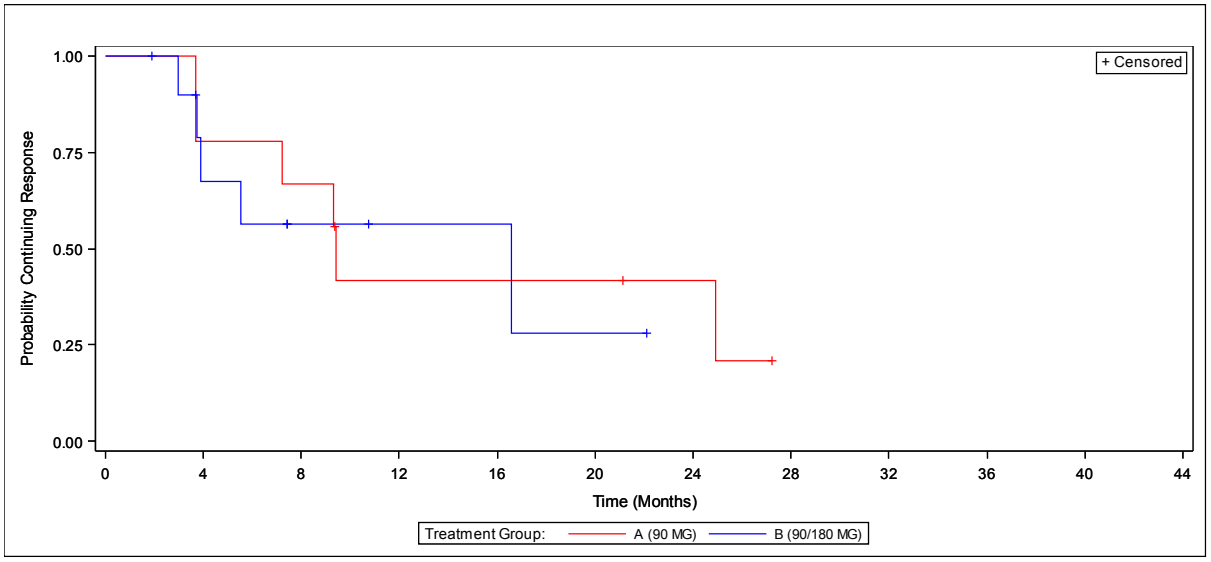
Source: CSR Addendum for Study AP26113-11-201, September 2017 data extraction (TLF 14.2.4.9)(35)

Figure 8: Kaplan-Meier plot of IRC-assessed CNS progression free survival in patients with measurable brain metastases at baseline (n=44)



Source: CSR Addendum for Study AP26113-11-201, September 2017 data extraction (TLF 14.2.5.7)(35)

Figure 9: Kaplan-Meier plot of IRC-assessed CNS duration of response in patients with active, measurable baseline metastases and a confirmed CNS response (n=20)



Source: CSR Addendum for Study AP26113-11-201, September 2017 data extraction (TLF 14.2.5.9)(35)

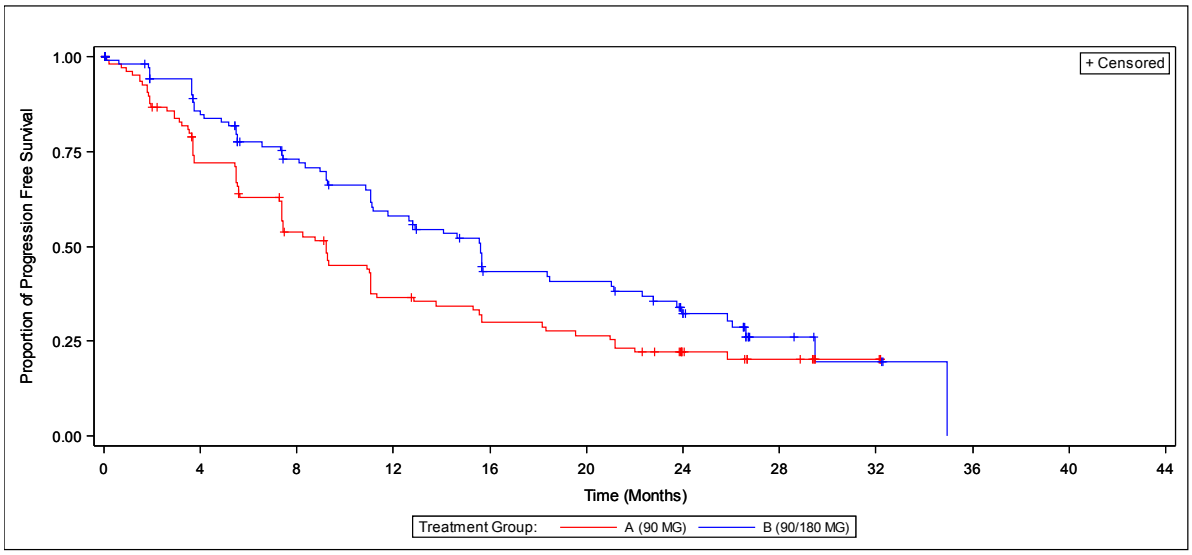
B.2.6.2.3 Progression-free survival

Brigatinib demonstrated a high rate of systemic response in patients with ALK+ NSCLC whose disease had progressed on prior crizotinib therapy for both dosing regimens tested (90mg and 180mg once daily [QD] with a 7-day lead-in at 90mg QD [90 mg QD→180 mg QD]). These responses were achieved rapidly and already evident at the February/May 2016 data cut. With additional follow-up at the 29 September 2017 data extraction, the data show that these responses are durable, and the median PFS was greater than 15 months in Arm B by both investigator and IRC assessment (15.6 and 16.7 months, respectively). The magnitude of effect on PFS is clinically meaningful. The data are mature, as evidenced by the duration of follow-up and the proportion of PFS events that have accrued. See Table 15.

Table 15: Progression-frees survival by treatment arm in ITT population

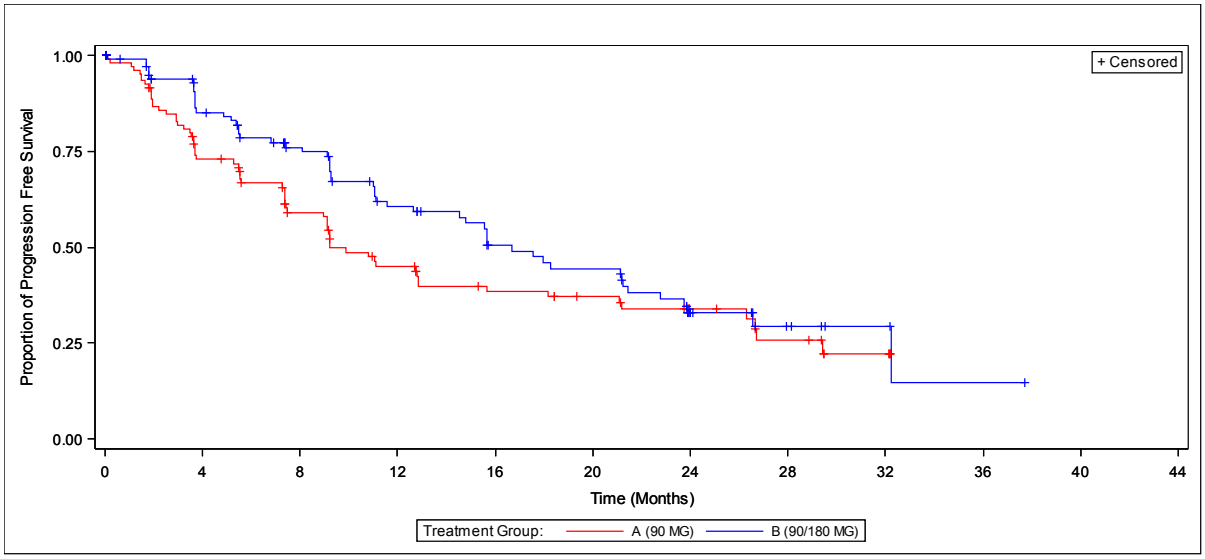
Trial name	ALTA											
Data cut	September 2017 (35)				February 2017 (31)				May 2016 (2, 32, 42)			
	Arm A		Arm B		Arm A		Arm B		Arm A		Arm B	
Median months duration of follow-up (range)	19.6 (0.1-35.2)		24.3 (0.1-39.2)		16.8 (0.1-28.5)		18.6 (0.1-32.0)		7.8 (0.1-16.7)		8.3 (0.1-20.2)	
Assessment	INV	IRC	INV	IRC	INV	IRC	INV	IRC	INV	IRC	INV	IRC
Median progression free survival (95% CI)	9.2 (7.4 - 11.1)	9.2 (7.4 - 12.8)	15.6 (11.1 - 21.0)	16.7 (11.6 - 21.4)	9.2 (7.4 - 11.1)	9.2 (7.4 - 12.8)	15.6 (11.1 - 19.4)	16.7 (11.6 -NR)	9.2 (7.4 - 15.6)	9.2 (7.4 - NR)	12.9 (11.1 -NR)	15.6 (11.0 -NR)
Number of events, (%)	68.8	58.0	58.2	49.1	65	54	50	41	44.6	44	28	28
Abbreviations: CI, confidence interval; ITT, intention to treat; INV, investigator-assessed; IRC, independent review committee-assessed; NE, not estimable; NR, not reported; PFS, progression free survival.												

Figure 10: Kaplan-Meier plot of Investigator-assessed progression-free survival by treatment arm in ITT population (September 2017)



Source: CSR Addendum for Study AP26113-11-201, September 2017 data extraction (TLF 14.2.1.7)(35)

Figure 11: Kaplan-Meier plot of IRC-assessed progression-free survival by treatment arm in ITT population (September 2017)



Source: CSR Addendum for Study AP26113-11-201, September 2017 data extraction (TLF 14.2.3.8)(35)

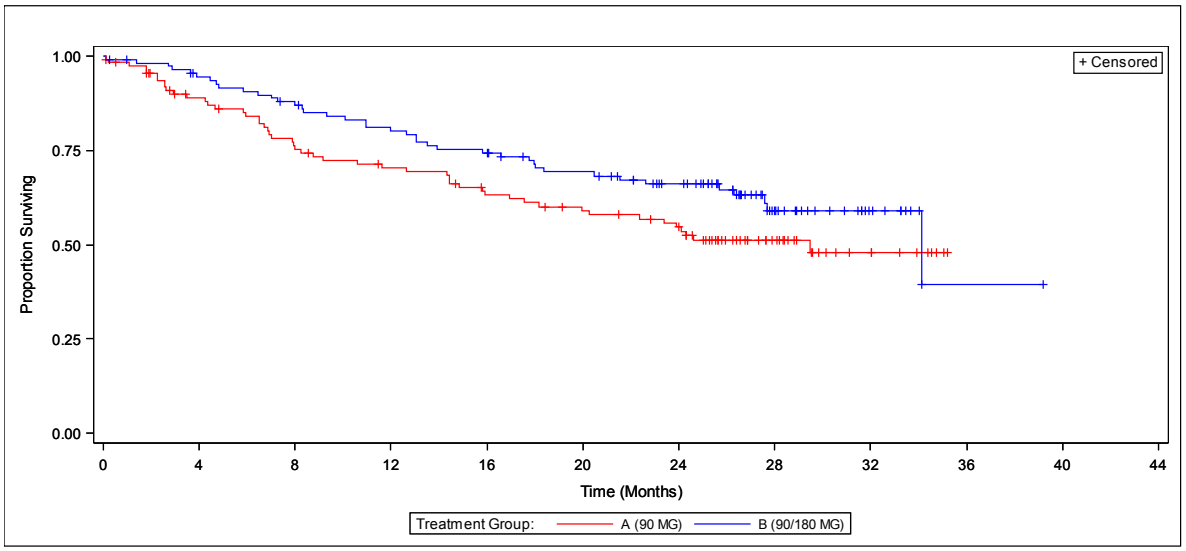
B.2.6.2.4 Overall survival

At the initial data extraction, estimates of overall survival (OS) were limited due to relatively few patients having died by the time of the data extraction (February 2016).(2) However, by the most recent September 2017 data extraction, data had matured as indicated by the number of events. The OS ranged from 0.1 to 35.2 months for patients in Arm A and from 0.1 to 39.2 months for patients in Arm B. The 12- and 24-month probabilities of survival were 70.3% and 54.6%, respectively, for patients in Arm A and 80.1% and 66.1%, respectively, for patients in Arm B.(35) See Table 16.

Table 16: Overall survival in ITT population

Trial	ALTA					
Data cut	September 2017 (35)		February 2017 (31, 34)		May 2016 (32)	
	Arm A	Arm B	Arm A	Arm B	Arm A	Arm B
Median months duration of follow- up (range)	19.6 (0.1-35.2)	24.3 (0.1-39.2)	16.8 (0.1-28.5)	18.6 (0.1-32.0)	7.8 (0.1 - 16.7)	8.3 (0.1-20.2)
Median months overall survival (95% CI)	29.5 (18.2-NR)	34.1 (27.7-NR)	NR (20.2-NR)	27.6 (27.6-NR)	NR (range: 0.1-16.7)	NR (range: 0.1-20.2)
Number of events, %	44.6	36.4	37.5	29.1	24.1	15.5
Abbreviations: CI, confidence interval; NR, not reached						

Figure 12: Kaplan-Meier plot of overall survival by treatment arm in ITT population (September 2017)



Source: CSR Addendum for Study AP26113-11-201, September 2017 data extraction (TLF 14.2.1.10)(35)

B.2.6.2.5 Health related quality of life

The ALTA trial of brigatinib reported HRQL using the EORTC QLQ-C30 v3.0 questionnaire (questions 29 and 30 only), which was later mapped to EQ-5D for use in the ITC analyses (see section B.3.4.1). In the analysis, the mean transformed global health status (GHS) gradually increased through approximately 7 months and then slowly declined but remained higher than baseline values. No significant difference was observed at baseline or during follow-up between the two different dose arms of 90mg and 180mg.(2)

In addition, a post hoc analysis performed utilising these patients reported outcomes (PROs) collected at baseline and on the first day of each treatment cycles were carried out by constructing multivariable mixed effect models and cumulative distribution frequency plots. These concluded that up to the time of analyses (cycle 5), 80% of all patients experienced an increase or no change in GHS/QOL scores with 50% of patients experiencing a clinically meaningful improvement.(43)

After a longer follow-up, the global HRQL scores did drop below baseline for Arm B, but not until cycle 30, with only 2 patients contributing to this data. Similarly, in Arm A, the HRQL score dropped below baseline value at Cycle 27, and only 8 patients contributed to this data.(35)

While the ALTA trial did collect HRQL data in the form of the EORTC QLQ-C30 v3.0 questionnaire, questions 29 and 30, it is acknowledged that there were limitations to this approach. This tool did not prove to be sensitive to analyses and did not reflect the positive improvements seen by patients in terms of reduced tumour burden and intracranial responses. The intracranial efficacy shown by brigatinib in patients with measurable and active bran metastases (see Table 14), could be reasonably predicted to infer considerable improvements to their HRQL.

B.2.6.3 Efficacy data from Study 101 of brigatinib

B.2.6.3.1 Overview

At the data cut-off in May 2016, median time on treatment for all ALK+ NSCLC patients previously-treated with crizotinib (N=71 patients) was 20.0 months (range: 1–47.5). For overall ALK+ NSCLC patients with prior crizotinib treatment, the ORR was 71.8% (51/71) with 44 of these responses confirmed (confirmed ORR: 62.0%) and 5 (7.0%) were complete responses (CRs). The median time to response was 1.8 months (range:1.2–6.9). ORR was highest in ALK+ NSCLC patients with prior crizotinib treatment in the 90mg QD → 180 mg QD group (80.0%, 20/25) and the proportion of confirmed responses were also highest in that dosing group (76.0%, 19/25). The KM estimate median duration of response was 26.1 months (95% CI: 7.4, 26.1; range: 1.9–26.1). The KM estimate median PFS 16.3 months (95% CI: 9.2, not reached; range: 0.5–27.8). The KM estimate median OS for all ALK+ NSCLC patients with prior crizotinib was 47.6 months (95% CI: 21.4, 47.6; range: 0.2–47.6).

Results for the subgroup of patients from Study 101 that are relevant to the scope of this decision problem are presented in sections B.2.6.3.2 – B.2.6.3.5.

B.2.6.3.2 Response rates

Overall Response

In Study 101, investigator-assessed confirmed objective response rate was the primary endpoint in the phase II portion of the trial (Table 17).

Table 17: Investigator-assessed response rates for selected patients receiving 90 → 180mg brigatinib in Study 101

Trial ID	Study 101 (36, 37)
	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)	

Time to response and duration of response

Table 18: Time to response and duration of response for selected patients receiving 90 → 180mg brigatinib in Study 101

Trial ID	Study 101 (36, 37)
	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)

Trial ID	Study 101 (36, 37)
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)	

Intracranial responses

Study 101 included intracranial responses as a secondary outcome, although data for the n=25 patients that are fully relevant to this decision problem are not reported independently of the n=28 full dosing cohort (of the 28, three patients did not have prior crizotinib). An overview of intracranial responses is provided below.

Of the 79 ALK+ NSCLC patients enrolled, 50 (63%) had brain metastases identified at baseline by central review of MRI scans. 17 had measurable brain metastases (15 of whom had follow-up scans), and 33 had only non-measurable brain metastases (31 of whom had follow-up scans). The intracranial ORR for patients with measurable brain metastases at baseline was 66.7% (10/15), with 8 patients with intracranial responses confirmed (intracranial confirmed ORR: 53.3%). For patients with only non-measurable brain metastases at baseline, the rate of intracranial complete responses was 41.9% (13/31), with 11 patients with intracranial responses confirmed (intracranial confirmed ORR: 35.5%). The intracranial ORR for patients in the 90 mg QD →180 mg QD cohort with measurable brain metastases at baseline, was 80.0% (4/5, 3 confirmed) and the intracranial ORR for patients with only non-measurable brain metastases at baseline was 46.2 % in the 90 mg QD →180 mg QD (6/13, 5 confirmed).(37)

B.2.6.3.3 Overall survival

By the May 2016 data extraction, KM median estimated OS had not been reached. For the 25 patients falling within scope of this indication, 12- and 24- month OS probabilities were 84.0% (95% CI: 62.8-93.7) and 64.0% (42.2-79.4), respectively.(38)

Table 19: Overall survival for selected patients receiving 90 → 180mg brigatinib in Study 101

Trial ID	Study 101 (37, 38)
	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)

Trial ID	Study 101 (37, 38)
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)	

B.2.6.3.4 Progression-free survival

Table 20: Investigator-assessed progression free survival for selected patients receiving 90 → 180mg brigatinib in Study 101

Trial ID	Study 101 (37, 38)
	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	

B.2.6.3.5 Health related quality of life

Quality of life data was not reported for patients in Study 101.

B.2.7 Subgroup analysis

No sub-groups were identified and included in specific subgroup analyses.

B.2.8 Meta-analysis

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.

B.2.9 Indirect and mixed treatment comparisons

B.2.9.1 Overview

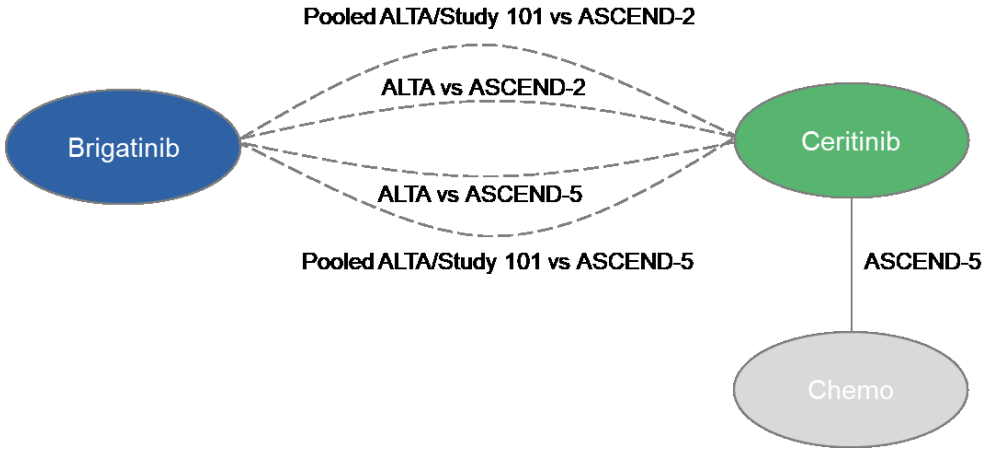
As detailed in the previous subsections, ALTA and Study 101 are the two studies identified to represent brigatinib evidence; and ASCEND-2 and ASCEND-5 are the two studies identified to represent ceritinib evidence as previously introduced in Section B2.1. A series of unanchored indirect treatment comparisons (ITCs) are required to estimate relative efficacy for OS and PFS, between brigatinib and ceritinib in the absence of head-to-head trial data.

Unanchored ITCs are prone to bias due to the lack of randomisation. A number of sensitivity analyses are presented in order to explore the uncertainty around the estimates; this includes conducting both naïve and population-adjusted ITCs, alternating the source of the brigatinib evidence (pooled data including ALTA and Study 101 versus ALTA only, PFS investigator (INV)-assessed versus PFS Independent Review Committee (IRC)-assessed), and varying the list of prognostic factors included in the population-adjusted ITCs.

Full details of the methodology used for the indirect treatment comparison are presented in Appendix D. All statistical analyses are conducting using software R and WinBUGS.

A summary of the available evidence informing the ITC is presented in Figure 13.

Figure 13: Summary of evidence informing ITC



Abbreviations: Chemo, chemotherapy; ITC, indirect treatment comparison; N, number of patients.
Notes: Dashed lines represent ITCs (e.g. MAIC analyses). Brigatinib data will comprise pooled ALTA/Study 101 (N=135) as well as ALTA alone (N=110). Chemotherapy arm is not of interest to the decision problem but is added to the figure for completeness.

B.2.9.2Naïve ITC

IPD were only available in ALTA and Study 101. For time-to-event outcomes, IPD of OS and PFS from both ASCEND-2 and ASCEND-5 (ceritinib arm only) were reconstructed using an algorithm proposed by Guyot *et al.* (2012).(44) The naïve ITC was formed by combining each of ASCEND-2 and ASCEND-5 with brigatinib data (pooled or ALTA only) to form two head-to-head 'trials'. A Cox regression model was then fitted to estimate the hazard ratio (HR) between brigatinib and ceritinib from each of the two 'trials'. For the binary endpoint – objective/overall response rates (ORR), a logistic regression model was fitted to estimate the odds ratio (OR) between brigatinib and ceritinib. Synthesis of these naïve-HRs and naïve-ORs was performed using standard meta-analysis methods to obtain an overall, pooled estimate of comparative efficacy between brigatinib and ceritinib.

This is considered a naïve comparison as no adjustment was made for differences in study baseline characteristics, however this provides a benchmark estimate of relative efficacy which are then compared with subsequent MAIC estimates. Further details of the standard meta-analysis are presented in Appendix D.

B.2.9.3Population-adjusted ITC

Brigatinib cannot be connected to ceritinib due to the absence of a common comparator arm in the ALTA/Study 101 trials and ASCEND-2 and ASCEND-5 studies. As such, a more focused approach to ITCs was required. The population adjustment approach is based on matching-adjusted indirect comparison (MAIC) methods proposed by Signorovitch *et a*l.(45) (2012), which enable to adjust the differences in study baseline characteristics. The NICE Decision Support Unit (DSU) Technical Support Document (TSD) 18 (46) suggests that both MAIC and simulated treatment comparison (STC) could be used for unanchored population adjustment approach. MAIC methods were chosen because it was recommended that the ITCs should use the same linear predictor scale as the regression/outcome model used in STC and this restricts the distribution choice when the data are time-to-event.

Broadly, MAIC analyses aim to estimate relative efficacy between brigatinib and other comparators within an adjusted trial population, i.e. once imbalances in patient baseline characteristics have been overcome through adjustment for prognostic factors (PF) and treatment-effect modifiers (TEM) believed to be influential on the outcome.

Standard pairwise meta-analyses were also conducted on MAIC data to estimate an overall, pooled estimate of comparative efficacy between brigatinib and ceritinib. The NICE DSU TSD 18,(46) which recommends performing individual MAIC analyses before pooling the relative effect estimates (i.e. HR/ORs) using standard meta-analysis methods. Further details of the ITC methodology are presented in Appendix D.

The unanchored MAIC replies on the strong assumption that all the prognostic factors (PF) and treatment-effect modifiers (TEM) are considered in the model. As suggested by the NICE DSU TSD 18,(46) choice of variables to be matched in MAIC should be carefully considered as including too many variables will reduce the effective sample size (ESS) and increasing uncertainty around the estimates as a consequence. A total of 20 potential PF and TEM were evaluated for inclusion within the MAIC analyses; these were factors which were available in the ALTA trial. In the first instance, multicollinearity was assessed between the 20 variables (using the ALTA IPD to explore this). No formal correlation tests were conducted, however exploratory analyses such as cross tabulations helped assess how strong the association was between pairs of factors. The correlation trends observed are summarised in Appendix D. Clinician feedback was obtained through interviews and completed questionnaires from five clinicians, who were asked to identify which factors were believed to be influential on survival outcomes. They were also asked to rank each factor by level of importance, to ascertain any notable trends across the clinician responses. In addition, clinical opinion was also sought to identify the classification of particular variables. A summary of the PF and TEM selection process is presented in Appendix D and further details are also presented in Section 3.5.10. A total of eight factors were taken though to inclusion in the MAIC analyses. Three factors were rated as prognostic by three or more clinicians, including best prior response to crizotinib, presence of active brain lesions and number of metastatic sites. These were not reported for either of the ceritinib studies and therefore could not be incorporated into the MAIC analyses. A qualitative assessment

providing a comparison of the two ceritinib studies and two brigatinib studies in terms of inclusion/exclusion criteria, study design and population is presented in Section 2.13). The distribution of the eight factors taken through into the MAIC analyses are summarised in Table 21. A qualitative assessment of these factors across the four studies is provided in Appendix D.

Table 21: Summary of selected variables included in the MAIC analyses

	Brigatinib		Ceritinib	
	ALTA (2, 32)	Pooled ALTA/Study 101 (36, 37)	ASCEND-2 (27)	ASCEND-5 (28)
Number of patients	110	135	140	115
Age (years) Median Range	 56.5 20-81	 57.0 20-81	 51 29-80	 54.0 44-63
Gender, n (%) Female Male	 64 (58.2) 46 (41.8)	 75 (55.6) 60 (44.4)	 70 (50.0) 70 (50.0)	 68 (59.0) 47 (41.0)
ECOG PS[a], n (%) 0-1 2	 101 (91.8) 9 (8.2)	 126 (93.3) 9 (6.7)	 120 (85.7) 20 (14.3)	 106 (92.2) 9 (7.8)
Presence of brain metastases, n (%) No Yes	 36 (32.7) 74 (67.3)	 44 (32.6) 91 (67.4)	 40 (28.6) 100 (71.4)	 50 (43.5) 65 (56.5)
Receipt of any prior, n (%) chemotherapy No Yes	 29 (26.4) 81 (73.6)	 37 (27.4) 98 (72.6)	 0 (0) 140 (100)	 1 (0.9) 114 (99.1)
Number of prior anti-cancer, n (%) regimens[a] 1-2 3+	 72 (65.4) 38 (34.6)	 NR[b] NR[b]	 61 (43.6) 79 (56.4)	 115 (100) 0 (0)
Receipt of crizotinib as last treatment, n (%) No Yes	 4 (3.6) 106 (96.3)	 7 (5.2) 128 (94.8)	 0 (0) 140 (100)	 21 (18.3) 94 (81.7)

Smoking history status, n (%) Former/current Never	 47 (42.7) 63 (57.3)	 NRb NRb	 NR NR	 43 (38.3) 71 (61.7)
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; NR, not reported. Notes: a, classification recommended by clinicians; b, not reported in Study 101 so not available in the pooled ALTA/Study 101 data.				

B.2.9.4 Results

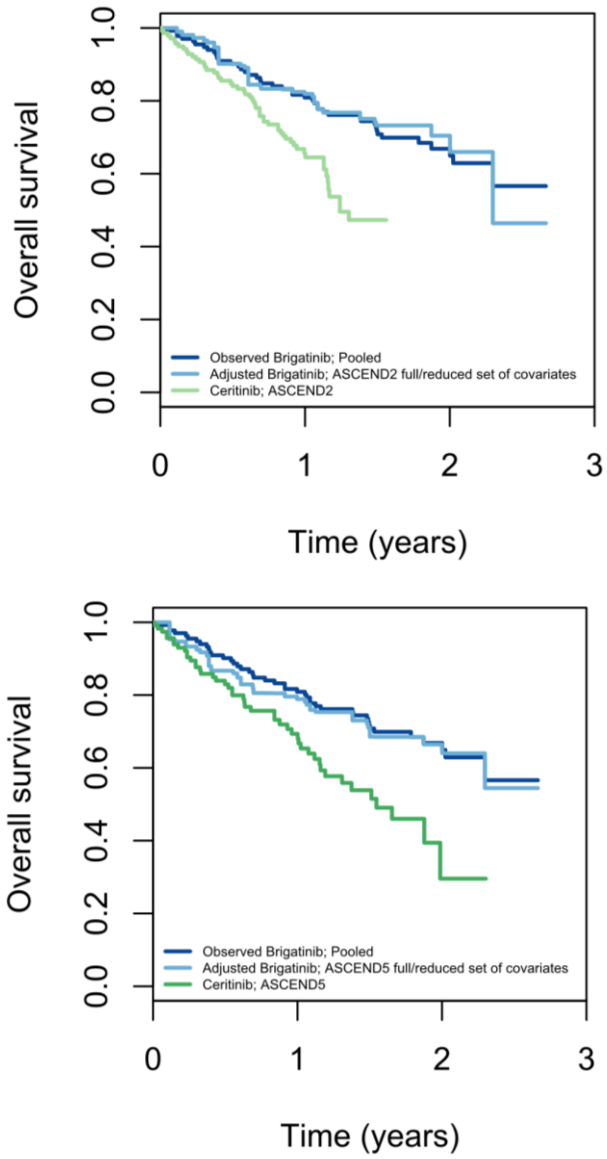
As outlined above, a number of analyses are conducted in order to explore the uncertainty around the estimates; this includes performing both naïve and population-adjusted ITCs, alternating the source of the brigatinib evidence (pooled data including ALTA and Study 101 vs. ALTA only, PFS INV vs. PFS IRC), and varying the list of prognostic factors included in the population-adjusted ITCs. Adjustment for the prognostic factors available in each of the ceritinib studies forms the MAIC [full] analysis, and adjustment for the prognostic factors commonly reported in both ceritinib studies forms the MAIC [reduced] analysis. For PFS, two types of assessment measures were available in ALTA; INV and IRC. To retain similarities within a comparison, the PFS data from ALTA were selected based on what was the primary assessment measure in the comparator study. ASCEND-2 reported both IRC and INV-assessed PFS, however INV-assessment was the primary outcome measure, whereas ASCEND-5 reported a Kaplan-Meier curve only IRC-assessed PFS. Whilst median INV-assessed PFS was reported for ASCEND-5, no Kaplan-Meier curve was reported which was required for inclusion within the MAIC analysis. ALTA PFS data were matched accordingly to each ceritinib study. Study 101 only reported INV-assessed PFS and therefore no comparison was made using the pooled ALTA/Study 101 data and ASCEND-5. The list of ITC analyses is presented in Appendix D.

B.2.9.4.1 Overall survival

The pooled ALTA/Study 101 brigatinib observed and MAIC Kaplan-Meier curves of OS are presented in

Figure *14* along with the ceritinib Kaplan-Meier curve based on reconstructed IPD from ASCEND-2 and ASCEND-5. The MAIC process yields very similar survival benefit for brigatinib (compared with the observed brigatinib data). Note that the full and reduced MAIC analyses are identical because the number of prior anti-cancer regimens and smoking status are not reported in Study 101 and so the full MAIC defaults to the reduced MAIC.

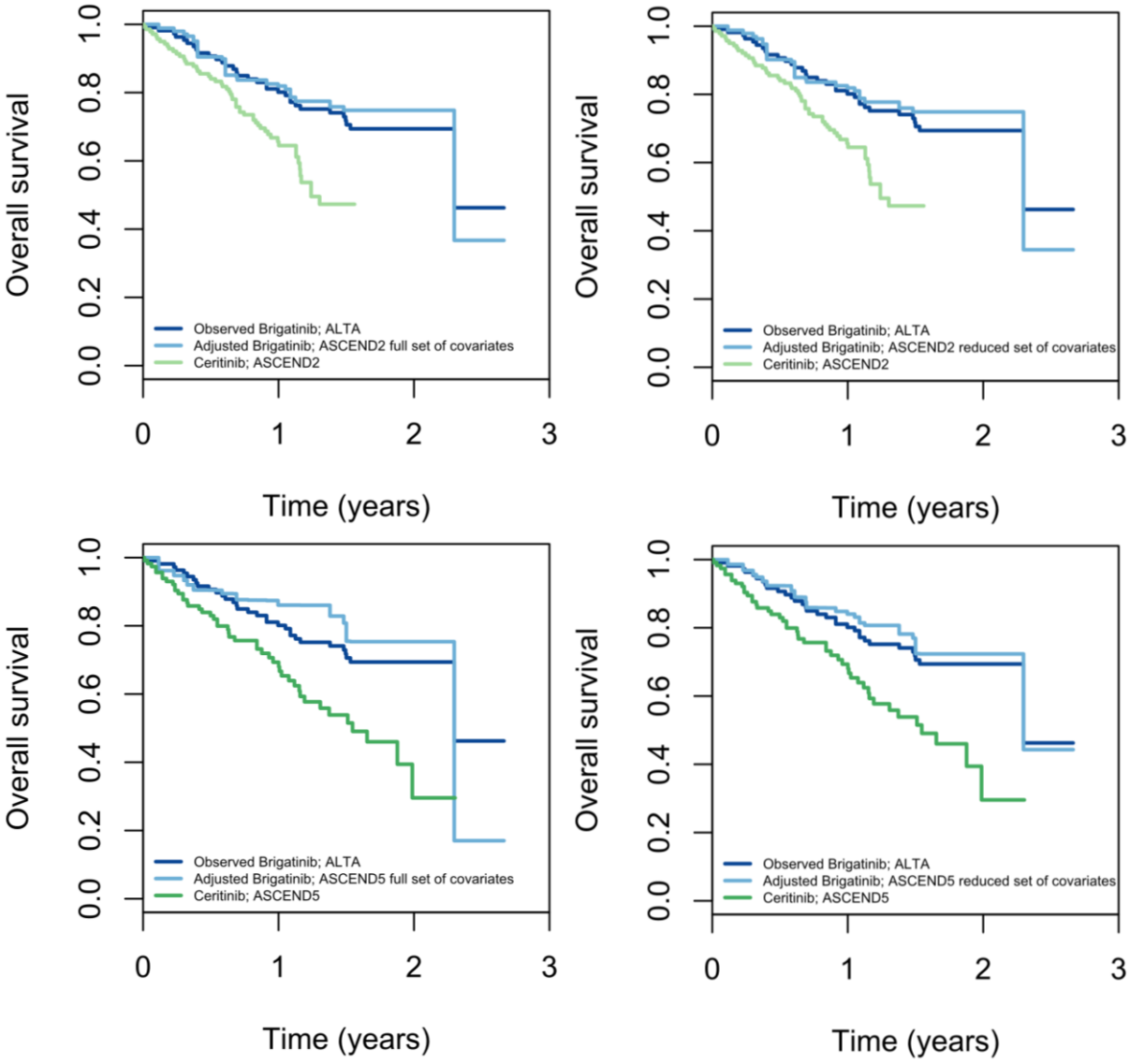
Figure 14: Observed and MAIC Kaplan-Meier curves of overall survival based on pooled ALTA/Study 101 and reconstructed ASCEND-2 and ASCEND-5



The ALTA brigatinib observed/unadjusted and MAIC Kaplan-Meier curves of OS are presented in

Figure **15**, along with the ceritinib curve based on reconstructed IPD from ASCEND-2 and ASCEND-5. Both adjusted Kaplan-Meier curves based on the MAIC [full] and [reduced] analyses using ASCEND-5 show an improved survival benefit for brigatinib (compared with the observed Kaplan-Meier curve), however, there is negligible difference between the MAIC [full] and MAIC [reduced] analyses. The ceritinib curve from ASCEND-5 is quite complete, with around 30% surviving at around 2.3 years post-randomisation. The survival prospects for brigatinib have improved in MAIC [full] analysis (compared to the observed Kaplan-Meier curve), however the tail of the Kaplan-Meier drops sharply at around 2.3 years. Survival prognosis for brigatinib has improved in the MAIC [reduced] analysis but is more comparable with the observed Kaplan-Meier curve.

Figure 15: Observed and MAIC Kaplan-Meier curves of overall survival based on ALTA and reconstructed ASCEND-2 and ASCEND-5

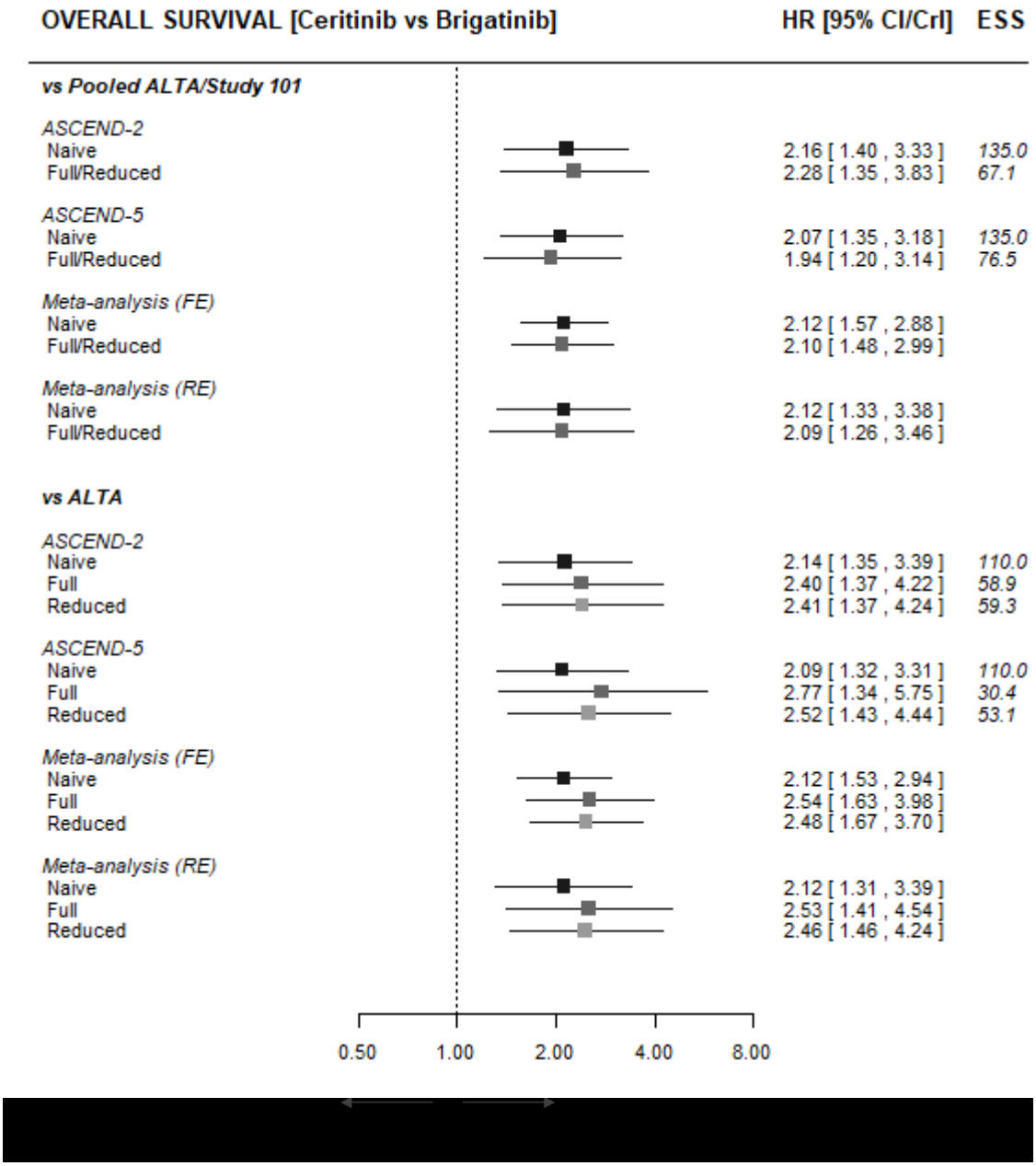


The MAIC Kaplan-Meier curves are utilised within univariate Cox regression models to estimate a MAIC-HR. Since there are multiple estimates of relative efficacy due to two sources of ceritinib data, a pairwise meta-analysis was conducted, synthesising the MAIC-HRs to obtain an overall pooled HR to represent comparative efficacy between brigatinib and ceritinib. A summary of the naïve-HRs and MAIC-HRs ceritinib versus brigatinib are presented in Figure 4 along with the respective effective sample size (ESS) and estimates from the pairwise meta-analyses. HRs less than 1 favours ceritinib and HRs greater than 1 favour brigatinib.

The MAIC-HRs reflect the trends which were observed when evaluating the Kaplan-Meier curves. When utilising the pooled ALTA/Study 101 data, the HR increases after the MAIC process for ASCEND-2, but reduces for ASCEND-5, therefore the meta-analysis results synthesising the MAIC-HRs shows similar results to the naïve estimate, with a HR of 2.09 using a random effects model. Brigatinib shows statistically significant superiority versus ceritinib. When utilising the ALTA data, the MAIC shows an improvement in the effect of

brigatinib (HR increases for ceritinib versus brigatinib) in both the ASCEND-2 and ASCEND-5 comparisons. The random-effects meta-analysis results for the MAIC [full] and MAIC [reduced] analyses show HRs of 2.53 and 2.46 respectively, compared to a naïve estimate of 2.12. Brigatinib shows statistically significant superiority versus ceritinib.

Figure 16: Summary of ITC results – overall survival



[redacted]

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.

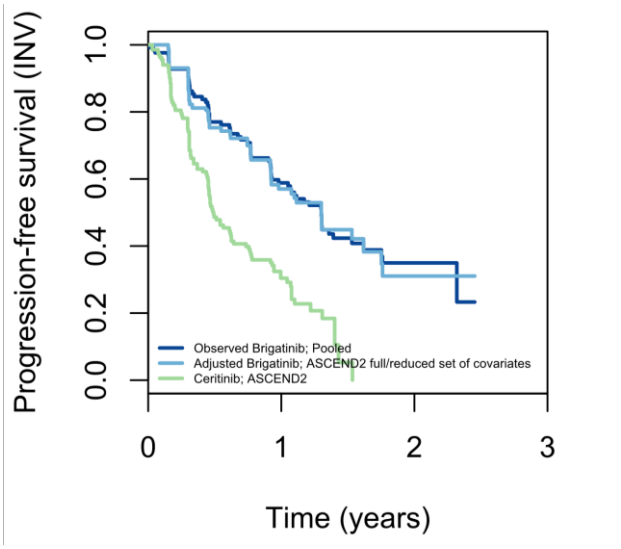
Supplementary OS results are presented in Appendix D, including a summary of median OS, a discussion around the ESS scores and the log cumulative hazard plots to assess the assumption of proportional hazards.

B.2.9.4.2 Progression-free survival

The pooled ALTA/Study 101 brigatinib observed/unadjusted and MAIC Kaplan Meier curves of PFS (INV) are presented in

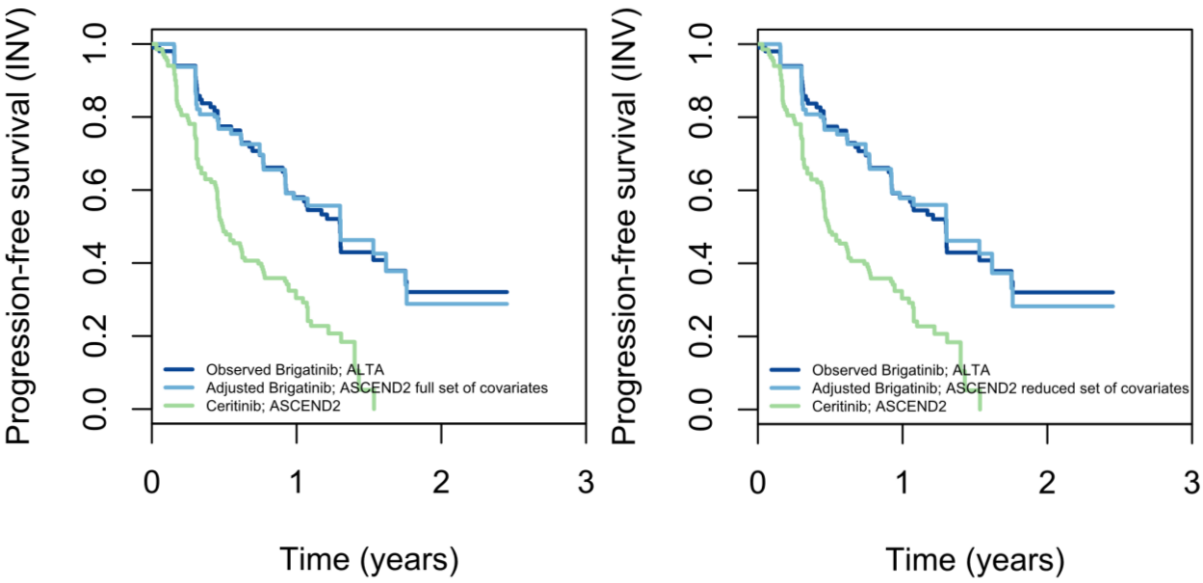
Figure 17 along with the ceritinib curve based on reconstructed IPD from ASCEND-2 only (because PFS was assessed by IRC in ASCEND-5). The MAIC process yields a very similar survival benefit for brigatinib (compared with the observed brigatinib data). Note that the full and reduced MAIC analyses are identical because the number of prior anti-cancer regimens is not reported in Study 101 and so the full MAIC defaults to the reduced MAIC.

Figure 17: Observed and MAIC Kaplan-Meier curves for progression-free survival (INV-assessed) based on pooled ALTA/Study 101 and reconstructed ASCEND-2



The ALTA brigatinib observed/unadjusted and MAIC Kaplan-Meier curves of PFS (INV) are presented in Figure 18 along with the ceritinib curve based on reconstructed IPD from ASCEND-2 only (because PFS was assessed by IRC in ASCEND-5). The MAIC process yields a very similar survival benefit for brigatinib (compared with the observed brigatinib data). Note that the full and reduced MAIC analyses are identical because the number of prior anti-cancer regimens is not reported in Study 101 and so the full MAIC simplifies to the reduced MAIC.

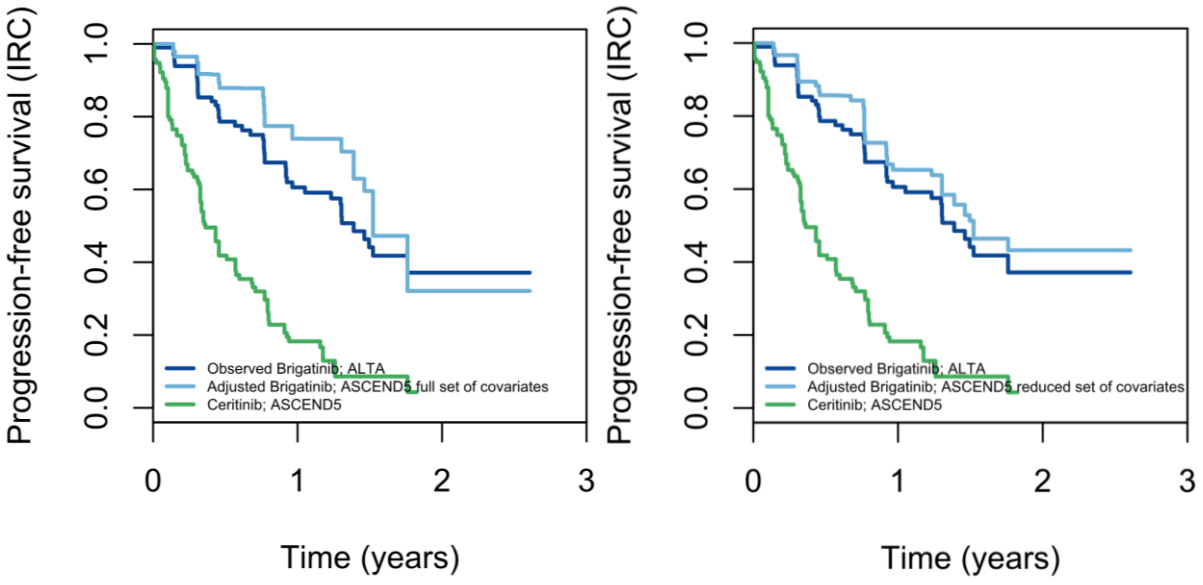
Figure 18: Observed and MAIC Kaplan-Meier curves for progression-free survival (INV-assessed) based on ALTA and reconstructed ASCEND-2



The ALTA brigatinib observed/unadjusted) and MAIC Kaplan-Meier curves of PFS (IRC) are presented in

Figure 19 along with the ceritinib curve based on reconstructed IPD from ASCEND-5. The ceritinib curve from ASCEND-5 is very complete, with around 5% surviving at around 1.8 years post-randomisation. The MAIC [full] analysis has notably improved survival prospects for brigatinib (compared to the observed Kaplan-Meier curve). The MAIC [reduced] analysis also improves the survival Kaplan-Meier for brigatinib but to a lesser extent than the MAIC [full] analysis.

Figure 19: Observed and MAIC Kaplan-Meier curves for progression-free survival (IRC-assessed) based on ALTA and reconstructed ASCEND-5



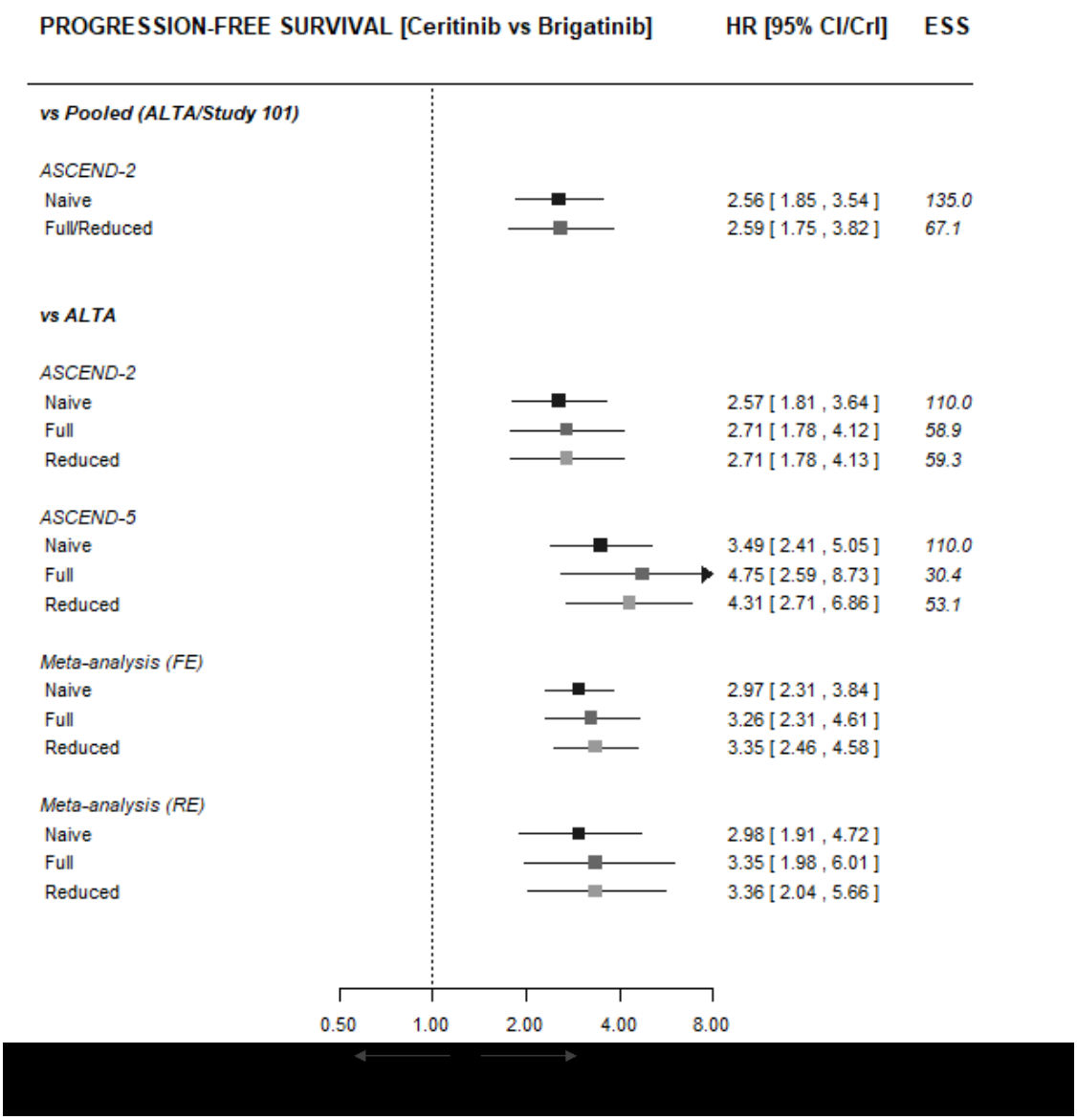
A summary of the naïve-HRs and MAIC-HRs ceritinib versus brigatinib are presented in Figure 20 (HR less than 1 favours ceritinib and HR greater than 1 favours brigatinib), along with the respective effective sample size (ESS) as well as the pooled estimates obtained from the pairwise meta-analysis.

The MAIC-HRs reflect the trends which were observed when evaluating the Kaplan-Meier curves; when utilising the pooled ALTA/Study 101 data, the HR increases ever so slightly after the MAIC process for ASCEND-2, (HR 2.59 with 95% CrI 1.75-3.82 of adjusted ITC and HR 2.56 with 95% CrI 1.85-3.54 of naïve ITC). Brigatinib shows statistically significant superiority versus ceritinib. No meta-analysis could be conducted for the pooled ALTA/Study 101 data since Study 101 did not report IRC-assessed PFS which was reported in ASCEND-5.

When utilising the ALTA data, the MAIC process improve the effect of brigatinib (HR increases for ceritinib versus brigatinib) in both the ASCEND-2 and ASCEND-5 comparisons, and notably so in the MAIC [full] analysis for ASCEND-5. Pairwise meta-analyses could be conducted when evaluating ALTA; the random effects meta-analysis results for the MAIC [full] and MAIC [reduced] analyses show HRs of 3.35 and 3.36 respectively, compared to a naïve estimate of 2.98. Brigatinib shows statistically significant superiority versus ceritinib.

Supplementary PFS results are presented in Appendix D, including a summary of median PFS, a discussion around the ESS scores and the log cumulative hazard plots to assess the assumption of proportional hazards.

Figure 20: 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.

B.2.9.4.3 Objective/overall response rates

Similar to PFS, ORR was measured either by INV or IRC-assessment, and the ALTA data were used accordingly dependent on what measure was reported in the comparator study under evaluation. ORR is defined as those patients achieving either complete or partial response to the treatment. The corresponding ORR data are presented in

Table 22; this includes the observed (ALTA) and MAIC brigatinib data, as well as the observed ceritinib data from ASCEND-2 and ASCEND-5. The relative measure is represented by an OR for ceritinib versus brigatinib (ORs less than 1 favours brigatinib and OR greater than 1 favours ceritinib).

For the comparison between ALTA and ASCEND-2, the naïve-OR estimate shows that brigatinib has increased odds of achieving ORR versus ceritinib (OR=0.50), and this is statistically significant as the 95% CI is less than 1. Both MAIC [full] and MAIC [reduced] ORs are similar to the naïve-ORs; increasing slightly but still showing superiority for brigatinib.

For the comparison between ALTA and ASCEND-5, the naïve-OR is similar to that from ASCEND-2, and the MAIC [reduced] OR is similar to the naïve-OR. However, the MAIC [full] OR favours brigatinib to a greater extent (OR=0.40) but note the ESS for this analysis is very low (ESS=30.4) and this may undermine the credibility of this result. However, in all ORR analyses (naïve or MAIC), the results do show increased odds of achieving ORR for brigatinib.

The results from the pairwise meta-analyses (fixed and random-effects models) show statistically significant superiority for brigatinib versus ceritinib. The OR estimate and corresponding 95% CrI are uniformly less than one in all pairwise meta-analyses, indicating that brigatinib has higher odds of achieving ORR than ceritinib.

Table 22: 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	61/110	55.5	ASCEND-2	INV	54/140	38.6	0.50 [0.30, 0.84] ESS=110	0.57 [0.31, 1.01] ESS=58.9	0.54 [0.30, 0.97] ESS=59.3
ALTA	IRC	60/110	54.5	ASCEND-5	IRC	45/115	39.1	0.54 [0.31, 0.91] ESS=110	0.40 [0.18, 0.83] ESS=30.4	0.56 [0.30, 1.01] ESS=53.1
Pairwise meta-analysis (fixed-effect)								0.52 [0.36, 0.75]	0.50 [0.32, 0.89]	0.55 [0.36, 0.84]
Pairwise meta-analysis (random-effects)								0.52 [0.31, 0.88]	0.49 [0.27, 0.90]	0.55 [0.32, 0.97]
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.										

B.2.9.5 Limitations of the ITC analyses

There is an absence of IPD for the comparator arm, and thus requiring reconstructing IPD given published Kaplan-Meier curves. This process is associated with uncertainty and reconstructed IPD cannot supersede access to IPD.

A MAIC approach to synthesis is limited especially when considering unanchored comparisons (in the absence of a common comparator arm). As stated in the NICE DSU TSD 18,(46) unanchored MAIC analyses assume that absolute outcomes may be predicted from factors adjusted for in the statistical model, i.e. assumes that all PF and TEM are accounted for, which is most likely not the case, which introduces an unknown amount of residual bias into the results. The selection of PF and TEM to include in the matching is a subjective judgement, and variation amongst clinician's responses resulting in some factors being included in the model, but not others. In addition, some factors which were identified as being prognostic on survival outcomes could not be adjusted for due to lack of reported comparator data (e.g. best prior response to crizotinib, number of metastatic sites and presence of active brain lesions); this means that the matching process is unlikely to have been based on all relevant PF and TEM however is limited by what data are available, particularly in the comparator studies. Unmeasured confounders which could not be incorporated into the MAIC analyses may result in biased comparative efficacy estimates.

The MAIC process attempts to balance patient populations in terms of differences in baseline characteristics, but in performing the matching, some patients in the index study

(ALTA/Study 101) are no longer included in the analysis. The weights obtained from the matching process show that there is a notable proportion of patients in the ALTA and Study 101 trials which are not considered useful and are thus excluded from the subsequent analyses (estimation of HR within a weighted Cox regression model), as the weights are zero or close to zero (see Appendix D). Since the weights might be considered highly variable, HR estimates may be unstable, and inferences are dependent on a notably reduced sample size.

The naïve ITC does not adjust for imbalance in both observed and unobserved variables. However, there are some merits in performing such analysis when the MAIC Kaplan-Meier were very similar to the observed data, as the ESS in the naïve approach is the original total number patients. This is the case for all the MAICs performed for OS, PFS and ORR, except when ALTA data were used to match to ASCEND-5 study. However, it was discussed that the ESS was small when ALTA data were matched to ASCEND-5 study because number of prior regimens factor level 3+ was 0%, which may result in unstable estimates.

B.2.9.6 Summary of ITC analyses

The naïve (unadjusted) and MAIC analyses all show numerical and statistical superiority for brigatinib versus ceritinib for OS, PFS and ORR, irrespective of the covariate list included within the MAIC analyses, or whether the pooled ALTA/Study 101 or ALTA data are used. However, for the time-to-event outcomes, a naïve approach may be considered as providing the most conservative estimates when using ALTA data versus both ASCEND-2 and ASCEND-5; the MAIC analyses show an improvement in relative efficacy for brigatinib. When using the pooled ALTA/Study 101 data, the naïve estimate from the meta-analysis is similar to the MAIC estimate however the MAIC estimate is slightly more conservative (i.e. produces the lowest HR closest to one for ceritinib versus brigatinib). All naïve and MAIC HRs are included in the economic model, as well as the pairwise meta-analysis results, in order to explore the sensitivity around the estimates.

B.2.10 Adverse reactions

B.2.10.1 Adverse effects of treatment in ALTA

B.2.10.1.1 Safety and tolerability profile

Of the 222 patients enrolled in ALTA, 219 patients received ≥1 dose and were included in the Safety Population (just 3 patients who were randomised did not go on to receive treatment, these were all in Arm A). By the May 2016 data cut,(32) the median duration of brigatinib exposure in patients was 236.0 days (range: 1–615), and longer in Arm B compared to Arm A (229.0 days [range: 1–508] in Arm A and 238.5 days [range: 2–615] in Arm B). Median dose intensity was 90.0 mg/day (range: 59–171) in Arm A and 174.1mg/day (range: 39-179) in Arm B. By the extended data cut in February 2017,(34) the median duration of study drug exposure was 469 days overall and was longer in Arm B compared to Arm A (522 vs. 402 median days, respectively). Dose intensity appears maintained in both arms, with median relative dose intensity of patients in arm A and Arm B observed at 100% and 98.5%, respectively. Median dose intensity remained at 90.0 mg/day (range:59-173) in

Arm A, and in Arm B was 169.1 mg/day (range: 39-182). The updated safety data from ALTA, as of September 2017, were consistent with those presented from the earlier data extraction points with no new categories of risk identified. The results observed are also consistent with those expected with longer duration of follow-up. This updated safety analysis will be made available from May 2018.

Table 23 presents the overall safety and tolerability profile of brigatinib in the ALTA trial.

Table 23: Safety and tolerability profile of ALTA

Trial	**ALTA**			
Data extraction	**February 2017 (34)**		**May 2016 (2, 32)**	
	Arm A	Arm B	Arm A	Arm B
Median follow up (range)	16.8 (0.1-28.5)	18.6 (0.1-32.0)	7.8 (0.1 -16.7)	8.3 (0.1-20.2)
≥Grade 3 AEs n/N (%)	64 (58.7)	72 (65.5)	53 (51.6)	60 (64.5)
Serious AEs n/N (%)	52 (47.7)	56 (50.9)	43 (39.4)	48 (43.6)
Discontinuation due to AEs n/N (%)	4 (3.7)	12 (10.9)	3 (2.8)	9 (8.2)
Dose reductions due to AEs	10 (9.2)	33 (30.0)	8 (7.0)	22 (20.0)
Deaths due to AEs n/N (%)	1/219* (0.5)			
Abbreviations: AE, adverse events; * It is not clear which treatment arm this patient was in, although death occurred during the first 7 days when all patients were receiving 90mg QD.				

By the February 2017 data extraction, all patients experienced at least one treatment-emergent adverse event (TEAE) with 62.1% of patients experiencing a Grade 3-5 TEAE and 49.3% of patients experiencing a serious TEAE. However, only 7.3% of patients experienced a TEAE leading to treatment discontinuation. The most common TEAEs of any grade, occurring in >20% of patients overall, were 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%).

Table **24** presents the TEAEs ≥3 grade 3, experienced by ≥2% of patients overall in the ALTA trial, as per the safety population.(34)

Serious adverse events (SAES) occurred in 49.3% of patients overall and occurred in a similar percentage of patients in Arm a and Arm B (47.7% and 50.9%, respectively). See Table 25.

Neoplasm progression was reported as an adverse event during the trial and therefore recorded as such (see

Table **24** and Table 25). However, neoplasm progression is widely regarded medically as part of progressive disease and as such, not an adverse effect of the treatment per se, but of the NSCLC disease. In light of this, the safety profile of brigatinib from the ALTA trial is actually more positive that it first appears since neoplasm progression accounts for the reason for discontinuation for two patients in Arm B, as well as 15.6% and 7.3% of ≥ grade 3 TEAEs in Arms A and B, respectively and 16.5% and 7.3% of serious adverse events (Arm A and Arm B, respectively).(34)

Table 24: Grade ≥3 Treatment-emergent adverse events experienced by ≥ 2% of patients, by treatment arm

Preferred term	ALTA (34)	
	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.		

Table 25: Serious adverse events experienced in ≥2% patients overall, by treatment arm

Preferred term	ALTA (34)	
	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.		

B.2.10.1.2 Special categories of adverse events

Early onset pulmonary events (EOPE)

One particular category of adverse events (AEs) of interest were those deemed to be early onset pulmonary events (EOPE), as these were identified as a brigatinib-specific AE in the phase I portion of Study 101 (see section B.2.10.2.2), although it should also be noted that pulmonary toxicity, including pneumonitis and interstitial lung disease have been observed with crizotinib, ceritinib and alectinib.(47-49) In the ALTA study, no patients had an EOPE after dose escalation to 180 mg or after re-initiation after treatment interruption. All EOPE described herein occurred following treatment initiation.(34)

As of the database extraction in May 2016,(37) out of 219 treated patients, 4 patient cases met the criteria for definite EOPE, and 10 cases met the criteria for possible EOPE. In total, 14/219 (6.4%) patients overall (Arm A: 5/109 [4.6%] and Arm B: 9/112 [8.0%]) had an event that was at least possibly an EOPE. All EOPEs occurred at a dose of 90 mg QD, regardless of arm (i.e., within the first 7 days of treatment in Arm B). No EOPE were identified after escalation to 180 mg QD in Arm B. Median time of onset of EOPE was Day 2 (range Day 1-9). Eleven EOPE patient cases included SAEs, and 3 EOPE patient cases included only non-serious events. Seven (3.2%) patients had events that were Grade 1 or 2 only. Seven (3.2%) patients had events that were Grade ≥3, all of whom permanently discontinued brigatinib after the EOPE. Six patients had an EOPE with highest Grade of 3–4 (pneumonitis [n=4], radiation pneumonitis [n=1], pneumonia [n=1]). One patient had a possible EOPE that was Grade 5, death. This patient developed pneumonia after taking brigatinib for 7 days (90 mg QD at event onset. In 7/14 (50.0%) patient cases, brigatinib was permanently discontinued after the EOPE (including the fatal case. Of the other 7 patients, events resolved with dose interruption or brigatinib discontinuation (drug withdrawn). Steroids and antibiotics were administered in 11/14(78.6%) and 4/14(28.6%) patient cases, respectively. No new early onset pulmonary events or later onset pneumonitis events occurred between the May 2106 data extraction and the later February and September 2017 extraction dates.(34)

To identify potential predictive and prognostic risk factors for EOPEs, a multivariate analysis was conducted to evaluate various baseline risk factors including age, washout interval from crizotinib, number of prior anticancer regimens, time from initial diagnosis, time from advanced stage diagnosis, baseline sum of target lesion measurements (i.e. a measure of overall tumour burden), and baseline sum of lung target lesion measurements (i.e. a measure of lung tumour burden). In the unadjusted analysis, only age (≥65years and continuous 10-year increases) was associated with a higher rate of EOPE. In the adjusted (i.e., multivariable) stepwise logistic regression analysis, age (OR: 2.10; p=0.0083) and shorter interval (<7 days) between last dose of crizotinib and first dose of brigatinib (OR: 3.88; p=0.0349) were significantly associated with an increased rate of EOPE. In the adjusted analysis, 10 mm increases in baseline sum diameter of lung target lesions, a measure of lung tumour burden, shows a trend towards an association with increased rate of EOPE (OR: 1.16, p=0.0523).(32)

In light of this patients should be closely monitored upon initiation of brigatinib as with any new antineoplastic therapy, but specifically for new or worsening respiratory symptoms after the initiation of brigatinib and particular if they have any of the risk factors stated above particular during the first week of treatment. Management of these symptoms should be via dose interruption and rapid clinical evaluation. Overall, EOPEs can be managed and often treatment can resume after resolution of symptoms.

B.2.10.2 Adverse effects of treatment in Study 101

B.2.10.2.1 Safety and tolerability profile

Adverse events were not reported independently for the subset of 25 patients who are relevant to this decision problem.(3, 37)

All 137 patients enrolled in the study received ≥1 dose of brigatinib. The median duration of brigatinib exposure in patients was 227 days (range: 1–1443 days). The median dose intensity of brigatinib was 170.7 mg/day (range: 19– 300) and the median relative dose intensity was 98.2% in patients overall. Dose reductions due to AE occurred in 13.1% (18/137) of patients.

In the 90 mg QD → 180 mg QD dose group as a whole (n=32, of which 7 are not relevant to this indication), TEAEs Grade ≥3 occurred in 71.9% (23/32) of patients and SAEs occurred in 34.4% (11/32) of patients. TEAEs led to dose interruption, reduction, or discontinuation in 59.4% (19/32), 21.9% (7/32), and 12.5% (4/32) of patients, respectively.

B.2.10.2.2 Special categories of adverse events

Early onset pulmonary events (EOPE)

In this study, a subset of patients with moderate and severe pulmonary adverse events (e.g., dyspnea, hypoxia, cough, pneumonia) was observed within 7 days following initiation of brigatinib.(3, 37) In order to better characterise the early pulmonary adverse events observed with brigatinib treatment, a strategy for systematic analysis of these events according to a case definition was developed. The pulmonary TEAEs were selected for

review based on when they occurred, if the vent was coded to a MedDRA Preferred Term and then reviewed to consider the strength of evidence for a causal relationship with the treatment. In addition, evidence of resolution of the event associated with dose interruption or recurrence of the event upon re-challenge was considered as supportive information. Based on this criteria events were categorised as: (i) a definite EOPE case, (ii) a possible EOPE case, or (iii) not an EOPE case.

In total, 11/137 (8.0%) patients had a pulmonary TEAE that was at least possibly an EOPE. The median time to onset of the pulmonary TEAE was on Day 2 (range: 1–4 days) after initiating or reinitiating dosing with brigatinib. All 11 patients with EOPEs had SAEs. Ten patients had TEAEs that were Grade ≥3. Two EOPEs cases were associated with a fatal outcome (hypoxia and pneumonia).

1/50 (2.0%) patients who started at 90 mg QD (including those [n=32] who escalated to 180 mg after 7 days), had a TEAE classified as an EOPE, this occurred before dose escalation to 180mg. Importantly, none of the patients who escalated to 180 mg after 7 days at 90 mg experienced an EOPE and hence this dose was taken forward to be investigated in the ALTA trial as the proposed recommended dose.

B.2.11 Ongoing studies

There are patients still being treated with brigatinib as part of the ALTA trial but there are to be no further data extraction points ahead of final analyses which are due for May 2018. There are no other current ongoing studies of brigatinib in ALK+ NSCLC in the population of interest for this submission, i.e. in patients who have previously been treated with crizotinib.

B.2.12 Innovation

In 2007, scientists discovered that ALK rearrangements are present in a small subset of NSCLC. The subsequent decade witnessed a major paradigm shift in the treatment of NSCLC patients, beginning soon after when early-phase studies of crizotinib validated ALK as a therapeutic target and ALK-positive cancers were proved to be highly sensitive to small-molecule ALK inhibitors.(50) The arrival of crizotinib (NICE approval for pre-treated ALK+ NSCLC in December 2016 [TA422],(14) as an update of TA296 published 25th September 2013; NICE approval for untreated ALK+ NSCLC in September 2016 [TA406])(13) was followed shortly after by that of ceritinib (NICE approval for pre-treated ALK+ NSCLC in June 2016 [TA395];(51) NICE approval for untreated ALK+ NSCLC January 2018 [TA500]),(30) giving ALK+ NSCLC patients two targeted therapies that could be used sequentially to give more positive outcomes. Alectinib is also an ALK-inhibitor licensed in this indication although the company chose not to pursue NICE approval in this setting and therefore it is not currently reimbursed in England. However, despite these advances, patients often progress on crizotinib within 12 months,(52) frequently develop brain metastases(18) and currently approved second-line treatments have demonstrated limited PFS of under a year(27, 28) and, according to expert clinicians, infer considerable toxicities. Here lies the unmet need that brigatinib addresses through it's highly effective, innovative activity both systemically and intra-cranially.

Brigatinib as an oral, CNS active, pan-ALK inhibitor represents an innovation in the treatment of ALK+ NSCLC by offering patients both an extended PFS of over 1-year and potent intracranial responses. Brigatinib targets ROS1 and EGFR in addition to ALK and is active over a wider range of resistance mutations compared to existing treatments, with proven activity against all 17 specific crizotinib-resistant mutations.(5, 53) Brigatinib is also well-tolerated by most patients with a manageable safety profile.(2) Clinical expert opinion (gained at a Takeda organised Advisory Board), suggests that currently, although the significant majority of ALK+ NSCLC patients are receiving crizotinib, how clinicians choose to treat their patients after progression on crizotinib is more variable. Experts suggest that there is reluctance amongst clinicians to use ceritinib in these advanced disease stage, pre-treated patients due to its toxicity profile where they consider the risk-benefit profile to be too unfavourable for their patients.(29) Retrospective studies of treatment patterns among ALK+ NSCLC patients also support the fact that there is real variation in post-crizotinib treatment with many receiving non-targeted chemotherapy (20%-54%) and a high proportion receiving no further antineoplastic therapy (37%-47%).(15, 16, 54) Given this treatment environment, introducing brigatinib as a sequential ALK-targeted therapy after crizotinib would represent a step change in the management of patients. Brigatinib would offer clinicians not only another treatment in the limited armamentarium of therapies available after progression on crizotinib, but one that could offer patients considerably more months of progression free survival (IRC PFS: 16.7 months) and considerable extension to life (OS: 34.1 months) through systemic and intracranial activity.

The general characteristics of ALK+ NSCLC patients may be another aspect of the potential benefit of brigatinib that would not be captured fully in the QALY. These patients have a tendency to present later and already be at a more advanced disease stage compared to other lung cancer patients.(21) This may be a function of the fact that they tend to be younger (median age 52, compared to 71 in all NSCLC),(22) and less likely to have smoking history(23) and therefore more likely to otherwise be in good health and working, leading to reduced suspicion of disease. Treatment with crizotinib often results in progression within one year(15) and is associated with high rates of brain metastases,(55) resulting in patients that are still relatively young but already in a disease state associated with high morbidity. The systemic and intracranial PFS demonstrated by brigatinib in ALTA (16.7 months and 18.5 months, respectively),(35) may offer these patients lower disease burden and alleviation of some intracranial symptoms, giving them an opportunity to continue work and participate in family life more fully, in addition to a greater extension to life than has currently been the case.

In conclusion, brigatinib at the proposed recommended dose (180mg with 7-day 90mg lead-in), offers clinicians and their patients a post-crizotinib treatment that bids encouraging response rates (56.4% [CI: 45.2-67.0] in ALTA;(35) 76% [CI: 54.9-90.6] in Study 101),(37) longer periods without progression (PFS: 16.7 months [CI: 11.6-21.4] in ALTA; 16.3 months [CI: 9.2-NR] in Study 101) and the potential for meaningful extension to life beyond that of existing treatment (OS: 34.1 months [CI: 27.7-NR]). The ALK+ NSCLC population is a small but very specific set of relatively young, late-presenting patients who currently have very limited options for effective, targeted treatment after crizotinib.

B.2.13 Interpretation of clinical effectiveness and safety evidence

B.2.13.1 Clinical effectiveness

The systematic literature review (SLR) presented in Appendix D (D1.1), identified two studies of brigatinib in the proposed licensed indication. ALTA recruited 222 patients with ALK+ NSCLC previously treated with crizotinib, 110 of which were treated with the proposed recommended dosing regimen of 7-days at 90mg once-daily, escalating to 180mg once daily, thereafter. Study 101 had 25 patients meeting the criteria of the proposed indication and treated with the proposed recommended dose. These patients form the evidence base of the efficacy and safety analyses for brigatinib.

Brigatinib demonstrated consistently high rates of response in ALK+ NSCLC patients whose disease had progressed on prior crizotinib therapy; these responses were rapid (as evidenced by time to response), deep (as evidenced by target lesion response), and durable (as evidenced by duration of response). PFS data are robust with estimated median IRC - assessed PFS of 16.7 months(35) (95% CI: 11.6-21.4) in Arm B where patients were treated with the proposed recommended dose. The large magnitude of effect on ORR and duration of response are clinically meaningful being 56.4% and 15.7 months, respectively and a median overall survival of 34.1 months (95% CI: 27.7-NR). The data are now judged more mature as evidenced by the duration of follow up and the proportion of PFS events that have accumulated.

The SLR also identified two studies of ceritinib, as the comparator for brigatinib in this post-crizotinib indication.(1) These were the single-arm ASCEND-2 trial and the ASCEND-5 RCT which compared ceritinib with chemotherapy for the treatment of ALK+ NSCLC in patients pre-treated with crizotinib (more detail can be found in Table 7 of Appendix D). Ceritinib demonstrated a confirmed IRC-assessed ORR of 35.7% and 39.1% in ASCEND-2 and ASCEND-5, respectively, with median PFS of 7.2 and 5.5 months, and median OS of 14.9 and 18.1 months, for ASCEND-2 and ASCEND-5, respectively.(27, 28)

Comparative systematic clinical effectiveness data for brigatinib and ceritinib can be found in Table 26.

Brain metastases are a significant feature of advanced ALK+ NSCLC and as such

Table 27
shows the comparative intracranial effectiveness of brigatinib and ceritinib. Intracranial responses with brigatinib in the ALTA trial were substantial in both patients with measurable brain metastases and those with measurable, active brain metastases (see Table 14).

Brigatinib demonstrates substantially higher response rates than ceritinib, of 66.7% and 73.3% in patients with measurables, and measurable, active brain metastases, respectively (ALTA Arm B), compared to 45% and 35% in ASCEND-2 and ASCEND-5 respectively, for patients with active target lesions and measurable, active target lesions.

In oncology there are a number of recognised limitations in the data collection from clinical trials, associated with the ethics of RCTs where controls/comparators may be less efficacious and particularly in rarer cancers that affect small numbers of individuals. As such, many trials are single arm, non-comparator trials with less restrictive inclusion/exclusion criteria than may be observed in other disease areas. As described in section B.2.6, brigatinib was evaluated in two single arm trials (ALTA(2) and Study 101),(3) and ceritinib in one single-arm and one RCT, where it was compared to chemotherapy (ASCEND-2 (27) and ASCEND-5,(28) respectively).

All trials relevant to this decision problem recruited ALK+ NSCLC patients who had been previously treated with crizotinib. Patients were all relatively young as is expected in ALK+ NSCLC, with median age ranging from 50.5 in Arm A of ALTA to 57.0 in Study 101, with both ASCEND-2 and -5 reported medians of 51.0 and 54.0 years, respectively. Smoking history was not reported in Study 101 or ASCEND-2, but in ALTA and ASCEND-5 these showed most patients to have little or no smoking history, as commonly seen in ALK+ NSCLC. More females than males were treated in ASCEND-5 and ALTA, with ASCEND-2 being 50% and Study 101 treating more males, but in such a small patient population this difference is unlikely to be significant. All four trials treated mainly White patients with smaller proportions of Asian and other, but again, this wasn't an area of considerable heterogeneity. In terms of ECOG PS, ALTA, ASCEND-2 and ASCEND-5 treated a large majority of patients with a PS of 0 or 1, with between 6-14% of PS 2 patients, the greatest proportion in ASCEND-2 (14.3%). However, it must be noted that in Study 101 all patients had a PS of 0 or 1. Virtually all patients across the four trials were in advanced disease stage IV, accounting for 97.3% and 98.2% of ALTA patients (Arm A and Arm B, respectively), 100% of patients in ASCEND-2 and 99% of patients in ASCEND-5. Brain metastases were present in the majority of patients across the trials accounting for 67.3% in Arm B of ALTA, 71.4% in ASCEND-2 and 57% of the ceritinib treated patients in ASCEND-5. Pre-treatment, apart from crizotinib, did vary between the trials with 100% of patients treated with ceritinib having also had prior chemotherapy where as in ALTA this was 74.1% and 73.6% (in Arms A and B, respectively) and 68% in Study 101, many patients in all trials had also received radiotherapy to the brain.

Overall, there were no considerable areas of heterogeneity across these trials in terms of inclusion criteria or recruited patient populations, and on consultation with expert clinicians and by consulting literature, it is believed that these patients are representative of ALK+ NSCLC patients currently in the UK. ALK+ NSCLC patients are consistently younger, less likely to have a smoking history than other lung cancer patients and crucially, more likely to present with advanced disease, as represented by patients across these clinical trials.

A full quality assessment for each trial is given in Appendix D (section D.1.3)

B.2.13.2 Safety and tolerability

Overall safety and tolerability data for brigatinib and ceritinib is presented in

Table 28. Safety and tolerability data for brigatinib comes solely from ALTA up to the February 2017 data extraction(34) (safety data not reported independently for the n=25 patients relevant to the scope), and from ASCEND-2 (27) and ASCEND-5 (28) for ceritinib.

The safety profile reported in ALTA was consistent with previous reports for brigatinib(3) and was acceptable in both dosing arms. The frequency of any individual ≥ grade 3 AE was low with the dose reduction rate at 9.2% and 30% in Arms A and B, respectively.(2) In contrast, at the recommended starting doses of ceritinib (750mg), reported dose reduction rates are 45% and 61%, in ASCEND-2 (27) and ASCEND-5,(28) respectively. In terms of the patients experiencing serious AEs, results for brigatinib were fairly similar in ALTA to those for ceritinib in ASCEND-2, reporting 50.9% and 40.7%, for each trial respectively. This could also be said for the number of patients experiencing AEs ≥ grade 3 in ALTA and ASCEND-2 which reported 65.5% and 71.4%, respectively but ASCEND-5 reported 90.4%.

Although consideration of the overall safety and tolerability profile of brigatinib and ceritinib does favour brigatinib, we have reason to believe that the comparative favourability of brigatinib is even greater than the data reflects. Expert clinician input (gained from an Advisory board organised by Takeda),(29) suggested that the differences in safety profile is far greater than this data suggests with brigatinib being perceived as much more tolerable than ceritinib. Clinicians deemed that the gastro-intestinal (GI) toxicity profile associated with ceritinib is not fully captured in most published data since symptoms are categorised as grade 1 and 2 in most instances and therefore are less frequently reported in publications. They also suggested that in ASCEND-5 for example where ceritinib was compared to chemotherapy, these GI toxicities would be offset by those also expected by users of more traditional antineoplastic therapy. Clinicians also made the point that the data on safety is also influenced by time on treatment (ToT) and dose intensity differences between trials of brigatinib and ceritinib. Patients in ASCEND-2 (27) were exposed to ceritinib for a median duration of 8.8 months with a median relative does intensity of 84.9% and in ASCEND-5,(28)

for patients treated with ceritinib, median treatment exposure was 30.3 weeks (approximate 7.6 months), with a median relative dose intensity of 82.0%. By comparison, the median duration of brigatinib exposure was reported as 522 days (approximate 17.4 months), for Arm B, treated with the proposed recommended dose (180mg with 7-day leading at 90mg), with a median relative dose intensity of 98.5%, by the February 2017 data extraction date.(34) Brigatinib patients in the ALTA trial were exposed to treatment for far longer and tolerated dosages nearer to proposed recommended dose. The clinicians consulted by Takeda unanimously agreed that brigatinib had a significantly more favourable risk-benefit profile, compared to ceritinib.(29)

Table 26: Comparative systemic clinical effectiveness data for brigatinib and ceritinib

Intervention	Brigatinib			Ceritinib			
Trial	ALTA(35)*		Study 101(3, 37)**	ASCEND-2 (27)		ASCEND-5 (28)	
Assessment	INV	IRC	INV	INV	IRC	INV	IRC
Confirmed ORR, % (95% CI)	56.4 (45.2-67.0)	56.4 (46.6-65.8)	76.0 (54.9-90.6)	38.6 (30.5-47.2)	35.7 (27.8-44.2)	42.6 (33.4-52.2)	39.1 (30.2-48.7)
Median PFS, months (95% CI)	15.6 (11.1-21.0)***	16.7 (11.6-21.4)	16.3 (9.2-NE)	5.7 (5.4-7.6)	7.2 (5.4-9.0)	6.7 (4.4-7.9)	5.4 (4.1-6.9)
Median OS, months (95% CI)	34.1 (27.7-NR)	- - - -	NR (1.4-24.3)	14.9 (13.5-NE)	- - - -	18.1 (13.4-23.9)	- - - -

Abbreviations: CI, confidence interval; INV, investigator; IRC, independent review committee; ORR, objective response rate; OS, overall survival; PFS, progression free survival; NE, not estimable; NR, not reached.

* Data reported is from the most recent data extraction (September 2017) and for Arm B only where patients were treated with the proposed recommended dose (180mg with a 7-day 90mg lead-in).

** Data reported for only the n=25 patients only (ALK+, pre-treated with crizotinib and treated with the proposed recommended dose [180mg with a 7-day 90mg lead-in])

*** 97.5% CI was used for the primary endpoint

Table 27: Comparative intracranial effectiveness data for brigatinib and ceritinib

Intervention	Brigatinib		Ceritinib	
Trial	ALTA(35)*		ASCEND-2 (27)	ASCEND-5 (28)
Population	Patients with measurable BM	Patients with measurable, active BM	Patients with active, target brain lesions	Patients with measurable, active, target lesions
Analysis group, n	18	15	20	17
Confirmed intracranial ORR, % (95% CI)	66.7 (41.0-86.7)	73.3 (44.9-92.2)	45 (23.1-68.5)	35 (14.2-61.7)
Median intracranial DOR, months (95% CI)	16.6 (3.7-NR)	16.6 (3.0-NR)	NR	6.9 (2.7-8.3)
Median intracranial PFS, months (95% CI)	18.5 (4.9-NR)	NR	NR	NR

Abbreviations: BM, brain metastases; DOR, duration of response; ORR, overall response rate; PFS, progression free survival

* Data reported is from the most recent data extraction (September 2017) and for Arm B only where patients were treated with the proposed recommended dose (180mg with a 7-day 90mg lead-in)

Table 28: Comparative safety and tolerability of brigatinib and ceritinib

Intervention	Brigatinib(31, 34)		Ceritinib	
Trial	ALTA		ASCEND-2	ASCEND-5 (28)
	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;				

B.2.13.3 End of life

The median OS of patients with ALK+ advanced NSCLC previously treated with crizotinib is considerably shorter than 24 months and ranges from 14.9 months to 18.1 months (ASCEND-2 and ASCEND-5, respectively). In the ALTA clinical trial, the median OS is reported to be 34.1 months based on the September 2017 data cut. Based on a naïve comparison, brigatinib is observed to extend survival by far more than the three months required by the NICE end-of-life criteria.

In the base case, the economic model uses OS data from ALTA and Study 101 for brigatinib. For ceritinib, hazard ratios derived from covariate adjusted ITCs are used based on data from ASCEND-2 and ASCEND-5. Therefore, OS estimations make use of all available data for brigatinib and ceritinib. The difference between predicted medians in the economic model is 17.48 months (36.80 months for brigatinib and 19.32 months for ceritinib) and between predicted means over a lifetime horizon is 20.42 months (44.74 months for brigatinib and 24.32 months for ceritinib). Therefore, the economic analysis indicates a significant extension in survival.

Finally, the eligible patient population for treatment with brigatinib is expected to be approximately 46 patients per year (see BIM section 3).

Table 29: End-of-life criteria

Criterion	Data available	Reference in submission (section and page number)
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	The comparator identified in the final scope for this decision problem is ceritinib,(1) as treatment for patients with ALK+ NSCLC previously treated with crizotinib, who are seeking further active treatment. The two trials identified by the systematic literature review (REF Appendix D) for ceritinib in this indication are ASCEND-2 (27) and ASCEND-5 (28) which report median overall survival (OS) estimates in these patients as 14.9 (95% CI: 13.5-NE) and 18.1 months (95% CI: 13.4-23.9), respectively. Mean OS is not reported.	**B.1.1 and B.2.6**
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Brigatinib offers an extension to life compared to ceritinib with trials of brigatinib reporting KM estimates of median OS as 34.1 months (95% CI: 27.7-NR) in the pivotal ALTA trial, at the proposed recommended dose.(35)	**B.2.6**

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

Table 30 presents a summary of the cost-effectiveness studies identified in the SLR. Appendix G provides the details associated with the SLR and the search strategy.

Seventeen economic models were identified for data extraction considering the cost-effectiveness of interventions in an ALK+ advanced NSCLC population; six from electronic searches and 11 from grey literature searches and HTA websites. Of the 17 identified studies, ten were HTA submissions, three were abstracts, two were posters and two were full publications. No cost-effectiveness studies were identified that evaluated brigatinib in the relevant patient population for this submission; that is the treatment of patients with ALK+ advanced NSCLC previously treated with crizotinib in England and Wales.

Table 30: Summary list of published cost-effectiveness studies

Study	Year	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
CADTH, Zykadia for NSCLC Re-submission(56)	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(57)	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)(49)	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.(58)	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.(59)	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*.(60)	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*.(61)	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)(51)	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)(62)	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)(13)	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)(63)	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)(14)	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(64)	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)(65)	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

Study	Year	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Zhou et al.(66)	(2015a)	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
Zhou et al.(67)	(2015b)	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

Study	Year	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
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						

Of the ten HTA submissions three were NICE submissions for ceritinib in ALK+ advanced NSCLC previously treated with crizotinib [TA395],(51) crizotinib in previously treated ALK+ advanced NSCLC [TA422](14) and crizotinib for untreated ALK+ advanced NSCLC [TA406].(13) The remaining HTA submissions were to: CADTH for alectinib for NSCLC with CNS metastases and crizotinib for NSCLC (original submission and re-submission) and SMC for the same populations as identified for NICE and an additional re-submission for crizotinib for previously treated patients.

As ceritinib is the comparator of brigatinib Table 30 presents the issues raised by NICE in the submission for ceritinib and how this submission addresses these limitations. As the limitations raised by the SMC and CADTH formed a subset of those raised by NICE, only the key issues raised by the ERG and the Appraisal Committee during the NICE appraisal TA395 are presented.

Table 31: Issues raised from the NICE submission for ceritinib [TA395]

Reference	Issues	How this submission addresses this
NICE TA395 (51)	Comparative efficacy Lack of head-to-head data for ceritinib and comparator. The company used a naïve indirect treatment comparison combining multiple sources of data. Bias may have been introduced for heterogenous patient populations and retrospective nature of included studies. It was considered that this was the best comparative efficacy information available.	There is a lack of head-to-head data for brigatinib compared with ceritinib. Only single arm data are available for these treatments (ALTA and Study 101 for brigatinib and ASCEND-2 and ASCEND-5 for ceritinib). The submission considers two methods of indirect treatment comparison (ITC) for OS, PFS and response outcomes: (1) naïve indirect comparisons and (2) matched adjusted indirect comparisons (MAICs). Where outcomes were available from both ASCEND-2 and ASCEND-5, meta-analyses of the MAICs are also considered (see Section B.3.3.3). Scenario analyses associated with each approach to ITC are presented within this submission. Sensitivity analyses around each method explore the uncertainty associated with comparative efficacy outcomes.
NICE TA395	Time on treatment Lack of long-term time on treatment (ToT) data for ceritinib. The company assumed that patients were treated with ceritinib until disease progression. A scenario analysis considered a median duration of 1.6 months for treatment continuation after disease progression (based on median ToT minus median PFS). The Evidence Review Group (ERG) and NICE Committee preferred this scenario to inform the base case, as it aligned with what was seen in the trial (ToT could surpass PFS).	There is a lack of long term ToT data for brigatinib. In line with the methods used in the NICE ceritinib submission, the base case will consider patients treated 1.53 months beyond progression for brigatinib (based on the difference between median PFS and median ToT observed in the ALTA data). As there is no clinical reason why patients would be treated further into progression when treated with ceritinib, the base case will also consider patients treated 1.53 months beyond progression for ceritinib. A scenario analysis considers patients treated 1.60 months beyond progression for ceritinib – in line with the NICE submission estimates. Scenario analyses explore the impact using the extrapolated ToT data for brigatinib, capping ToT by PFS and applying the hazard ratio for PFS for ceritinib relative to brigatinib to the brigatinib ToT data.
NICE TA395	Long-term treatment benefit Lack of data associated with the long-term treatment benefit on OS outcomes for ceritinib. The company assumed that the OS benefit	There is a lack of data associated with the long-term treatment benefit on OS outcomes for brigatinib. The economic analysis uses data from ALTA, from the February 2017 data cut which reports on a median follow-up of 18.6 months for Arm B (90mg daily lead-in followed by 180mg daily). Shortly before the submission date, the September

Reference	Issues	How this submission addresses this
	with ceritinib was maintained over the model's time horizon. The ERG explored scenarios where the length of treatment benefit was varied from 2-years to 10-years (lifetime). The NICE Committee was not given evidence that the treatment benefit from ceritinib would continue after the end of treatment but concluded that the company had shown that this had minimal impact on cost-effectiveness.	2017 data cut became available reporting outcomes up to a median follow-up of 24.3 months for Arm B. Due to time constraints, this later data cut is not used in the economic analysis. Within the economic analysis the February 2017 data cut has been used, the parametric form of the extrapolated curves was informed by a resource use questionnaire completed via semi-structured interviews and an advisory board conducted by Takeda on the 29th January 2018 (see Section B.3.3.5). The proportion predicted to survive having received brigatinib treatment at 5-, 10- and 20-years was elicited from UK clinical experts (average of responses reflected 28.50%, 5.83% and 0.00%, respectively). The fit of the parametric curves to the OS data from ALTA and from the pooled cohort were presented at the advisory board with the estimated outcomes at 5-, 10- and 20-years. It was commented that the Gompertz curve fit to the pooled data aligned with expectations of long-term survival (28.71%, 4.23% and 0.00% surviving at 5-, 10- and 20-years, respectively). Scenario analyses explore the impact of treatment benefit discontinuation at 2-, 3-, 4-, 5- and 10-years for the OS outcomes for brigatinib and ceritinib. Additional scenarios explore the impact of choice of parametric curve on results.
NICE TA395	Health-related quality of life (HRQL) The company mapped the EORTC-QLQ-C30 data from the ASCEND-2 clinical trial to the EQ-5D-3L. Linear mixed models were fit to these utility data and accounted for response status: responding disease (complete response and partial response), stable disease and progressive disease. No data were available for BSC and, as such, the company stated that the utility values associated with BSC were equal to ceritinib. However, the ERG argued that the company did not apply equal utilities for ceritinib and BSC as the	This submission used mapped EQ-5D-3L values (from the EORTC-QLQ-C30 collected in the ALTA clinical trial). These data were mapped to the EQ-5D-3L using the algorithm published in Longworth *et al.* (2014).(68) Mapping from the EORTC-QLQ-C30 was also conducted in the NICE ceritinib submission. Utility values were estimated as a (1) function of response (based on the RECIST criteria) and as a (2) function of pre- and post-progression. The base case considers option (2) – in line with the NICE Committee's feedback to ceritinib. The regression equations adjust for a number of covariates including: baseline utility, age, race, gender and experience of grade 3/4 adverse events (see Section B.3.4.1). Similar to the ASCEND-2 clinical trial, patients were only followed up in ALTA until treatment discontinuation, as such, there are limited data available for post-progression. Therefore, the model used estimates calculated from the ALTA data for pre-progression only and the literature informs the estimate for post-progression. Scenario analyses

Reference	Issues	How this submission addresses this
	utilities in the model were weighted based on response. Furthermore, utilities were not adjusted for baseline utility. Therefore, to avoid unexplainable differences in the utility values between ceritinib and BSC, the ERG assumed the same utility for patients in the progression-free health state (0.713). The NICE Committee accepted this approach. The company did not include utility decrements associated with adverse events in the base case, as it was considered that any HRQL impact associated with ceritinib treatment would be captured in the collected utility data. However, the ERG commented that utility increments should have been included for the BSC arm, as patients would not experience treatment-related adverse events in this arm.	consider utility values obtained from the literature for both the pre-progression and progressed disease health state. Utility decrements associated with adverse events are accounted for within the linear mixed models – in line with the NICE Committee's feedback to ceritinib (see Section B.3.4.1).
Abbreviations: BSC, best supportive care; EQ-5D-3L, EuroQol 5-dimensions 3-levels; EORTC-QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; ERG, evidence review group; HRQL, health-related quality of life; ITC, indirect treatment comparison; MAIC, matched adjusted indirect comparison; NICE, National Institute for Health and Care Excellence; OS, overall survival; PFS, progression-free survival; ToT, time on treatment		

B.3.2 Economic analysis

B.3.2.1 Patient population

Brigatinib is indicated as monotherapy for the treatment of adult patients with ALK+ advanced NSCLC previously treated with crizotinib. This economic evaluation considers the role of brigatinib for this population, represented by patients included in the ALTA clinical trial (Arm B) and a subgroup from the Study 101 trial. This population is consistent with the NICE final scope for this technology appraisal.(1)

Data from Arm B of the ALTA trial informs the economic model as these data align with the proposed dosing regimen submitted as part of the Marketing Authorisation Application (MAA) (90mg daily lead in for 7-days followed by an up-titration to 180mg daily). A subgroup was selected from the Study 101 trial to reflect this dosing, the post-crizotinib positioning and the ALK+ nature of disease. Evidence for the clinical efficacy and safety of brigatinib in these patient populations are reported in Section B.2.6.

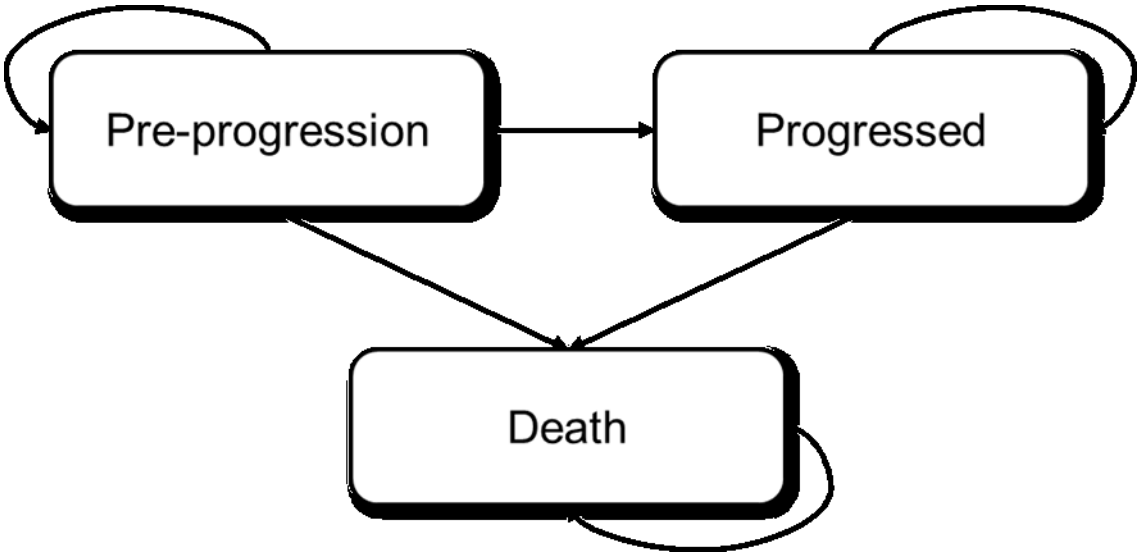
B.3.2.2 Model structure

An economic model has been developed to conform with the NICE Guide to the Methods of Technology Appraisal (69)and the NICE reference case criteria. This model was developed in Microsoft Excel® 2010 as an area under the curve (AUC) partitioned survival model with three health states (pre-progression, progressed disease and death). An AUC analysis is a typical approach in modelling metastatic cancers and has been used in many previous NICE submissions including: ceritinib for ALK+ NSCLC (TA395),(51) crizotinib for untreated ALK+ advanced NSCLC (TA406)(13) and crizotinib for previously treated ALK+ advanced NSCLC (TA422).(14)

Disease progression was defined as the time from the date of randomisation to the date of first documentation of disease progression based on investigator assessment (INV) and the RECIST response criteria version 1.1, or death due to any cause, whichever occurred first. Similar AUC approaches have been previously used in ALK+ NSCLC, including the NICE submission [TA395](51) for ceritinib, the NICE submission [TA406](13) for crizotinib in untreated patients and the NICE submission [TA422](14) for crizotinib in previously treated patients.

The model structure is depicted in Figure 21. The health states were designed to capture the factors most important to patients with ALK+ advanced NSCLC at this stage of disease, including: whether the patient is responding to treatment or maintaining a stable disease (pre-progression) and whether a patient has progressed disease which impacts the HRQL and costs of managing disease and survival.

Figure 21: Model structure



The AUC model considered estimates for each clinical endpoint separately (i.e. OS and PFS are modelled independently) and, as such, maintains consistency between the endpoints used in the cost-effectiveness analysis and the published clinical data. This approach also enables external data sources to be incorporated into the model for each of the clinical endpoints, for example: indirect treatment comparisons (ITCs). A scenario analysis explores the impact on HRQL of stratifying patients based on response (responding and stable disease) in the pre-progression health state.

The base case analysis considered a lifetime perspective based on 99% of patients predicted to have died in the brigatinib arm; this equated to 12.65 years in the base case. Scenario analyses considered the impact of a 5-year and 10-year time horizon. The model used a 28-day cycle length with a half-cycle correction applied. Costs and health outcomes (QALYs) were discounted at the annual rate of 3.5%.

Table 32 summarises the key features of this economic analysis.

Table 32: Features of the economic analysis

Factor	NICE submission [TA395](51)	Current appraisal	
		Chosen values	Justification
Time horizon	10-years	Lifetime (12.65 years)	99% of patients have died in the brigatinib arm
Treatment waning effect	Not applied in base case. Scenario analyses conducted by the evidence review group (ERG) varied the length of treatment benefit from 2-years to 10-years.	Not applied in base case	Chosen methods based on statistical and clinical plausibility. Treatment benefit discontinuation scenarios considered in scenario analyses from 2-years to 10-years.
Source of utilities	EORTC-QLQ-C30 data from the ASCEND-2 clinical trial mapped to the EQ-5D-3L and fit linear mixed models to these data accounting for response status (responding disease and stable disease) for the pre-progression health state. The literature informed the utility value for the progressed health state.	EORTC-QLQ-C30 data from the ALTA clinical trial mapped to the EQ-5D-3L and fit linear mixed models to these data accounting for response status (pre-progression vs. complete response, partial response and stable disease), see Section B.3.4.1. The literature informed the utility value for the progressed health state.	The NICE Methods Guide (2013) (69)stipulates that, where available, the patient level data should inform the HRQL estimates in the model. Patients are followed in the ALTA clinical trial until treatment discontinuation, as such, limited information is available on HRQL associated with progressed disease. Therefore, the literature will inform the progressed disease utility value in the base case. Scenario analyses will explore the impact of alternative utility sources for both pre-progression and progressed disease.
Source of costs	NHS Reference Costs 2013/14(70) PSSRU 2013 (71) eMIT (accessed May 2015) (72) BNF (accessed May 2015) (73) Coyle *et al*. (1999)(74)	NHS Reference Costs 2016/17 (70) PSSRU 2017 (71) eMIT (accessed 2018)(72) BNF (accessed 2018)(73)	As per the NICE Methods Guide (2013)

Abbreviations: BNF, British National Formulary; EORTC-QLQ-C30, European Organisation for Research and Treatment in Cancer Quality of Life Questionnaire Core 30; EQ-5D-3L, EuroQol 5-dimensions 3-levels; eMIT, electronic marketing information tool; ERG, evidence review group; HRQL, health related quality of life; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSSRU, Personal Social Services Research Unit

B.3.2.3 Intervention technology and comparators

B.3.2.3.1 Intervention

The intervention assessed in the cost-effectiveness model is brigatinib. Within the model, brigatinib is evaluated in line its proposed marketing authorisation for the treatment of adults with ALK+ advanced NSCLC previously treated with crizotinib. This is reflected using the ALTA trial and the subgroup of ALK+ and post-crizotinib patients receiving the relevant dose of brigatinib from Study 101 to inform clinical input parameters within the model.

The ALTA clinical trial protocol stated that participants will receive treatment until disease progression, intolerable toxicity, consent withdrawal or death – whichever occurs first. However, the protocol also specifies that treatment could continue beyond progression if the investigator believed that the patient was continuing to receive clinical benefit. The observed data shows that some patients in ALTA were treated beyond progression. In the ALTA trial, at the data cut-off of February 2017, patients had been exposed to brigatinib for a median duration of 17.15 months (74.57 weeks) while the median PFS INV was 15.62 months (67.90 weeks). Therefore, in the model patients are treated with brigatinib 1.53 months beyond progression. This is in line with the methods seen in the NICE submission [TA395](51) for ceritinib and consistent with clinical feedback received at a UK advisory board conducted by Takeda on the 29th January 2018; it was agreed by six clinicians that patients would be assessed as progressed and then followed up approximately 6-weeks later to discuss treatment discontinuation – which explains why patients appear to be treated 1.53 months beyond progression. Further details of the advisory board are provided in Section B.3.3.5 and B.3.10.

B.3.2.3.2 Comparator

As discussed in Section B.1.1, the comparator defined by the final NICE scope for this appraisal is ceritinib. This comparator aligns with the treatment pathway described in Section B.1.3.2. There is no clinical rationale to assume that patients treated with ceritinib receive treatment for a shorter nor longer time in the progression state compared with brigatinib. Therefore, the base case assumes that patients treated with ceritinib receive treatment for 1.53 months beyond progression. A scenario analysis considers patients treated with ceritinib receiving treatment for 1.60 months beyond progression in line with the NICE submission [TA395].(51)

B.3.3 Clinical parameters and variables

B.3.3.1 Primary clinical data sources

The evidence used within the economic model to inform the comparative effectiveness is in line with the clinical evidence presented in Section B.2.6.

Key model inputs related to brigatinib were obtained from the ALTA (n=110) and Study 101 (n=25) clinical trials. Pooled data were used for OS and PFS INV. Scenario analyses consider the impact of ALTA data only for OS and PFS INV outcomes. Additional scenarios consider the impact of PFS as measured by the independent review committee (IRC), use of extrapolated time on treatment (ToT) and the impact of response (overall response rate (ORR) and best overall response (BoR) as measured by INV and IRC) on HRQL. PFS IRC and ToT outcomes were unavailable from Study 101. Therefore, these scenarios consider the use of ALTA data only. ORR data were also sourced from the ALTA trial only to align with the HRQL analyses.

Patient level data relevant to Arm B (90mg 7-day lead in followed by up-titration to 180mg) from the ALTA trial were used, in line with the indication for brigatinib. The subgroup selected from Study 101 was also in line with the indicated population; post-crizotinib, ALK+ and patients received the 90mg 7-day lead in followed by the up-titration to 180mg. The February 2017 data cut recording outcomes up to a median follow-up of 18.6 months for Arm B was used from the ALTA clinical trial. A more recent data cut, September 2017, has since become available from this trial. The analytical work on this later data cut is ongoing and is anticipated to be complete in time for the clarification questions. The September 2017 data cut extends the median follow-up of Arm B to 24.3 months. However, due to time constraints these data are not included in the economic analysis presented in this submission. The May 2016 data cut recording outcomes up to a median follow-up of 20.0 months was used from Study 101.

Comparative efficacy for ceritinib was based on data from ASCEND-2 and ASCEND-5. Due to lack of head-to-head data, two methods of unanchored indirect treatment comparisons (ITCs) were conducted to obtain comparative efficacy estimates (see Section B.3.3.3):

1. Naïve indirect comparison
2. Matched adjusted indirect comparison (MAIC)

These methods were applied for the following outcomes relevant for the economic model: OS, PFS (INV and IRC), ORR (INV and IRC). The methods provided hazard ratios or odds ratios of observed (unadjusted) and population adjusted brigatinib data versus observed ceritinib data, which were applied to the brigatinib data to obtain a relative estimate for each of the clinical endpoints. Where data were available for ceritinib from both ASCEND-2 and ASCEND-5, fixed effects (FE) and random effects (RE) meta-analyses were performed for the relevant clinical endpoints to obtain overall relative effects.

The base case uses the estimates from the meta-analysis of MAICs for OS using pooled brigatinib data as this approach utilises all data for brigatinib and ceritinib. The RE method was used as it allows for heterogeneity to be present between the studies and is more conservative. Furthermore, there are no significant differences in model fit statistics between RE and FE. For PFS INV outcomes, the base case uses the estimates from the MAIC using pooled brigatinib data and ASCEND-2 data – PFS INV outcomes are not reported in ASCEND-5. Scenario analyses consider the impact on results of the different methods of ITCs on OS and PFS INV. In the scenario assessing the impact of response on HRQL in the pre-progression health state, different outcomes (ORR INV, ORR IRC, BoR INV and BoR IRC) and different methods of ITCs are explored.

B.3.3.2 Extrapolated outcomes

To estimate OS and PFS INV outcomes associated with brigatinib across a lifetime horizon, extrapolation of the data beyond the trial follow-up period was required. Seven parametric distributions (exponential, Weibull, Gompertz, gamma, log-normal, log-logistic and generalized gamma) were fit to the patient level data from the pooled cohort for each clinical outcome (OS and PFS INV), in line with the NICE Decision Support Unit (DSU) guidance.(75) The fit of each parametric model to the survival data was assessed via both internal and external validity using visual inspection of the fitted curves against the Kaplan-Meier curves, Akaike information criterion (AIC) and Bayesian information criterion (BIC) goodness-of-fit statistics and experts' judgments on long-term clinical plausibility. All curves were fitted using the flexsurv package in the statistical software R.(76)

These methods were also employed for outcomes relevant to scenario analyses; scenario analyses required the extrapolation of ALTA data only for OS, PFS INV, PFS IRC and ToT outcomes. Results associated with these outcomes are presented in Appendix L.

B.3.3.2.1 Overall survival (pooled data)

The pooled data for OS were obtained from pooling the observed brigatinib data from ALTA and Study 101 (n=135). Table 33 summarises AIC and BIC values for each parametric survival distribution. The statistical goodness-of-fit indicates that all the models fit the observed data well; the AIC values are less than 5 points between the models.(77) BIC penalizes on the number of parameters used in a model, this suggests that the exponential distribution is the best fitting model. The Kaplan-Meier curve and fitted parametric distributions are presented in Figure 23.

The visual inspection of the fitted curves suggests that all models fit the observed data well. However, the observed data are immature and provide no information relevant to the long-term predictions. Table 34 provides the extrapolated long-term brigatinib survival rates for 3-years, 5-years, 10-years and 20-years associated with each parametric curve and compares these estimates with experts' judgements on clinical plausibility (see Section B.3.3.5 and B.3.10 for full details of expert elicitation). The Gompertz, followed by the Weibull, provide the long-term estimates that align most closely with what would be expected in clinical practice.

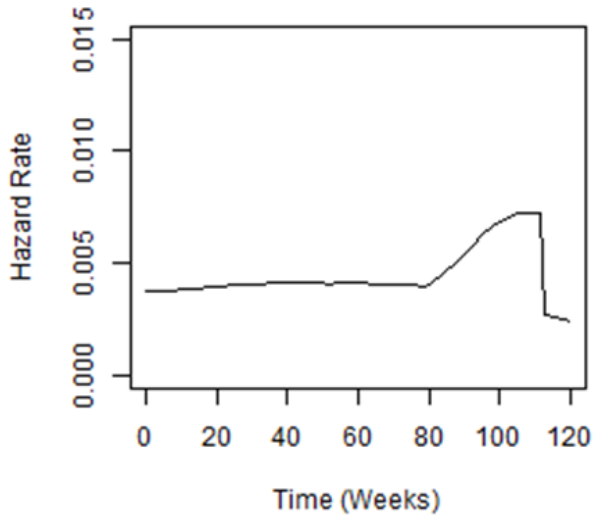
Table 35 presents the long-term extrapolated survival estimated for brigatinib for each of the parametric curves and compares these estimates with the observed median and mean. The median is not yet available from the pooled data. Based on assessing both internal and external validity, the Gompertz distribution was determined to be the most appropriate model in the base case for the OS pooled data. Scenario analyses consider the impact of the alternative parametric distributions and the impact of using ALTA data only – the methods and results of extrapolation for OS from ALTA only are presented in Appendix L.

The model includes an option to cap the predicted survival by the England and Wales background mortality obtained from the Office of National Statistics (ONS)(78) – this is only relevant when log-normal and log-logistic curves are selected and so does not impact the base case results. Scenario analyses considering the impact of log-normal and log-logistic parametric distributions will apply this cap.

Table 33: Goodness-of-fit statistics for overall survival (OS), pooled data

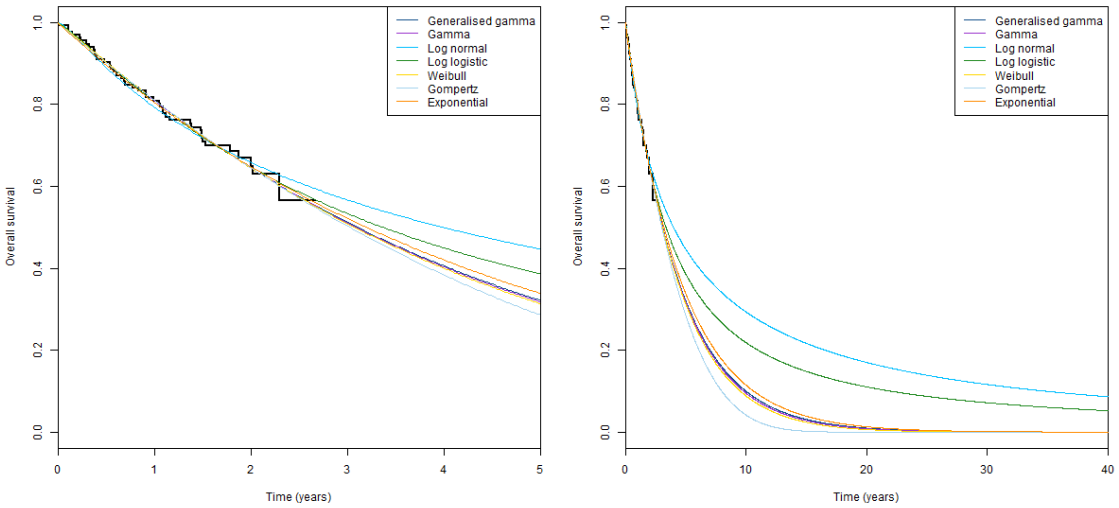
Model	AIC	BIC
Generalised gamma	563.44	572.15
Gamma	561.44	567.25
Log normal	564.14	569.95
Log logistic	561.53	567.34
Weibull	561.44	567.25
Gompertz	561.52	567.33
Exponential	559.63	562.53
Abbreviations: AIC, Akaike information criterion; BIC, Bayes information criterion; OS, overall survival		

Figure 22: Empirical hazard plot for overall survival (OS), pooled data



Abbreviations: OS, overall survival

Figure 23: Kaplan-Meier curve and fitted parametric distributions for overall survival (OS), pooled data



Abbreviations: OS, overall survival

Table 34: Extrapolated long-term survival rates for brigatinib, pooled data

	3-years	5-years	10-years	20-years
Extrapolated outcomes				
Generalised gamma	51.35%	32.27%	10.06%	0.99%
Gamma	51.22%	31.92%	9.58%	0.84%
Log-normal	56.80%	44.78%	29.40%	17.05%
Log-logistic	53.49%	38.73%	21.91%	11.07%
Weibull	51.06%	31.43%	8.90%	0.64%
Gompertz	50.46%	28.71%	4.23%	0.00%
Exponential	52.32%	33.97%	11.54%	1.33%
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%

Table 35: Extrapolated long-term survival outcomes for brigatinib, pooled data

	Predicted median (months)	Predicted mean over trial period (months)	Predicted mean over lifetime (months)	Median from pooled data (months)	Mean from pooled data (months)
Generalised gamma	37.72	21.80	52.81	NA	24.13
Gamma	37.72	21.81	52.00		
Log-normal	48.76	21.70	116.69		
Log-logistic	40.48	21.78	92.42		
Weibull	37.72	21.81	50.88		
Gompertz	36.80	21.80	44.74		
Exponential	38.64	21.73	55.38		
Abbreviations: NA, not applicable; OS, overall survival					

In the base case, the model assumes a continued treatment benefit associated with OS and PFS for brigatinib and ceritinib. Therefore, the extrapolated curves presented above for OS and below for PFS INV are used for the duration of the model time horizon. Scenario analyses consider the impact of varying the time point at which the treatment benefit stops for brigatinib and ceritinib. This scenario implies that after a specified cut-off the hazard of survival and progression are equal to what would be observed with BSC – which is considered the relevant subsequent therapy following treatment with brigatinib or ceritinib based on clinician feedback to resource use questionnaires. The scenario uses a hazard ratio for OS for brigatinib relative to BSC (hazard ratio: 0.13) – obtained from a naïve ITC using data from an observational French study.(79) This study reports no PFS and as such the hazard ratio associated with PFS is assumed equal to OS. These methods are naïve and are not intended to provide sufficient data to explore outcomes associated with subsequent therapy, but instead are intended to explore the uncertainty associated with the duration of a treatment benefit. The impact of five arbitrarily chosen cut-off points are explored: 2-, 3-, 4-, 5- and 10-years.

B.3.3.2.2 Progression-free survival investigator assessed (pooled data)

The pooled data for PFS INV were obtained from the observed brigatinib data from ALTA and Study 101 (n=135). Table 36 summarises AIC and BIC values for each parametric survival distribution. The statistical goodness-of-fit indicates that all the models fit the observed data well; the AIC values are less than 5 points between the models. BIC suggests that the exponential distribution is the best fitting model. However, the empirical hazard plot indicates that the hazard rate may not be constant over time (see Figure 24); hence the exponential distribution may not be appropriate.

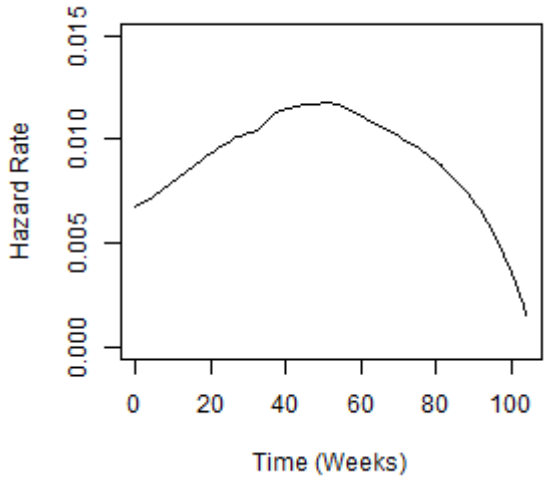
The Kaplan-Meier curve and fitted parametric distributions are presented in Figure 25. The visual inspection of the fitted curves suggests that the generalised gamma, gamma, Weibull and Gompertz fit the observed data well. Table 37 provides the long-term extrapolated estimates of brigatinib associated with PFS INV for each of the parametric curves in the model compared with the observed median and mean. Based on assessing both internal and external validity, the Gompertz distribution was selected in the base case for the PFS INV outcome. This is aligned with the distribution applied to the OS pooled data – as such, the OS and PFS investigator assessed curves follow the same shape and extrapolated curves do not cross, avoiding clinically implausible outcomes.

Scenario analyses consider the impact of the alternative parametric distributions and the impact of using ALTA data only (PFS INV and PFS IRC) – the methods and results of extrapolation for PFS INV and PFS IRC from ALTA only are presented in Appendix L.

Table 36: Goodness-of-fit statistics for progression-free survival (PFS) investigator assessed (INV), pooled data

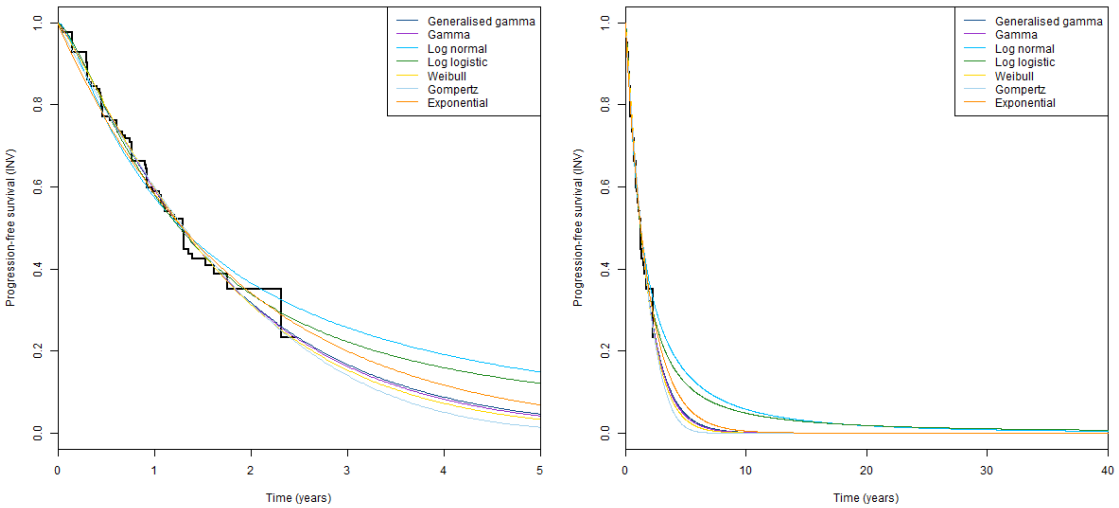
Model	AIC	BIC
Generalised gamma	773.19	781.90
Gamma	771.20	777.01
Log normal	777.20	783.01
Log logistic	771.43	777.24
Weibull	771.33	777.14
Gompertz	772.59	778.40
Exponential	771.63	774.53
Abbreviations: AIC, Akaike information criterion; BIC, Bayes information criterion; INV, investigator assessed; PFS, progression-free survival		

Figure 24: Empirical hazard for progression-free survival (PFS) investigator assessed (INV), pooled data



Abbreviations: INV, investigator assessed; PFS, progression free survival

Figure 25: Kaplan-Meier curve and fitted parametric distributions for progression-free survival (PFS) investigator assessed (INV), pooled data



Abbreviations: INV, investigator assessed; PFS, progression free survival

Table 37: Extrapolated long-term progression-free survival (PFS) investigator assessed (INV) outcomes for brigatinib, pooled data

	Predicted median	Predicted mean over trial period	Predicted mean over lifetime	Median from pooled data	Mean from pooled data
Generalised gamma	15.64	13.90	20.79	15.61	16.57
Gamma	15.64	13.91	20.50		
Log-normal	15.64	13.73	29.55		
Log-logistic	15.64	13.84	27.49		
Weibull	15.64	13.94	19.98		
Gompertz	16.56	13.90	19.04		
Exponential	15.64	13.68	22.36		
Abbreviations: INV, investigator assessed; PFS, progression-free survival					

B.3.3.2.3 Time on treatment (ToT)

In the base case, the model assumes that patients treated with brigatinib and ceritinib receive treatment for 1.53 months beyond progression. This is in line with the methods used in the NICE submission [TA395] for ceritinib and is calculated by the difference in median ToT and median PFS observed in the ALTA clinical trial. The median PFS associated with ALTA is 15.62 months and the median ToT is 17.15 months, resulting in a difference of 1.53 months. These estimates were presented to six UK clinicians at an advisory board held by

Takeda on the 29th January 2018 where it was considered clinically relevant that patients would be treated for approximately 6-weeks beyond progression (patients are evaluated for progression and then followed up approximately 6-weeks later to discuss treatment discontinuation or modification) – further details of the advisory board are provided in Section B.3.3.5 and B.3.10. Therefore, this method is supported by both case precedence and UK clinician support. The difference from ASCEND-2, as reported in the NICE submission [TA395],(51) was 1.6 months. Therefore, a scenario analysis considers the impact on results of assuming patients receive ceritinib for 1.60 months beyond progression.

Additional scenario analyses consider the impact of:

- Extrapolated ToT curves (capped by OS) for brigatinib and 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)
- Extrapolated ToT curves (capped by OS and PFS) for brigatinib and 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)
- Extrapolated ToT curves (capped by OS) for brigatinib and equal ToT assumed for ceritinib (capped by OS)
- Extrapolated ToT curves (capped by OS and PFS) for brigatinib and equal ToT assumed for ceritinib (capped by OS and PFS)

The methods and results associated with extrapolation of ToT are presented in Appendix L.

B.3.3.3 Indirect treatment comparisons (ITCs)

Due to lack of head-to-head data and the single-arm nature of the brigatinib data, two methods of unanchored ITCs were conducted to obtain comparative efficacy estimates (see Section B.2.9):

1. Naïve indirect comparison
2. MAIC

These methods were applied for the following outcomes: OS, PFS (INV and IRC), response (ORR INV, ORR IRC, BoR INV and BoR IRC). Each MAIC analysis adjusted for the full list of prognostic factors and treatment effect modifiers identified through clinician elicitation termed “MAIC full” and for a reduced list capturing only the variables that were reported across all studies (ALTA, Study 101, ASCEND-2 and ASCEND-5), termed “MAIC reduced”. Both methods were included in the model to consider the impact of uncertainty associated with prognostic factors and treatment effect modifiers on results.

Where data were available for ceritinib from both ASCEND-2 and ASCEND-5, FE and RE meta-analyses were performed for the relevant clinical endpoints to obtain overall relative effects. In line with the base case, methods of estimating relative efficacy associated with OS and PFS are presented in this Section. Appendix L presents the odds ratios associated with the relative efficacy relevant to response outcomes.

Section B.2.9.4 presents the results of the ITCs for ceritinib vs. brigatinib. The economic analysis uses the inverse of these results – i.e. brigatinib vs. ceritinib.

B.3.3.3.1 Overall survival (OS)

Table 38 presents the hazard ratios for brigatinib relative to ceritinib for OS associated with each combination of ITC method, covariate list, brigatinib data source and ceritinib data source. As data were available for OS associated with brigatinib from ALTA and Study 101 and with ceritinib from both ASCEND-2 and ASCEND-5, FE and RE meta-analyses were performed on the ITC methods to obtain overall relative effects comprising all brigatinib and ceritinib data.

The base case uses the hazard ratio from the RE meta-analysis of MAICs using pooled brigatinib data as this approach utilises all data for brigatinib and ceritinib. This hazard ratio is applied to the extrapolated curve for pooled OS brigatinib. Scenario analyses consider the impact on results of the different methods of ITCs for OS.

B.3.3.3.2 Progression free survival (PFS)

Table 38 presents the hazard ratios for brigatinib relative to ceritinib for PFS associated with each combination of ITC method, covariate list, brigatinib data source, ceritinib data source and PFS assessment. Study 101 only reported PFS INV and ASCEND-5 only reported PFS IRC outcomes. Therefore, no meta-analyses could be conducted to obtain overall relative effects comprising all brigatinib and ceritinib data. Data were available for PFS INV and PFS IRC from the ALTA trial. Therefore, FE and RE meta-analyses were performed on the ITC methods to obtain overall relative effects comprising ALTA brigatinib data and all ceritinib data.

The base case uses the hazard ratio from the MAIC using pooled brigatinib data and data from ASCEND-2 for ceritinib as this approach utilises all data for brigatinib and is consistent with the base case in terms of the assessment of PFS INV. This hazard ratio is applied to the extrapolated PFS INV brigatinib curve. Scenario analyses consider the impact on results of the different methods of ITCs for PFS.

Table 38: Hazard ratios for brigatinib vs. ceritinib associated with overall survival (OS)

Method	Covariate list	Brigatinib data source	Ceritinib data source	HR brigatinib vs. ceritinib
Naïve ITC	NA	ALTA	ASCEND-2	0.47
MAIC	Full	ALTA	ASCEND-2	0.42
MAIC	Reduced	ALTA	ASCEND-2	0.41
Naïve ITC	NA	Pooled (ALTA and Study 101)	ASCEND-2	0.46

Method	Covariate list	Brigatinib data source	Ceritinib data source	HR brigatinib vs. ceritinib
MAIC	Full	Pooled (ALTA and Study 101)	ASCEND-2	0.44
MAIC	Reduced	Pooled (ALTA and Study 101)	ASCEND-2	0.44
Naïve ITC	NA	ALTA	ASCEND-5	0.48
MAIC	Full	ALTA	ASCEND-5	0.36
MAIC	Reduced	ALTA	ASCEND-5	0.40
Naïve ITC	NA	Pooled (ALTA and Study 101)	ASCEND-5	0.48
MAIC	Full	Pooled (ALTA and Study 101)	ASCEND-5	0.51
MAIC	Reduced	Pooled (ALTA and Study 101)	ASCEND-5	0.51
FE meta-analysis of naïve ITC	NA	ALTA	ASCEND-2 and ASCEND-5	0.47
RE meta-analysis of naïve ITC	NA	ALTA	ASCEND-2 and ASCEND-5	0.47
FE meta-analysis of MAICs	Full	ALTA	ASCEND-2 and ASCEND-5	0.39
RE meta-analysis of MAICs	Full	ALTA	ASCEND-2 and ASCEND-5	0.39
FE meta-analysis of MAICs	Reduced	ALTA	ASCEND-2 and ASCEND-5	0.40
RE meta-analysis of MAICs	Reduced	ALTA	ASCEND-2 and ASCEND-5	0.41
FE meta-analysis of naïve ITC	NA	Pooled (ALTA and Study 101)	ASCEND-2 and ASCEND-5	0.47
RE meta-analysis of naïve ITC	NA	Pooled (ALTA and Study 101)	ASCEND-2 and ASCEND-5	0.47
FE meta-analysis of MAICs	Full	Pooled (ALTA and Study 101)	ASCEND-2 and ASCEND-5	0.48
RE meta-analysis of MAICs (base case)	Full	Pooled (ALTA and Study 101)	ASCEND-2 and ASCEND-5	0.48
FE meta-analysis of MAICs	Reduced	Pooled (ALTA and Study 101)	ASCEND-2 and ASCEND-5	0.48
RE meta-analysis of MAICs	Reduced	Pooled (ALTA and Study 101)	ASCEND-2 and ASCEND-5	0.48

Abbreviations: FE, fixed effects; HR, hazard ratio; ITC, indirect treatment comparison; MAIC, matched adjusted indirect comparison; NA, not applicable; OS, overall survival; RE, random effects

Table 39: Hazard ratios for brigatinib vs. ceritinib associated with progression-free survival (PFS)

Method	Covariate list	Brigatinib data source	Ceritinib data source	PFS assessment	HR brigatinib vs. ceritinib
Naïve ITC	NA	ALTA	ASCEND-2	INV	0.39
MAIC	Full	ALTA	ASCEND-2	INV	0.37
MAIC	Reduced	ALTA	ASCEND-2	INV	0.37
Naïve ITC	NA	Pooled (ALTA and Study 101)	ASCEND-2	INV	0.39
MAIC (base case)	Full	Pooled (ALTA and Study 101)	ASCEND-2	INV	0.39
MAIC	Reduced	Pooled (ALTA and Study 101)	ASCEND-2	INV	0.39
Naïve ITC	NA	ALTA	ASCEND-5	IRC	0.29
MAIC	Full	ALTA	ASCEND-5	IRC	0.21
MAIC	Reduced	ALTA	ASCEND-5	IRC	0.23
FE meta-analysis of naïve ITC	NA	ALTA	ASCEND-2 and ASCEND-5	Pooled	0.34
RE meta-analysis of naïve ITC	NA	ALTA	ASCEND-2 and ASCEND-5	Pooled	0.34
FE meta-analysis of MAICs	Full	ALTA	ASCEND-2 and ASCEND-5	Pooled	0.31
RE meta-analysis of MAICs	Full	ALTA	ASCEND-2 and ASCEND-5	Pooled	0.30
FE meta-analysis of MAICs	Reduced	ALTA	ASCEND-2 and ASCEND-5	Pooled	0.30
RE meta-analysis of MAICs	Reduced	ALTA	ASCEND-2 and ASCEND-5	Pooled	0.30

Abbreviations: FE, fixed effects; HR, hazard ratio; INV, investigator assessed; IRC, independent review committee; ITC, indirect treatment comparison; MAIC, matched adjusted indirect comparison; NA, not applicable; PFS, progression-free survival; RE, random effects

B.3.3.4 Adverse events

Treatment with TKIs result in a variety of adverse events. Furthermore, the type, severity and rate of adverse events can vary between treatments leading to differences in overall HRQL, resource use and costs. All any cause grade 3/4 adverse events were included in the economic analysis using data from ALTA for brigatinib – this is aligned with the final economic analysis submitted as part of the NICE submission [TA395] for ceritinib.(51) Adverse events were modelled only for patients on treatment; it was assumed that adverse events for all therapies cease once treatment is discontinued. In total, 60 different adverse events were included in the analysis as shown in Appendix L. The incidence rate per cycle for each adverse event was estimated for brigatinib. This approach considers both the number of events occurring, the follow-up period or exposure time in person-years (i.e. incidence rate) and the cycle length within the model. The average treatment exposure was obtained from the ALTA data: 34-weeks.

The rates of adverse events for ceritinib were calculated using data reported in Crino *et al*. (2016)(27) and Shaw *et al*. (2017)(28) for ASCEND-2 and ASCEND-5, respectively. These data were pooled, and relative risks were applied to the incidence rates per cycle for brigatinib. Crino *et al.* (2016) reported grade 3/4 adverse events occurring in ≥2% of patients. Shaw *et al*. (2017) reported grade 3/4 adverse events occurring in ≥10% of patients. Therefore, this approach is conservative as it underestimates the number of grade 3/4 adverse events occurring in all patients in the ceritinib arm.

Where it was not possible for relative risks to be calculated (data not reported for all adverse events) the rates of adverse events observed in the ALTA study were applied. This was the case for 47 adverse events (marked with an asterisk in Table 27, Appendix L). A scenario analysis considers the impact of this assumption by setting these relative risks equal to zero.

The incidence rates associated with any cause grade 3/4 adverse events per cycle for brigatinib and ceritinib are presented in Appendix L.

B.3.3.5 Validation of clinical parameters

Section B.3.10 presents the validation undertaken for all the variables and outcomes in the economic model. This Section summarises the validation undertaken for the clinical parameters only. The clinical parameters were validated by:

- Clinical outcomes were compared with those from the relevant clinical trials: ALTA, Study 101, ASCEND-2 and ASCEND-5
- Semi-structured interviews with five UK clinical experts
- Advisory board conducted with six UK clinical experts

Table 40 compares the median and mean clinical outcomes from the trial data with the predicted model outcomes for OS, PFS INV and ToT. The results of extrapolation are shown to inflate median survival for both brigatinib and ceritinib. However, the degree of inflation is larger in the ceritinib arm with the predicted survival for brigatinib (36.80 months) being approximate to the observed data in the September 2017 ALTA data cut (34.14 months).

The median clinical outcomes for PFS INV and ToT are shown to closely match the median trial outcomes. In replicating these outcomes, the economic model gives an accurate representation of the short-medium term clinical outcomes experienced by patients.

When looking at the long-term outcomes, the estimated mean survival in the model appears higher than the restricted means calculated based on the observed trial data for brigatinib. These data are unavailable to make this comparison with ceritinib. The immaturity of the data introduces uncertainty associated with long-term survival estimates. The proportion surviving at 3-, 5-, 10- and 20-years when using the Gompertz curve for OS data (base case) aligned with the expectations of UK clinicians. The submission explores the uncertainty by assuming different parametric curve choices and applying treatment benefit discontinuation scenarios.

Estimated mean PFS INV and ToT were in line with the restricted means calculated based on the observed trial data for brigatinib. In replicating these outcomes, the economic model gives an accurate representation of the long-term PFS INV and ToT outcomes experienced by patients.

Table 40: Comparison of clinical outcomes with model outcomes

	Brigatinib		Ceritinib	
Outcome	Clinical trial result	Model result	Clinical trial result	Model result
Median outcomes (months)				
OS	Pooled = NA ALTA (Feb 2017) = 27.57 ALTA (Sept 2017) = 34.14	36.80	ASCEND-2 = 14.9 (95% CI: 13.5-NE) ASCEND-5 = 18.1 (95% CI: 13.4-23.9)	19.32
PFS INV	Pooled (Feb 2017) = 15.61 Pooled (Sept 2017) = 15.61 ALTA (Feb 2017) = 15.62 ALTA (Sept 2017) = 15.61	16.56	ASCEND-2 = 5.7 (95% CI: 5.4-7.6) ASCEND-5 = 6.7 (95% CI: 4.4-7.9)	7.36
ToT	ALTA (Feb 2017) = 17.15 ALTA (Sept 2017) = 17.15	16.56	NR	7.36
Mean outcomes (months)				
OS	Pooled (Feb 2017) = 24.31	44.74	NR	24.32

	Brigatinib		Ceritinib	
Outcome	Clinical trial result	Model result	Clinical trial result	Model result
	Pooled (Sept 2017) = 27.50 ALTA (Feb 2017) = 24.11 Pooled (Sept 2017) = 27.68			
PFS INV	Pooled (Feb 2017) = 16.57 Pooled (Sept 2017) = 17.62 ALTA (Feb 2017) = 16.49 ALTA (Sept 2017) = 17.58	19.04	NR	8.74
ToT	ALTA (Feb 2017) = 17.81 ALTA (Sept 2017) = 19.20	20.57	NR	10.27
Abbreviations: CI, confidence interval; INV, investigator; NE, not evaluable; OS, overall survival; PFS, progression free survival; ToT, time on treatment				

Long-term predictions of OS outcomes were validated through a questionnaire administered in semi-structured telephone interviews and through an advisory board conducted by Takeda on 29th January 2018 – each described in more detail in Section B.3.10.

The semi-structured interviews requested that clinicians provide an estimate of the proportion of patients surviving at 3-, 5-, 10- and 20-years to obtain long-term estimates of survival for patients with ALK+ advanced NSCLC treated with an ALK inhibitor. Clinicians were specifically asked: "*In the absence of longer term follow-up data, what would be the expected survival probability for the patient population of ALK+ NSCLC patients post-crizotinib at 3-, 5-, 10- and 20-years?"*

Table 41 presents the responses from each clinician and the averaged responses: 50.00%, 28.50%, 5.83% and 0.00% at 3-, 5-, 10- and 20-years, respectively. These values align closely with the estimates for brigatinib predicted by the model when the Gompertz distribution is fit to the pooled OS data. This confirms the clinical plausibility and appropriateness of using the Gompertz parametric curve for OS outcomes in the base case. Furthermore, in the base case, the treatment benefit associated with brigatinib is assumed to be maintained over the model time horizon. The averaged estimates from clinicians support this assumption. Scenario analyses consider the impact of different parametric curves and treatment benefit discontinuation scenarios.

Table 41: Long-term OS estimations from clinicians

	3-years	5-years	10-years	20-years
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%
Modelled outcomes				
Brigatinib	50.46%	28.71%	4.23%	0.00%
Ceritinib	23.96%	7.37%	0.13%	0.00%
Key: OS, overall survival				

Further validation of the modelled OS outcomes was undertaken at an advisory board with six clinical experts present. The outcomes from the questionnaire were presented to clinical experts at the advisory board for validation. Clinical experts considered that the long-term outcomes associated with ALK inhibitor treatments are unknown. However, it was considered that the Gompertz approach to modelling OS most closely aligned with expectations and that scenario analyses should explore the uncertainties associated with these estimates.

B.3.4 Measurement and valuation of health effects

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

The ALTA clinical study used the EORTC-QLQ-C30 to measure HRQL. HRQL data were not included in Study 101 and thus all utility estimates are based on IPD from ALTA. The EORTC-QLQ-C30 assesses the quality of life of cancer patients. These questionnaires were provided in electronic format to each patient to complete on the first day of every cycle, including cycle 1, and at study discontinuation. The EORTC-QLQ-C30 cannot be used directly in economic evaluation as it does not incorporate preference information. Therefore, a mapping exercise was required to convert the EORTC-QLQ-C30 data into EQ-5D utility scores. Following this, a HRQL analysis has been conducted to estimate utility values for different health states in the economic model.

B.3.4.1.1 Mapping from EORTC-QLQ-C30 to EQ-5D

The EORTC QLQ-C30 is a 30-item cancer-specific instrument. Multi-trait scaling was used to create five functional domain scales: Physical, Role, Emotional, Social, and Cognitive; two items evaluate Global QOL; in addition, three symptom scales assess Fatigue, Pain, and

Emesis; and six single items assess other symptoms. The EQ-5D is the most commonly used generic preference-based measure and is currently recommended by NICE for use in economic models.(69) The EQ-5D-3L is a self-administered questionnaire consisting of five 3-level questions pertaining to specific health dimensions (i.e., mobility, self-care, pain, usual activities, and anxiety/depression), and a health status rating scale. Each dimension has 3 levels of "severity" corresponding to no problems, some problems, and extreme problems. The mapping algorithm used to convert EORTC QLQ-C30 into EQ-5D-3L utility values is one published by Longworth *et al*. (2014).(68) A summary of utility values after the mapping procedure are presented in Table 42.

Table 42: Summary of mapped utility values

	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.					

A total of 103 patients (out of 110) had at least one mapped EQ-5D utility value, 101 of these had at least one investigator-assessed overall response measured, but this reduced to 99 patients who had at least one investigator-assessed overall response measure (i.e. complete response, partial response, stable disease or progressive disease) captured at the same time the response to the EORTC QLQ-C30 questionnaire was recorded. All patients had a mapped baseline EQ-5D utility score. When considering the data set based on best overall response (i.e. the best response achieved by each patient which is therefore not required to be captured at the same time as the HRQL questionnaire), patients had an average (mean) of 17 measurements recorded over time, one patient had one measurement recorded post-baseline and one patient had 30 or more mapped utility scores. A maximum of 35 cycles of HRQL data were included in the statistical model, however HRQL was also captured at baseline, at unscheduled visits, at the end of treatment as well as follow-up 30 days after last dose for some patients.

B.3.4.1.2 HRQL analyses

Four sets of HRQoL analyses were conducted: one using four individual categories of ORR (complete response, partial response, stable disease or progressive disease), one using two categories of ORR (progression-free versus progressed, where progression-free comprised complete response, partial response and stable disease), and four categories of BoR and two categories of BoR. This results in a total of four HRQoL models fitted to the ALTA data. Note: HRQL was not reported in Study 101 and therefore HRQL analysis of a pooled ALTA/Study 101 dataset could not be conducted.

ORRs were captured at the same time that the EORTC QLQ-C30 questionnaire was completed and was therefore time-varying, however BoR was recorded as the best response achieved by each patient over the entire follow-up period. The sample sizes of the data vary substantially depending on whether BoR or ORR assessments are included in the statistical model; this is due to overall response not being measured at the time of the EQ-5D questionnaire.

In addition to response categories, other factors were incorporated into the statistical model which were believed to be influential on HRQL. This was an exploratory analysis conducted to identify any increment/decrement in HRQL associated with response and adverse events. Clinical input was sought to help identify which explanatory variables should be included in the regression model. All 20 factors detailed previously in the ITC section were considered for inclusion within the statistical HRQL model. Furthermore, variables which were previously excluded from the ITC analyses due to missing comparator data were considered for inclusion in the HRQL analysis, as the HRQL analysis utilises only brigatinib evidence arising from ALTA. Variables included in the analyses were those which at least eighty percent of clinicians (i.e. four out of five) agreed were prognostic on HRQL. A total of nine variables met this criterion, including: ECOG PS, disease stage at study entry, presence of brain metastases, presence of liver metastases, presence of bone metastases, receipt of prior chemotherapy, receipt of prior radiotherapy to brain, number of metastatic sites and presence of active brain lesions. Disease stage at study entry could not be included in the analyses due to too many patients classed as stage 4 in the ALTA data; an insufficient number of patients in the other level of this factor are available, leading to lack of robust regression results. Age and gender were also included, as these are standard baseline characteristics which are commonly adjusted for. Grade 3/4 adverse events were also included as this is required for the economic model; HRQL is then estimated for those with and without a grade 3/4 adverse event. Due to the classification of this variable, the HRQL analysis estimates a utility value for patients experiencing none versus at least one grade 3/4 adverse event. One additional variable was also included: time from prior crizotinib therapy to brigatinib treatment. This was considered prognostic because it is thought to be associated with early onset pulmonary events. Table 43 shows a summary of the covariates included in the HRQL models.

Table 43: Summary of HRQL models fitted to ALTA data

	HRQL model 1	**HRQL model 2**	**HRQL model 3**	**HRQL model 4**
	Outcome			
Mapped EQ-5D	3L	3L	3L	3L
	Covariates			
Mapped Baseline EQ-5D score	Continuous	Continuous	Continuous	Continuous
Response	Overall response (CR vs PR vs SD vs PD)	Best overall response (CR vs PR vs SD vs PD)	Overall response (PF vs PD)	Best overall response (PF vs PD)
ECOG PS	0-1 vs 2	0-1 vs 2	0-1 vs 2	0-1 vs 2

Grade 3/4 AE	Y vs N	Y vs N	Y vs N	Y vs N
Age	Continuous	Continuous	Continuous	Continuous
Gender	M vs F	M vs F	M vs F	M vs F
Presence of brain metastases	Y vs N	Y vs N	Y vs N	Y vs N
Presence of liver metastases	Y vs N	Y vs N	Y vs N	Y vs N
Presence of bone metastases	Y vs N	Y vs N	Y vs N	Y vs N
Number of metastatic sites	Continuous	Continuous	Continuous	Continuous
Receipt of prior chemotherapy (including platinum)	Y vs N	Y vs N	Y vs N	Y vs N
Presence of active brain lesions	Y vs N	Y vs N	Y vs N	Y vs N
Time from prior crizotinib to brigatinib	Continuous	Continuous	Continuous	Continuous
Key: AE, adverse event; CR, complete response; F, female; HRQL, health-related quality of life; M, male; N, no; PD, progressive disease; PF, progression-free; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor; Y, yes. **Notes:** blue highlights the only differences between the different HRQL models.				

A longitudinal mixed-effects regression model was fitted to the data, which accounted for the repeated measures structure of the data. The model was then used to predict EQ-5D utility values, whereby EQ-5D data had been mapped from EORTC QLQ-C30 which were then converted into utilities using the EQ-5D UK Tariff values.(80) The utility scores were then used as dependent variables in the regression model whilst incorporating the explanatory variable specified in Table 43. No selection procedures were implemented (i.e. stepwise selection) as the saturated model included all factors deemed relevant and prognostic of HRQL outcomes by the five clinicians. Results from the four regression models are presented in Table 43. When evaluating ORR (split into two or four categories), ECOG PS of 2 shows a reduction in HRQL versus a status of 0-1. Experience of at least one grade 3/4 adverse event, increase in age, male patients, presence of brain metastases, receipt of prior chemotherapy and an increase in the time since receipt of prior crizotinib therapy all show a trend of negatively impacting HRQL. Using BoR (split into two or four categories), ECOG PS of 2, experience of at least on grade 3/4 adverse event, male patients, receipt of prior chemotherapy, increase in time since prior crizotinib therapy, an increase in age and the presence of brain metastases all show a reduction in HRQL.

Table 44: HRQL regression results

	HRQL model 1		HRQL model 2		HRQL model 3		HRQL model 4	
Covariate	**Mean**	**SE**	**Mean**	**SE**	**Mean**	**SE**	**Mean**	**SE**
Number of patients Number of records	99 564				101 1708			
Intercept	0.508	0.095	0.531	0.089	0.523	0.082	0.507	0.070
Overall response [4 categories] (ref=Complete response) Partial response Progressive disease Stable disease	 0.026 -0.008 0.027	 0.036 0.038 0.039	NA		NA		NA	
Overall response [2 categories] (ref=Progression-free) Progressive disease	NA		-0.033	0.018				
Best overall response [4 categories] (ref=Complete response) Confirmed partial response Progressive disease Stable disease			NA		-0.021 -0.194 -0.014	0.050 0.069 0.051		
Best overall response [2 categories] (ref=Progression-free) Progressive disease					NA		-0.177	0.049
Baseline EQ-5D score	0.452	0.069	0.450	0.069	0.514	0.054	0.516	0.054
ECOG PS (ref=0-1) 2	 -0.143	 0.058	 -0.143	 0.058	 -0.061	 0.046	 -0.060	 0.045

Experience of 1+ grade 3/4 AE (ref=No) Yes	-0.053	0.030	-0.053	0.030	-0.056	0.024	-0.057	0.024
Age (years)	-0.002	0.001	-0.002	0.001	-0.002	0.001	-0.002	0.001
Gender (ref=Female) Male	-0.014	0.029	-0.014	0.029	-0.020	0.022	-0.021	0.022
Presence of brain metastases (ref=No) Yes	-0.091	0.048	-0.088	0.048	-0.095	0.038	-0.097	0.038
Presence of liver metastases (ref=No) Yes	0.027	0.038	0.026	0.038	0.031	0.030	0.030	0.030
Presence of bone metastases (ref=No) Yes	0.003	0.037	0.003	0.037	0.011	0.029	0.010	0.029
Number of metastatic sites (continuous)	0.023	0.015	0.024	0.015	0.017	0.012	0.017	0.012
Receipt of prior chemotherapy (ref=No) Yes	-0.013	0.032	-0.012	0.032	-0.007	0.025	-0.009	0.025
Presence of active brain lesions (ref=No) Yes	0.050	0.041	0.050	0.041	0.059	0.032	0.059	0.032
Time since prior crizotinib therapy to receipt of brigatinib (months)	-0.004	0.006	-0.004	0.006	-0.002	0.005	-0.002	0.005
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; NA, not applicable; SE, standard error.								

There was very minimal difference in utility scores between the overall response states; none of the states showed statistically significant differences in utility values versus complete response, and this was also the case when response was dichotomised into two categories of progressed vs progression-free. Resulting utility values by response status (based on a mean of covariates approach) are presented in Table 45. These mean utility scores are then applied in the economic model and described further in Section B.3.4.4.

Table 45: Mean utility values by response category

	Overall response (4 categories)	Overall response (2 categories)	Best overall response (4 categories)	Best overall response (2 categories)
Complete response	0.719	NA	0.759	NA
Partial response	0.745		0.738	
Stable disease	0.747		0.746	
Progressive disease	0.711		0.566	
Progression-free	NA	0.744	NA	0.742
Progressed		0.711		0.565
Abbreviations: NA, not applicable.				

HRQL analyses considering the impact of time to death on utility values were initially considered at the analysis planning stage. However, these were not explored in more detail due to the limited number of deaths in the brigatinib data and the feedback from clinicians which highlighted that only narrow time categories would show clinically meaningful differences – thus reducing the data further.

B.3.4.2 Health-related quality-of-life studies

Appendix H describes how relevant HRQL data were identified in a HRQL SLR.

In line with the NICE Methods Guide 2013, utility associated with pre-progression is informed by patients from the ALTA clinical trial. However, due to limitations associated with progressed disease utility values, the analysis considers the utility decrement associated with progression from the literature.

B.3.4.3 Adverse events

The impact of adverse events on HRQL was included in the HRQL analyses by including a variable capturing the experience of at least one grade 3/4 adverse event. The utility decrement associated with experience of at least one grade 3/4 adverse event, based on the base case HRQL model (model 2), is -0.0528. The utility decrement was multiplied by the per-cycle probability of a grade 3/4 adverse event and by the weighted number of cycles of duration of grade 3/4 adverse events obtained from the ALTA data. Where the mean duration of an adverse event was unavailable in the ALTA data set, the average of the

reported durations of adverse events was assumed. This was the case for 13 of the 60 adverse events.

Table 27 in Appendix L presents the mean cycles of duration for each adverse event. The utility decrements associated with adverse events per cycle are -0.0083 and -0.0095 for brigatinib and ceritinib, respectively.

A scenario analysis considers utility values for pre-progression and progressed disease obtained from Nafees *et al*. (2008).(81) This scenario also considers the utility decrements reported in the study: -0.0897 for neutropenia, -0.0480 for nausea and vomiting, -0.0325 for rash and -0.0735 for fatigue.

B.3.4.4 Health-related quality-of-life data used in the cost-effectiveness analysis

Within the model, base case data are taken from the HRQL analyses on the ALTA data for pre-progression (Section B.3.4.1) and from Chouaid *et al.* (2013)(82) for progressed disease.

The pre-progression utility values were derived using two categories of ORR (progression-free versus progressed, where progression-free comprised complete response, partial response and stable disease) in the base case. This aligns with the feedback to the NICE submission for ceritinib [TA395] where the ERG used the same utility value for both ceritinib and BSC and then adjusted these values for adverse events using the literature. As the ALTA trial was a single arm study, the model assumes that the results of the HRQL analyses are applicable to ceritinib as well as brigatinib. Scenario analyses explore the impact of using four categories of ORR, two categories of BoR and four categories of BoR to estimate pre-progression utility values. The results from the four regression models are presented in Table 44 with the base case corresponding to HRQL model 2. Resulting utility values by response status (based on a mean of covariates approach) are presented in Table 45.

The model used the intercept and the coefficients associated with each of the included variables to estimate the utility of patients in the pre-progression health state for brigatinib and ceritinib. The model used the mean of covariates approach, which involved multiplying the average of each covariate, obtained from the ALTA trial, with the coefficient estimated from the HRQL analysis. This estimate was then added to the intercept to provide the utility value for the pre-progression health state. Table 45 presents the mean covariates and the coefficients used in the base case. Appendix L summarises the HRQL variables applied in the economic model in more detail (mean values and 95% confidence interval). The mean utility value associated with the progression-free health state (0.744) is in line with the estimates identified by the HRQL SLR for treatment with ALK-inhibitors. Chouaid *et al*. (2013), used in the NICE submission for ceritinib [TA395], reported a utility of 0.74 for 2nd line pre-progression which is in line with the HRQL analyses.

Using the base case method, a patient's HRQL is not constant over time. Across the model time horizon, patients progress, age and experience adverse events. Each of these events are captured within the HRQL estimates. The utility decrement associated with progression is applied to the proportion of patients in the progressed health state. The utility decrement associated with age is multiplied by the age in the model each cycle to reflect the declining HRQL associated with aging. The utility decrement associated with adverse events is multiplied by the rate of adverse events per cycle and the weighted average of duration of adverse events to calculate a utility decrement associated with adverse events applied per cycle, described in Appendix L.

In the scenario where the utility value associated with progressed disease is sourced from ALTA, the utility decrement associated with progressed disease is applied to the proportion of patients in the progressed health state each cycle.

Table 46: Mean covariates, base case intercept and coefficients

	Mean covariate	Estimate
Intercept	NA	0.5311
Baseline EQ-5D-3L score	0.71	0.4501
Progressed	NA	-0.0330
ECOG PS	9.09%	-0.1426
≥1 grade 3/4 adverse event	NA	-0.0528
Age	54.79	-0.0017
Gender (male)	38.38%	-0.0141
Presence of brain metastases = yes	68.69%	-0.0885
Presence of liver metastases = yes	21.21%	0.0261
Presence of bone metastases = yes	33.33%	0.0026
Number of metastatic sites	3.36	0.0236
Receipt of prior chemotherapy = yes	72.73%	-0.0116
Presence of active brain lesions = yes	51.52%	0.0496
Time since prior crizotinib therapy	0.73	-0.0043
Abbreviations: ECOG, Eastern Cooperative Oncology Group; EQ-5D-3L, EuroQol 5-dimensions 3-levels; NA, not applicable; PS, performance score		

The ALTA clinical trial only followed patients until treatment discontinuation. Therefore, there are limited data associated with progressed disease. Furthermore, the data available reflected patients whose disease had progressed recently and so their HRQL is likely to be higher than for patients at a later stage of progression. Therefore, in line with the NICE Methods Guide 2013, which specifies that the preferred measurement of HRQL is using the EQ-5D, and the NICE submission for ceritinib [TA395] – Chouaid *et al.* (2013) provides the utility decrement associated with progressed disease. This paper reports on a prospective HRQL survey on advanced NSCLC patients in 25 hospitals in Europe, Canada, Australia and Turkey. HRQL was assessed using the EQ-5D questionnaire and evaluable data was obtained from 263 patients. The mean utility associated with 2nd line progression-free was 0.74 and for 2nd line progressed disease was 0.59, resulting in a utility decrement of -0.15 associated with progression. This utility decrement was applied to patients in the progressed disease health state in the base case.

A scenario analysis considers the impact of using the progressed disease utility value derived from the HRQL analyses and the utility decrement from Nafees *et al*. (2008).(81) Additional scenario analyses explore the impact of applying both the pre-progression and progressed disease utility values from Chouaid *et al*. (2013)(82) and Nafees *et al*. (2008).(81)

Table 47 summarises the utility values used in the cost-effectiveness analysis.

Table 47: Summary of utility values used in the cost-effectiveness analysis

Health state	Mean value	Justification
Progression free (whether on brigatinib or ceritinib)	0.744*	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)	0.594*	Utility based on the progressed disease decrement published in Chouaid *et al*. (2013)(82) (-0.15). This is in line with the NICE Methods Guide 2013(69) and the NICE submission for ceritinib [TA395].(51) Limited data associated with progressed disease from ALTA study. The data that are available reflects patients whose disease had progressed recently.
Age	-0.0017	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	-0.0528	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		

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

B.3.5.1 Resource identification, measurement and valuation studies

Appendix I describes how relevant cost and healthcare resource use data for England were identified in a cost and resource use SLR.

The cost and resource use SLR did not identify any treatment specific or health state specific UK resource use for the population relevant to brigatinib. In the NICE submission for ceritinib [TA395](51) resource use was primarily obtained from previous NICE submissions [TA162,(83) TA258](84) based on a NSCLC population – not specific to an ALK-rearrangement. Therefore, a resource use questionnaire was conducted with five UK clinicians, methods and results associated with the expert elicitation are presented in Appendix I.

B.3.5.2 Intervention and comparators' costs and resource use

B.3.5.2.1 Treatment costs

The unit costs associated with treatment acquisition are shown in Table 48 at list price. A PAS is currently going through PASLU for brigatinib that reduces the net price from £4,900 per pack to £[redacted], a [redacted] discount from list price for the starter pack (7x90mg + 21x180mg) and the full 180mg strength (28x180mg) i.e. recommended dose pack). Results are shown at list price for brigatinib. A PAS is in place for ceritinib, but as this is confidential, this has not been included and comparisons are presented at list price.

The dose schedule of brigatinib is aligned with arm B from ALTA and the selected subgroup from Study 101. This is in line with the proposed marketing authorisation for brigatinib. The dose schedule of ceritinib is aligned with the SmPC. (85)

The base case accounts for patients who may not take the full course of doses due to dose interruption or reduction associated with adverse events or non-compliance. The dose intensity for brigatinib was based on the mean dose intensity from the ALTA clinical trial: 88.90%.(32) These data were unavailable for the subgroup selected from Study 101. The dose intensity for ceritinib was based on the weighted median dose intensities reported in Shaw *et al*. (2017)(28) and Crino *et al*. (2016)(27) for ASCEND-5 and ASCEND-2, respectively: 83.59%. A scenario analysis considers the impact of results when dose intensity is excluded.

Table 48: Unit costs associated with the technology in the economic model

	Brigatinib	Ceritinib
Unit dose	180mg once daily with a 7-day lead-in at 90mg	750mg orally once daily
Pack size	28 tablets	150 capsules
Unit cost at list price	£4,900 for a 28-tablet pack	£4,923.45 for three packs of 50 capsules
Cost per 28-days – dose intensity applied	£4,356.10	£3,841.24
Cost per 28-days – dose intensity not applied	£4,900	£4,595.22
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		

B.3.5.2.2 Administration costs

Brigatinib and ceritinib are both orally administered. Therefore, the base case assumes no administration costs for these treatments.

A scenario analysis considers the impact of applying the cost of oral chemotherapy administration obtained from the NHS Reference Costs 2016/2017 (SB11Z, £170.75).(70)

B.3.5.2.3 Concomitant medications

Concomitant medications (CMs) were obtained from arm B of the ALTA clinical trial.(32) These data were unavailable from Study 101, ASCEND-2 and ASCEND-5. CMs were included if they were received by ≥5% of patients. A total of 37 CMs were included in the model. Due to lack of comparator evidence, the model assumes that the type and proportion of patients receiving CMs whilst on treatment are the same for both brigatinib and ceritinib. In UK clinical practice, it is likely that patients treated with ceritinib would require additional medication to manage the GI toxicity which is not captured by this assumption. Therefore, assuming equal costs of CMs per cycle for brigatinib and ceritinib is a conservative assumption. In the model, the cost of CMs is only considered for patients on treatment.

Dosing information associated with each CM was obtained from the British National Formulary (BNF). Costs were obtained from the electronic marketing information tool (eMIT)(72) where available. Where unavailable, costs were obtained from the BNF. One CM required weight-based dosing – the mean weight of patients in Arm B of the ALTA clinical trial was used in this calculation (70.43kg).

Appendix L presents the dosing information and costs associated with each CM. The drug cost per cycle (28-days) assuming no drug wastage and the proportion of patients receiving each CM derived from the ALTA CSR(32) are also presented in Appendix L. The total cost per model cycle was £68.45.

B.3.5.3 Health-state unit costs and resource use

Resource use was obtained from resource use questionnaires completed using semi-structured interviews with five UK clinicians, see Appendix I. The average reported across the completed questionnaires for resource use was implemented within the economic model.

B.3.5.3.1 Pre-progression costs

Costs associated with the pre-progression state included: oncology outpatient visits, pharmacists, general practitioner (GP) visits, cancer nurses, complete blood count, serum chemistry, CT-scan and X-ray. Frequencies of resource use per cycle (28-days) were obtained from the averaged responses of the resource use questionnaire. Clinical expert input indicated that, apart from differences in resource use due to different rates of adverse events, resource use was considered the same for patients treated with brigatinib and ceritinib.

The unit cost associated with a pharmacist and GP was obtained from the PSSRU (2017).(71) All other pre-progression resource use costs were obtained from the NHS Reference Costs (2016/2017).(70)

Table 49 presents the frequencies of resource use associated with the first cycle and subsequent cycles and associated first cycle and subsequent cycle costs. The total cost associated with the first cycle in pre-progression was £640.17. Total pre-progression costs per cycle in subsequent cycles were estimated to be £326.27.

Table 49: 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);(70) 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);(71) 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

B.3.5.3.2 Progressed disease costs

Costs associated with the progressed disease state included: oncology outpatient visits, GP visits, cancer nurses, complete blood count, serum chemistry, CT-scan, X-ray and dietician visits. Clinical expert input indicated that subsequent therapy for patients progressing on brigatinib or ceritinib would be best supportive care (BSC), comprising home oxygen, radiotherapy, steroids, NSAIDs, morphine, bisphosphonate and denosumab. The frequencies of resource use associated with subsequent therapy was averaged across clinician responses and applied to all patients in the progressed disease health state.

The unit cost associated with a pharmacist and GP was obtained from the PSSRU (2017).(71) Costs and dosing information associated with steroids, NSAIDs, morphine, bisphosphonate and denosumab were obtained from the BNF. All other progressed disease resource use costs were obtained from the NHS Reference Costs (2016/2017).(70)

Table 50 presents the frequencies of resource use associated with each cycle in the progressed disease health state and associated cycle costs. The total cost associated with each cycle in progressed disease was £513.34.

All post-progression costs were applied for the entire time patients were in the progressed disease state, regardless of the treatment they received before progression.

Table 50: 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);(70) 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);(71) 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
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)

	Dose	Frequency per cycle	Unit cost	Total cost per cycle	Source
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
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
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					

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

Table 51 describes each of the costs associated with each health state for brigatinib and ceritinib.

Table 51: Breakdown of costs in each health state

Health states	Items	Cost per cycle
Pre-progression	Technology	Brigatinib: £4,900 (list price) Ceritinib: £4,923.45 (list price) Brigatinib: £4,356 (list price, dose intensity applied) per cycle Ceritinib: £3,841 (dose intensity applied) per cycle
	Administration	£0. A scenario analysis considers the impact of a cost associated with oral administration
	Concomitant medications	£68.45 per cycle
	Resource use	£640.17 in first cycle £326.27 in subsequent cycles
	Adverse events	Brigatinib: £263.47 per cycle Ceritinib: £275.03 per cycle
Progressed disease	Resource use (including subsequent therapy)	£513.34 per cycle
Death	Terminal care	£1,705.53 lump sum applied on death. A scenario analysis considers £852.76 as a lump sum applied on death.

B.3.5.4 Adverse reaction unit costs and resource use

Section B.3.3.4 describes how adverse events were included in the economic model. In line with case precedence with the NICE submission for ceritinib [TA395](51) and clinician feedback from an advisory board conducted by Takeda, all grade 3/4 adverse events were included in the model.

Adverse events were costed using the NHS Reference Costs 2016/2017. The costs associated with laboratory abnormalities were assumed to include the cost of a medical oncology outpatient visit and a blood test. It was assumed that no cost was associated with weight decreased, fatigue, general health deterioration and dehydration. Within the model, patients incurred a one-time cost for the management of adverse events. The unit costs used in the model for each included adverse event are presented in Appendix L. The total

cost per cycle associated with adverse events was estimated as £263.47 and £275.03 for brigatinib and ceritinib, respectively.

B.3.5.5 Miscellaneous unit costs and resource use

No miscellaneous unit cost or resource use were incorporated in the model.

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

B.3.6.1 Summary of base-case analysis inputs

In line with the NICE reference case, the model considers a UK treatment provider's perspective and discounts costs and QALY using a 3.5% discount rate. Results are presented over a lifetime (12.65 years) time horizon.

Where possible, the totality of clinical trial data is utilized; both the ALTA data and the subgroup from Study 101 inform the OS and PFS INV outcomes used in the base case for brigatinib. Data from ASCEND-2 and ASCEND-5 inform the comparative efficacy estimate for ceritinib relative to brigatinib for the OS outcome. However, data are only available from ASCEND-2 for PFS INV outcomes. ToT measurement was based on assumptions derived from the ALTA and ASCEND-2 reported medians (not reported for the subgroup in Study 101 nor in ASCEND-5).

Adverse event data are sourced from ALTA only for brigatinib as no adverse events were reported for the subgroup considered from Study 101. Adverse events data were pooled across ASCEND-2 and ASCEND-5 for ceritinib.

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

B.3.6.2 Assumptions

Table 52 details the key assumptions used in the base case of the economic model and provides a justification for each one. A column is presented showing the scenario analyses associated with each assumption.

Table 52: Base case assumptions

Base case assumption	Justification	Scenario analysis
Pooled data are used for brigatinib for OS and PFS INV. Pooled meta-analyses are used for relative efficacy of ceritinib for OS.	Use totality of clinical trial data where available.	Explore the impact of using individual clinical trial data sets (ALTA, ASCEND-2 and ASCEND-5 only)
Assume a Gompertz distribution for the OS brigatinib pooled data	All curves show a similar fit to the observed data based on AIC and BIC. The gompertz curve most aligns with the long-term outcomes provided by five clinicians in semi-structured interviews and the response at the advisory board held by Takeda.	Explore the impact of the generalized gamma, gamma, log-normal, log-logistic, Weibull and exponential.
Assume investigator assessed PFS	Available from both ALTA and Study 101 for brigatinib	Explore the impact of PFS IRC which will default to ALTA data only for brigatinib
Assume a Gompertz distribution for the PFS INV	All curves show a similar fit to the observed data based on AIC and BIC. This is aligned with the distribution applied to the OS pooled data – as such, the OS and PFS INV curves follow the same shape and extrapolated curves do not cross, avoiding clinically implausible outcomes	Explore the impact of the generalized gamma, gamma, log-normal, log-logistic, Weibull and exponential.
Assume patients treated with brigatinib and ceritinib are treated 1.53 months beyond progression	Based on the difference between median ToT and median PFS observed in the ALTA clinical trial for brigatinib. In line with the methods used in the ceritinib NICE submission [TA395](86)	Explore the impact of patients treated with ceritinib 1.60 months beyond progression Explore the impact of using the extrapolated ToT outcomes for brigatinib from the ALTA clinical trial and capping the extrapolated ToT by PFS. Explore the impact of applying the hazard ratio for PFS for ceritinib relative to brigatinib to the brigatinib ToT data and capping the ToT by PFS.

Base case assumption	Justification	Scenario analysis
Relative efficacy for OS for ceritinib relative to brigatinib obtained from a meta-analysis using RE of the MAICs using the pooled brigatinib data, ASCEND-2 and ASCEND-5.	Use totality of clinical trial data where available. There are no significant differences in model fit statistics between RE and FE. RE allows for heterogeneity to be present between the studies and is more conservative.	Explore the impact of using the individual MAICs using pooled data for brigatinib or ALTA data only. Explore the differences between the naïve ITC, the MAICs adjusted for the full covariate list and the MAICs adjusted only for the covariates reported across all publications (MAIC reduced). Explore the impact of the meta-analyses using the FE method and the ALTA data only.
Relative efficacy for PFS INV for ceritinib relative to brigatinib obtained from a MAIC adjusting for the full covariate list using the pooled brigatinib data and ASCEND-2	PFS INV was not available from ASCEND-5.	Explore the impact of using relative efficacy estimates based on PFS IRC. Using this outcome, naïve ITCs, MAICs and meta-analyses of MAICs are explored (using both FE and RE). Explore the impact of using the individual MAICs using pooled data for brigatinib or ALTA data only. Explore the differences between the naïve ITC, the MAICs adjusted for the full covariate list and the MAICs adjusted only for the covariates reported across all publications (MAIC reduced).
Assume a continued treatment benefit on survival for brigatinib and ceritinib over a lifetime horizon	The long-term estimates of survival at 3-, 5-, 10- and 20-years when using the Gompertz parametric curve align with clinicians' expectations.	Explore the impact of a treatment benefit discontinuation for both brigatinib and ceritinib at 2-, 3-, 4-, 5- and 10-years.
Assume drug wastage is excluded i.e. the full cost of unused tablets can be saved	In line with NICE ceritinib submission [TA395]	Drug wastage included i.e. unused tablets are wasted
Assume no administration costs for brigatinib nor ceritinib	Brigatinib and ceritinib are both orally administered.	Assume the cost of administration of oral chemotherapy as an administration cost for brigatinib and ceritinib

Base case assumption	Justification	Scenario analysis
HRQL obtained from the mapped EQ-5D values from the ALTA clinical trial for pre-progression and adjusted for key variables, where pre-progression is defined by ORR. HRQL obtained from Chouaid et al. (2013)(87) for progressed disease.	HRQL obtained from the clinical trial in line with the NICE Methods Guide 2013. In line with the response to the ceritinib NICE submission [TA395] (86)	HRQL for pre-progression and progressed disease from the mapped EQ-5D values from ALTA. Explore the impact of using ORR or BoR defined response. Explore the impact of adjusting for differences in response rates (partial response and stable disease) pre-progression using ORR and BoR. Explore the impact of using Nafees *et al*. (2008) (81)for progressed disease. All utilities obtained from Chouaid *et al*. (2013) All utilities obtained from Nafees *et al*. (2008)
Assumed a lifetime horizon	In line with the NICE Methods Guide 2013	Explore the impact of a 5- and 10-year time horizon
Abbreviations: AIC, Akaike Information Criterion; BIC, Bayes Information Criterion; BoR, best overall response; EQ-5D, EuroQol 5-dimensions; FE, fixed effects; HRQL, health-related quality of life; INV, investigator assessed; IRC, independent review committee; MAIC, matched adjusted indirect comparison; NICE, National Institute for Health and Care Excellence; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RE, random effects; ToT, time on treatment		

B.3.7 Base-case results

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

The base case results for brigatinib compared with ceritinib are shown in Table 53. Results were subject to discounting at a rate of 3.5% per annum. Brigatinib is associated with a gain of 1.45 incremental life years and 1.02 incremental QALYs per patient, and an increase in overall costs of £62,041 per patient. Based on list prices for brigatinib and ceritinib, the ICER is £61,062 per additional QALY gained.

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

Table 53: Base case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Brigatinib	£120,364	3.36	2.31				
Ceritinib	£58,322	1.91	1.29	£62,041	1.45	1.02	£61,062
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year							

B.3.8 Sensitivity analyses

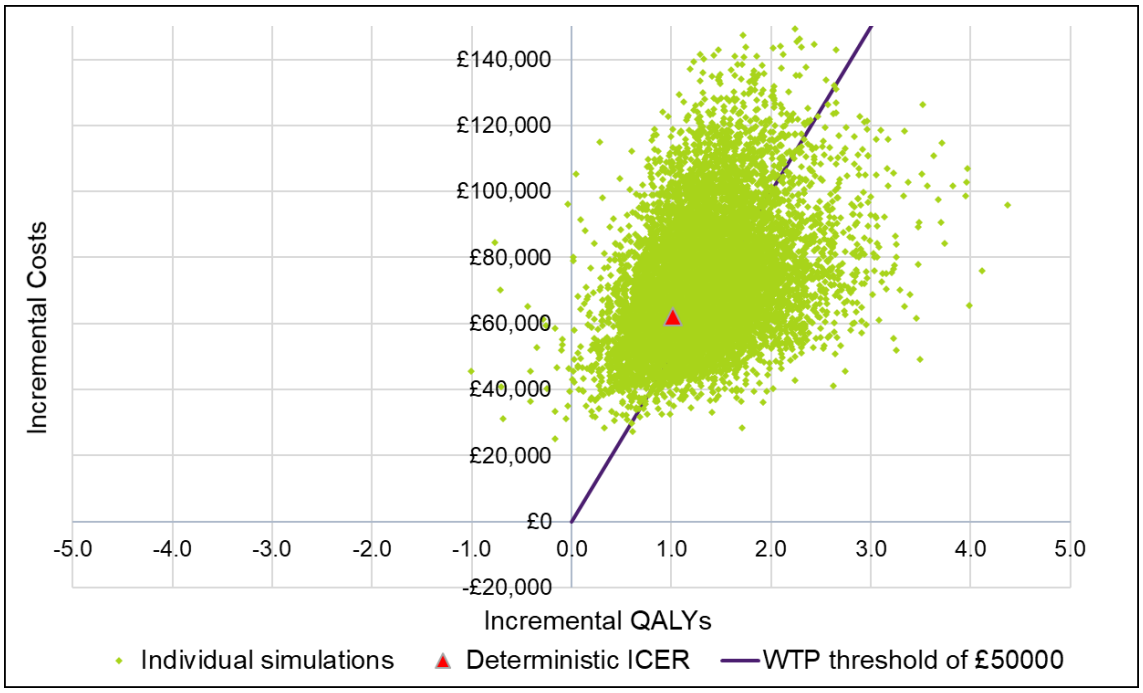
B.3.8.1 Probabilistic sensitivity analysis

To characterise uncertainty in model inputs a PSA was performed. A PSA varies all inputs simultaneously, based upon their distributional information (see Appendix L) and records a resulting ICER which may conceivable be the "true" underlying ICER. The results of 10,000 PSA iterations are presented in Figure 26 (cost-effectiveness plane) and Figure 27 (cost-effectiveness acceptability curve (CEAC)). The cost-effectiveness plane shows the incremental QALYs and costs of brigatinib relative to ceritinib and the CEAC shows the likelihood of brigatinib being cost-effective at different WTP thresholds.

The PSA included the uncertainty around the choice of parametric OS and PFS curve by selecting the choice of curve by sampling from the probability that each parametric model is the best of the fitted parametric models using the AIC estimates (see Section B.3.3.2). Different PSA runs therefore have different curve selections, dependent on the likelihood of each being the best fit to the data. This considers the uncertainty associated with parametric curve choice. Uncertainty around the parameters of the selected curves was also included, as per a standard PSA. As parametric curves are not fit to the ToT data in the base case, this is not included in the model for the ToT outcome.

Mean probabilistic incremental QALYs gained from brigatinib were 1.34 (SD: 0.51). Mean probabilistic incremental costs were £72,260 (SD: £18,568). The resulting probabilistic ICER from 10,000 iterations was £53,898.

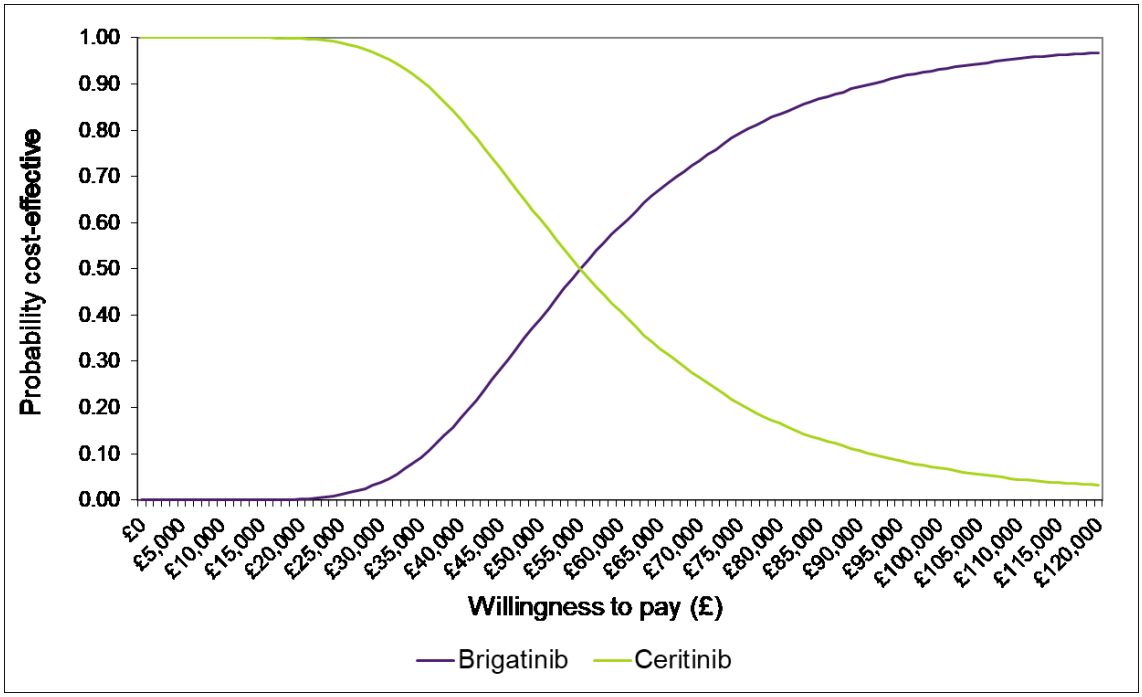
Figure 26: Cost-effectiveness plane from 10,000 iterations with uncertainty in OS and PFS curve selection accounted for



Abbreviations: ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality adjusted life year; WTP, willingness-to-pay threshold.

Based on these 10,000 PSA iterations and the list price for brigatinib and ceritinib, the CEAC (Figure 27) suggests that there is an 39.27% likelihood of brigatinib being cost-effectiveness at a WTP of £50,000 per QALY (end of life threshold advocated by NICE).

Figure 27: CEAC with uncertainty in OS and PFS selection accounted for



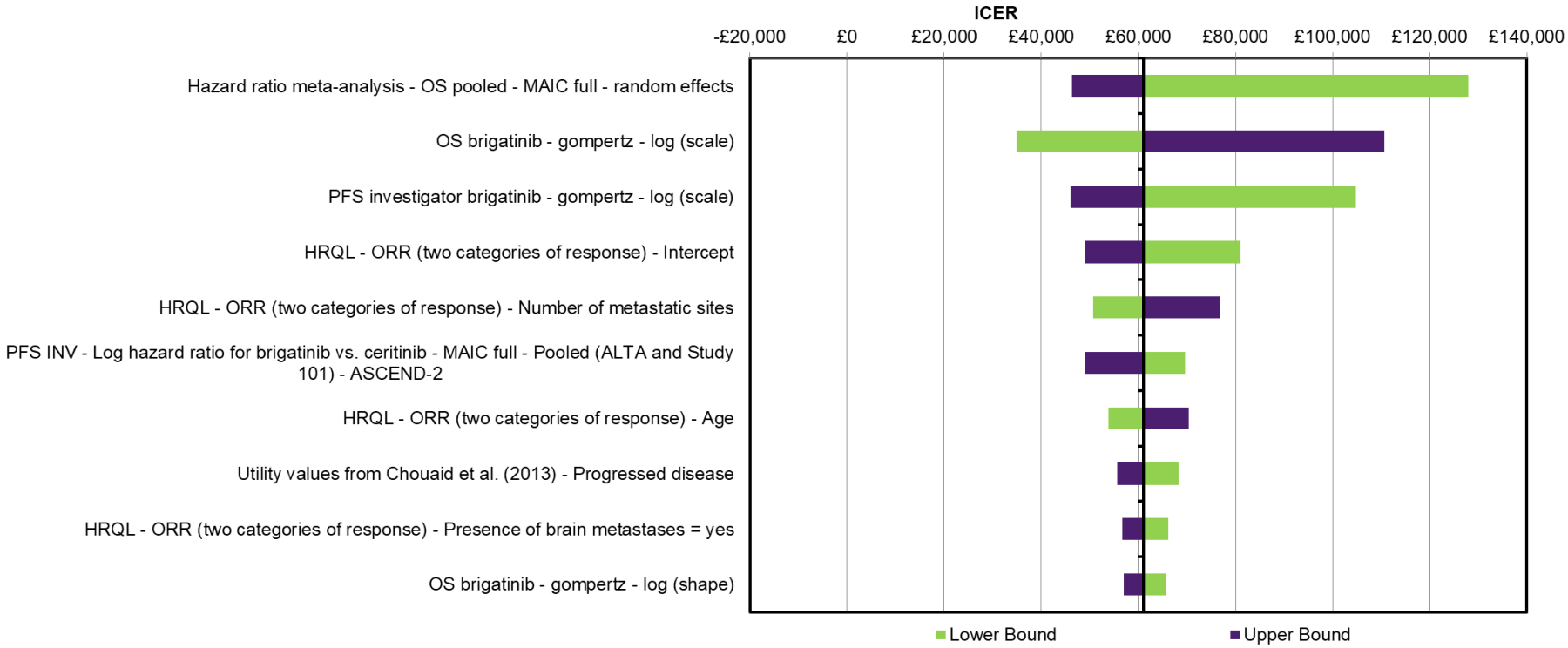
Abbreviations: CEAC, cost-effectiveness acceptability curve; OS, overall survival; PFS, progression-free survival

B.3.8.2 Deterministic sensitivity analysis

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

Figure 28 presents a tornado diagram with the ten most influential parameters shown in descending order of ICER sensitivity. Table 54 displays this information in a tabular format. The variables with the greatest impact on model outcomes were the parameters associated with brigatinib OS and PFS estimation, the hazard ratio applied for OS and PFS for ceritinib relative to brigatinib and utility values applied to the health states. The model is relatively insensitive to remaining parameters.

Figure 28: Tornado diagram



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

Table 54: Numerical results of one-way sensitivity analysis

Parameter	Lower Bound	Upper Bound	Difference
Hazard ratio meta-analysis - OS pooled - MAIC full - random effects	£127,994	£46,368	£81,626
OS brigatinib - gompertz - log (scale)	£34,851	£110,615	£75,763
PFS investigator brigatinib - gompertz - log (scale)	£104,867	£45,974	£58,894
HRQL - ORR (two categories of response) - Intercept	£81,064	£48,977	£32,087
HRQL - ORR (two categories of response) - Number of metastatic sites	£50,664	£76,831	£26,167
PFS INV - Log hazard ratio for brigatinib vs. ceritinib - MAIC full - Pooled (ALTA and Study 101) - ASCEND-2	£69,565	£48,990	£20,576
HRQL - ORR (two categories of response) - Age	£53,900	£70,419	£16,520
Utility values from Chouaid et al. (2013) - Progressed disease	£68,227	£55,574	£12,653
HRQL - ORR (two categories of response) - Presence of brain metastases = yes	£66,201	£56,663	£9,538
OS brigatinib - gompertz - log (shape)	£65,712	£57,014	£8,698

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

B.3.8.3 Scenario analysis

The scenario analyses conducted within the model are presented in Table 55. These scenarios aim to assess the impact of key assumptions on the cost-effectiveness results within the economic model.

The results from each of these scenarios are given in Table 56.

Table 55: Scenario analyses

Assumption in the base case	Scenario analysis
Brigatinib outcomes	
Gompertz curve fit to pooled (ALTA and Study 101) brigatinib OS data	Parametric curves based on generalised gamma, gamma, log-normal, log-logistic, Weibull and exponential.
Gompertz curve fit to pooled (ALTA and Study 101) brigatinib PFS INV data	Parametric curves based on generalised gamma, gamma, log-normal, log-logistic, Weibull and exponential.
Pooled data (ALTA and Study 101) informing OS and PFS outcomes	OS and PFS parametric curves based on data from ALTA only considering the gompertz, generalised gamma, gamma, log-normal, log-logistic, Weibull and exponential.
PFS INV obtained from the pooled (ALTA and Study 101) data	PFS based on IRC assessment (ALTA only) considering the Gompertz, generalised gamma, gamma, log-normal, log-logistic, Weibull and exponential. These scenarios assume OS data from ALTA only for consistency.
Patients are treated 1.53 months beyond progression in the brigatinib and ceritinib arm	Patients treated with brigatinib 1.53 months beyond progression and patients treated with ceritinib 1.6 months beyond progression ToT based on parametric curves fit to ToT data from ALTA for brigatinib and PFS hazard ratio applied to brigatinib data to obtain ceritinib estimates (uncapped and capped by PFS) ToT based on parametric curves fit to ToT data from ALTA for brigatinib and ceritinib ToT equal to brigatinib (capped by PFS)
Relative efficacy	
Hazard ratio for OS for ceritinib relative to brigatinib obtained from a meta-analysis using RE of MAICs adjusting for the full list of covariates and combining data from ALTA, Study 101, ASCEND-2 and ASCEND-5	Scenarios using hazard ratios from naïve ITCs, MAICs adjusting for a reduced covariate list, MAICs adjusting for a full covariate list and meta-analyses of MAICs. Each scenario considers ALTA data only and pooled (ALTA and Study 101) data. Each meta-analysis considers both FE an RE. In total there are 24 scenarios for OS hazard ratios within the model.
Hazard ratio for PFS for ceritinib relative to brigatinib obtained from a MAIC adjusting for the full list of covariates and combining data from ALTA, Study 101 and ASCEND-2.	Scenarios using hazard ratios from naïve ITCs, MAICs adjusting for a reduced covariate list, MAICs adjusting for a full covariate list and meta-analyses of MAICs. Each scenario considers ALTA data only and pooled (ALTA and Study 101) data. Each meta-analysis considers both FE an RE. In total there are 15 scenarios for PFS hazard ratios within the model.
Long-term treatment effect	
Treatment benefit associated with brigatinib and ceritinib is maintained over the model time horizon	Treatment benefit associated with brigatinib and ceritinib is discontinued at 2-, 3-, 4-, 5- and 10-years, where the hazard of progression and death equals those observed

Assumption in the base case	Scenario analysis
	with BSC. These scenarios are conducted when a Gompertz, Weibull and exponential distribution are assumed for the parametric fit to the OS data.
Cost inputs	
To account for end-of-life costs a lump sum of £1,705.53 is applied over 8-weeks	A lump sum of £852.76 is applied over 4-weeks
Drug wastage is excluded i.e. the NHS saves all costs associated with reduced dose intensity	Drug wastage is included i.e. the costs associated with reduced dose intensity are not recovered
Administration costs associated with oral therapies are excluded	Administration costs are included
Adverse events rates not reported in the published literature for ceritinib are assumed equal to brigatinib	Unreported adverse event rates are assumed as zero
HRQL inputs	
Utility data associated with pre-progression are obtained from a regression analysis fit to the ALTA patient level data, using ORR based on two categories of response (pre- and post-progression). The utility decrement associated with progressed disease is obtained from Chouaid et al. (2013)	Utility data associated with pre-progression are obtained from a regression analysis fit to the ALTA patient level data, using (1) ORR based on four categories of response (complete response, partial response, stable disease and progressed disease), (2) BoR based on two categories of response and (3) BoR based on four categories of response. The utility decrement associated with progressed disease is obtained from Nafees *et al.* (2008)(81) The utility decrement associated with progressed disease is obtained from the ALTA patient level data. All utilities from Chouaid *et al.* (2013)(82) All utilities from Nafees et *al.* (2008)(81)
Controls	
Cost-effectiveness results over a lifetime (12.65 years) horizon	5- and 10-year time horizon

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

Table 56: Scenario analyses results

Scenario	Incremental costs	Incremental QALYs	ICER	Difference from base case ICER
Brigatinib outcomes				
Brigatinib OS data – pooled data for OS and PFS				
Generalised gamma	£64,226	1.2317	£52,143	-14.61%
Gamma	£64,005	1.2112	£52,846	-13.45%
Log-normal	£71,943	1.9548	£36,804	-39.73%
Log-logistic	£69,325	1.7202	£40,300	-34.00%
Weibull	£63,706	1.1828	£53,859	-11.80%
Gompertz (base case)	£62,041	1.0160	£61,062	0.00%
Exponential	£64,865	1.2923	£50,194	-17.80%
Brigatinib OS data – ALTA data for OS and PFS				
Generalised gamma	£62,392	1.4410	£43,298	-29.09%
Gamma	£60,459	1.2535	£48,234	-21.01%
Log-normal	£68,519	2.0059	£34,158	-44.06%
Log-logistic	£65,741	1.7576	£37,404	-38.75%
Weibull	£60,343	1.2421	£48,580	-20.44%
Gompertz	£63,228	1.5218	£41,548	-31.96%
Exponential	£61,129	1.3175	£46,396	-24.02%
Brigatinib PFS INV data – pooled data for OS and PFS				
Generalised gamma	£68,542	1.0315	£66,450	8.82%
Gamma	£67,366	1.0287	£65,489	7.25%
Log-normal	£101,304	1.1094	£91,313	49.54%
Log-logistic	£93,100	1.0898	£85,429	39.90%
Weibull	£65,260	1.0236	£63,756	4.41%
Gompertz (base case)	£62,041	1.0160	£61,062	0.00%

Scenario	Incremental costs	Incremental QALYs	ICER	Difference from base case ICER
Exponential	£76,109	1.0501	£72,480	18.70%
Brigatinib PFS INV data – ALTA data for OS and PFS				
Generalised gamma	£69,664	1.5371	£45,321	-25.78%
Gamma	£69,411	1.5365	£45,174	-26.02%
Log-normal	£110,519	1.6352	£67,588	10.69%
Log-logistic	£100,437	1.6109	£62,349	2.11%
Weibull	£66,920	1.5305	£43,724	-28.39%
Gompertz	£63,228	1.5218	£41,548	-31.96%
Exponential	£79,933	1.5624	£51,160	-16.22%
Brigatinib PFS IRC data – ALTA data for OS and PFS				
Generalised gamma	£76,038	1.5516	£49,006	-19.74%
Gamma	£74,926	1.5489	£48,373	-20.78%
Log-normal	£126,471	1.6721	£75,637	23.87%
Log-logistic	£111,599	1.6367	£68,187	11.67%
Weibull	£71,932	1.5417	£46,657	-23.59%
Gompertz	£66,541	1.5288	£43,524	-28.72%
Exponential	£87,508	1.5795	£55,402	-9.27%
ToT scenarios				
Patients treated with brigatinib 1.53 months beyond progression and patients treated with ceritinib treated 1.6 months beyond progression	£61,748	1.0161	£60,770	-0.48%
Brigatinib extrapolated ToT curves (uncapped) and PFS hazard ratio applied to brigatinib ToT data for ceritinib	£96,380	1.0111	£95,317	56.10%
Brigatinib extrapolated ToT curves (capped for PFS) and PFS hazard ratio applied to brigatinib ToT data for ceritinib	£63,143	1.0155	£62,179	1.83%
Brigatinib extrapolated ToT curves (uncapped) and ceritinib ToT equal to brigatinib's ToT (uncapped)	£36,608	1.0216	£35,836	-41.31%

Scenario	Incremental costs	Incremental QALYs	ICER	Difference from base case ICER
Brigatinib extrapolated ToT curves (capped for PFS) and ceritinib ToT equal to brigatinib's ToT (capped for PFS)	£59,229	1.0162	£58,286	-4.55%
Relative efficacy				
OS				
Naïve ITC - ALTA - ASCEND-2	£62,270	1.0380	£59,988	-1.76%
MAIC full - ALTA - ASCEND-2	£63,399	1.1468	£55,285	-9.46%
MAIC reduced - ALTA - ASCEND-2	£63,432	1.1500	£55,159	-9.67%
Naïve ITC - Pooled (ALTA and Study 101) - ASCEND-2	£62,381	1.0487	£59,482	-2.59%
MAIC full - Pooled (ALTA and Study 101) - ASCEND-2	£62,895	1.0982	£57,271	-6.21%
MAIC reduced - Pooled (ALTA and Study 101) - ASCEND-2	£62,895	1.0982	£57,271	-6.21%
Naïve ITC - ALTA - ASCEND-5	£62,044	1.0163	£61,051	-0.02%
MAIC full - ALTA - ASCEND-5	£64,640	1.2664	£51,044	-16.41%
MAIC reduced - ALTA - ASCEND-5	£63,832	1.1885	£53,709	-12.04%
Naïve ITC - Pooled (ALTA and Study 101) - ASCEND-5	£61,964	1.0086	£61,435	0.61%
MAIC full - Pooled (ALTA and Study 101) - ASCEND-5	£61,293	0.9440	£64,929	6.33%
MAIC reduced - Pooled (ALTA and Study 101) - ASCEND-5	£61,293	0.9440	£64,929	6.33%
Meta-analysis ALTA - MAIC full - fixed effects	£63,909	1.1959	£53,439	-12.48%
Meta-analysis ALTA - MAIC full - random effects	£63,867	1.1919	£53,584	-12.25%
Meta-analysis ALTA - Naïve ITC - fixed effects	£62,185	1.0299	£60,382	-1.11%
Meta-analysis ALTA - Naïve ITC - random effects	£62,176	1.0289	£60,426	-1.04%
Meta-analysis ALTA - MAIC reduced - fixed effects	£63,664	1.1723	£54,306	-11.06%
Meta-analysis ALTA - MAIC reduced - random effects	£63,619	1.1679	£54,471	-10.79%
Meta-analysis pooled data - MAIC full - fixed effects	£62,080	1.0198	£60,877	-0.30%
Meta-analysis pooled data - MAIC full - random effects (base case)	£62,041	1.0160	£61,062	0.00%
Meta-analysis pooled data - Naïve ITC - fixed effects	£62,199	1.0312	£60,316	-1.22%
Meta-analysis pooled data - Naïve ITC - random effects	£62,183	1.0296	£60,393	-1.10%

Scenario	Incremental costs	Incremental QALYs	ICER	Difference from base case ICER
Meta-analysis pooled data - MAIC reduced - fixed effects	£62,080	1.0198	£60,877	-0.30%
Meta-analysis pooled data - MAIC reduced - random effects	£62,041	1.0160	£61,062	0.00%
PFS				
Naïve ITC - ALTA - ASCEND-2	£61,805	1.0154	£60,868	-0.32%
MAIC full - ALTA - ASCEND-2	£63,479	1.0199	£62,239	1.93%
MAIC reduced - ALTA - ASCEND-2	£63,507	1.0200	£62,262	1.96%
Naïve ITC - Pooled (ALTA and Study 101) - ASCEND-2	£61,721	1.0152	£60,799	-0.43%
MAIC full - Pooled (ALTA and Study 101) - ASCEND-2 (base case)	£62,041	1.0160	£61,062	0.00%
MAIC reduced - Pooled (ALTA and Study 101) - ASCEND-2	£62,041	1.0160	£61,062	0.00%
Naïve ITC - ALTA - ASCEND-5	£70,498	1.0389	£67,858	11.13%
MAIC full - ALTA - ASCEND-5	£77,378	1.0575	£73,170	19.83%
MAIC reduced - ALTA - ASCEND-5	£75,386	1.0521	£71,651	17.34%
Meta-analysis ALTA - MAIC full - fixed effects	£68,732	1.0341	£66,464	8.85%
Meta-analysis ALTA - MAIC full - random effects	£69,485	1.0362	£67,060	9.82%
Meta-analysis ALTA - Naïve ITC - fixed effects	£66,201	1.0273	£64,442	5.54%
Meta-analysis ALTA - Naïve ITC - random effects	£66,239	1.0274	£64,473	5.59%
Meta-analysis ALTA - MAIC reduced - fixed effects	£69,447	1.0361	£67,029	9.77%
Meta-analysis ALTA - MAIC reduced - random effects	£69,524	1.0363	£67,090	9.87%
Long-term treatment effect				
OS – gompertz distribution				
Treatment benefit discontinues at 2-years	£39,567	0.3420	£115,700	89.48%
Treatment benefit discontinues at 3-years	£51,297	0.5172	£99,184	62.43%
Treatment benefit discontinues at 4-years	£56,892	0.6613	£86,031	40.89%
Treatment benefit discontinues at 5-years	£59,322	0.7732	£76,720	25.64%
Treatment benefit discontinues at 10-years	£61,909	0.9988	£61,981	1.50%
OS – Weibull distribution				

Scenario	Incremental costs	Incremental QALYs	ICER	Difference from base case ICER
Treatment benefit discontinues at 2-years	£39,667	0.3425	£115,805	89.65%
Treatment benefit discontinues at 3-years	£51,352	0.5177	£99,184	62.43%
Treatment benefit discontinues at 4-years	£56,933	0.6636	£85,794	40.50%
Treatment benefit discontinues at 5-years	£59,419	0.7818	£76,002	24.47%
Treatment benefit discontinues at 10-years	£62,847	1.0887	£57,725	-5.47%
OS – exponential distribution				
Treatment benefit discontinues at 2-years	£39,490	0.3422	£115,389	88.97%
Treatment benefit discontinues at 3-years	£51,259	0.5170	£99,150	62.38%
Treatment benefit discontinues at 4-years	£56,932	0.6658	£85,506	40.03%
Treatment benefit discontinues at 5-years	£59,503	0.7898	£75,340	23.38%
Treatment benefit discontinues at 10-years	£63,452	1.1445	£55,439	-9.21%
Cost inputs				
End-of-life cost applied as a lump sum over 4-weeks	£62,090	1.0160	£61,109	0.08%
Include drug wastage	£65,444	1.0160	£64,411	5.48%
Include administration costs for oral therapies	£69,168	1.0160	£68,076	11.49%
Assume relative risks of unreported adverse events equal to zero for ceritinib	£63,610	1.0117	£62,877	2.97%
HRQL inputs				
ALTA data, ORR four categories and Chouaid et al. (2013) for progressed disease	£62,041	1.0168	£61,018	-0.07%
ALTA data, BoR two categories and Chouaid et al. (2013) for progressed disease	£62,041	1.0129	£61,249	0.31%
ALTA data, BoR four categories and Chouaid et al. (2013) for progressed disease	£62,041	1.0142	£61,171	0.18%
ALTA data, ORR two categories and Nafees et al. (2008) for progressed disease	£62,041	0.9968	£62,239	1.93%
ALTA data, ORR two categories and progressed disease	£62,041	1.0915	£56,842	-6.91%
Utilities from Chouaid et al. (2013)	£62,041	0.9778	£63,447	3.91%
Utilities from Nafees et al. (2008)	£62,041	0.8453	£73,399	20.20%
Controls				
5-year time horizon	£56,537	0.7166	£78,895	29.21%

Scenario	Incremental costs	Incremental QALYs	ICER	Difference from base case ICER
10-year time horizon	£61,599	0.9920	£62,095	1.69%

Abbreviations: BoR, best overall response; FE, fixed effects; HRQL, health-related quality of life; ICER, incremental cost-effectiveness ratio; IRC, independent review committee; MAIC, matched 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

The scenario analyses indicated that the ICER is relatively insensitive to the choice of brigatinib OS data and parametric curve fit, with ICERs varying from £34,158 to £61,062. The choice of PFS INV data and parametric curve fit was shown to estimate ICERs ranging from £41,548 to £72,480, excluding the log-normal and log-logistic distributions which give clinically implausible results. Use of PFS IRC data was shown to reduce the ICER for all parametric curve choices except from the log-normal and log-logistic distributions.

The scenarios conducted exploring ToT indicate the uncertainty associated with the duration of ceritinib treatment. Although these scenarios show a range of possibilities, the base case is supported clinically (patients treated on average 1.53 months beyond progression) as agreed by six UK clinicians at the advisory board conducted by Takeda (see Section B.3.10). Therefore, we believe that the base case adequately reflects current UK clinical practice.

The scenarios exploring relative efficacy estimates for OS and PFS outcomes indicate that the base case ICER is relatively robust; ICERs were shown to range from £57,271 to £64,929 when using all the data available for brigatinib (ALTA and Study 101).

The base case assumes that the treatment benefit associated with brigatinib and ceritinib is maintained over the model time horizon (12.65 years). Clinical expert feedback suggests that the most clinically plausible long-term outcomes align with the predictions from the gompertz curve at 3-, 5- 10- and 20-years, without any adjustment for treatment effect discontinuation (see Section B.3.3.5). The NICE guidance states that “the impact of the uncertainty on estimates of cost effectiveness should be explored in separate analyses of a representative range of plausible scenarios. Examples of when this type of scenario analysis should be conducted are: when there is uncertainty about the most appropriate assumption to use for extrapolation of costs and outcomes beyond trial follow-up” (see Section 5.8, page 35, Guide to the methods of technology appraisal 2013).(88) Therefore, to explore the impact of the uncertainty associated with the long-term treatment benefits scenario analyses curtailed the treatment benefit of brigatinib and ceritinib at 2-, 3-, 4-, 5- and 10-years. Theses cut-off points are arbitrary. As expected, the earlier the treatment benefit was curtailed the higher the ICER.

The ICER was shown to be relatively insensitive to cost scenarios associated with end-of-life, adverse events and drug wastage. However, the ICER increased by 11.49% with the inclusion of chemotherapy administration costs. As both brigatinib and ceritinib are oral therapies no administration costs are included in the base case. However, both treatments are or would be available only through cancer centres, and so pharmacy costs for a specialist cancer centre may be accrued. As this cost is unknown, the cost of chemotherapy administration is assumed in the scenario analysis. It is likely that this cost is higher than what would be anticipated in UK practice.(86)

The ICER was shown to be relatively insensitive to HRQL scenarios. Reducing the time horizon increased the ICER; a time horizon of 5-years and 10-years is associated with an ICER of £78,895 and £62,095, respectively. However, this is unlikely to capture all the

relevant outcomes associated with brigatinib, which provides important long-term survival benefits.

Summary of sensitivity analyses results

Model results were reasonably robust to sensitivity analysis with the key areas of uncertainty surrounding:

- Parameters associated with brigatinib OS estimation, the magnitude of survival benefit for ceritinib relative to brigatinib and the duration of the long-term survival benefit associated with both brigatinib and ceritinib.
- Parameters associated with brigatinib PFS estimation, the source and magnitude of PFS benefit for ceritinib relative to brigatinib.
- Cost inputs associated with administration of oral therapies from specialist cancer centres.

Probabilistic analysis which included the uncertainty around curve fit choice indicated that there is a 39.27% likelihood of brigatinib being cost-effective at a WTP of £50,000 per QALY.

B.3.9 Subgroup analysis

No subgroup analyses were specified within the NICE decision problem and therefore no subgroup analysis has been provided.

B.3.10 Validation

B.3.10.1 Validation of cost-effectiveness analysis

B.3.10.1.1 Internal validation

The model was quality-assured by the internal processes of the external economists who developed the economic model. In these processes, an economist not involved in model building reviewed the model for coding errors, inconsistencies and the plausibility of inputs. The model was also put through a checklist of known modelling errors and questioning of the assumptions based upon the Phillips checklist. (89)

B.3.10.1.2 External validation

External validation included:

- Clinical outcomes were compared with those from the relevant clinical trials: ALTA, Study 101, ASCEND-2 and ASCEND-5 (Section B.3.3.5)
- Semi-structured interviews with five UK clinical experts
- Advisory board conducted with six UK clinical experts
- Efficacy outcomes were compared with other cost-effectiveness studies identified as part of the economic SLR

Semi-structured interviews were conducted with five UK clinical experts experienced in treating ALK+ advanced NSCLC and were actively treating such patients at the time the interviews were conducted (Table 57). Interviews were guided by a questionnaire sent to clinicians prior to the telephone interview. The questionnaire was intended to collect resource use inputs for the economic model, identify the key prognostic factors and treatment effect modifiers for use in the ITCs and to provide estimates of survival for patients with ALK+ advanced NSCLC treated with an ALK inhibitor at 3-, 5-, 10- and 20-years based on their experience.

Table 57: Characteristics of clinical expert respondents

Clinician	Job title	Location	Hospital
1	Consultant Medical Oncologist	Leicester, England	NHS University Hospital & Private
2	Consultant Medical Oncologist / Lecturer in Medical Oncology	Newcastle, England	NHS Foundation Trust
3	Consultant Clinical Oncologist	London, England	NHS Trust & Private
4	Consultant Clinical Oncologist	Cambridge, England	NHS Trust
5	Consultant Medical Oncologist / Clinical Senior Lecturer	London, England	NHS University College Hospital & Private
6	Oncologist	Oslo, Norway	University Hospital
Abbreviations: NHS, National Health Service			

The interviews with clinical experts took place between December 2017 and January 2018. Appendix I details the responses associated with resource use. Section B.2.9 and Section B.3.3.5 describe the responses associated with prognostic factors/treatment effect modifiers and estimates of survival, respectively. These responses directly informed the resource use estimates for pre-progression and progressed disease health states, the prognostic factors and treatment effect modifiers adjusted for within the ITCs and the choice of parametric curve applied in the base case.

An advisory board was conducted by Takeda on the 29th January 2018 with six clinical experts and four health economic experts present. The purpose of the advisory board was to validate the inputs and assumptions used in the economic model, ahead of the submission to NICE. The clinical experts were practicing oncologists in the UK from the University of Leicester, Aberdeen Royal Infirmary, St. Bartholomew's hospital, The Christie, Guy's and St. Thomas and the Ipswich Hospital NHS trust. Based on their experience in UK clinical practice, clinicians were asked to provide their opinion on the following questions:

- Which data best reflected the UK population for brigatinib (ALTA, Study 101, or pooled) and ceritinib (ASCEND-2, ASCEND-5, or pooled)?

- Which method of extrapolation provided the most clinically plausible and economically robust outcomes for OS, PFS and ToT for brigatinib?
- How clinically plausible is the assumption of a lifetime treatment benefit? Which scenarios should explore the uncertainty associated with this assumption?
- Which methods of ITCs provide the most clinically plausible output when applied to the extrapolated outcomes?
- Which method of HRQL best captures the nature of the ALK+ advanced NSCLC disease?
- Validation of assumptions on adverse events and resource use.

It was considered that, where available, all data should be used for both brigatinib and ceritinib. The subgroup from Study 101 falls within scope and hence the pooled brigatinib data set (pooled with ALTA) should be used in the base case.

The Kaplan-Meier curves, the fitted parametric curves and the AIC and BIC goodness of fit statistics for brigatinib were presented at the advisory board for OS, PFS and ToT outcomes. Furthermore, the estimates of survival at 3-, 5-, 10- and 20-years obtained through the semi-structured interviews were presented. It was commented that the OS data were immature and so the long-term averaged estimates from the interviews are important in informing the base case parametric model. Clinicians agreed that median OS for patients treated with brigatinib across all available treatment sequences was 2.5-3.0 years and that no patients would be expected to survive to 20-years. Based on all available information, it was considered that the exponential, Weibull and gompertz fit to the pooled data provide internally and externally valid parametric curve choices for OS. Experts considered that the exponential, Weibull and gamma provide the best fit to the PFS data. However, it was commented that the AIC and BIC statistics appeared similar across all parametric distributions. In light of this, it was considered that the gompertz distribution could be applied to the PFS data in the base case to align with the OS curve choice, with scenario analyses exploring additional curve options.

The panel were tasked with assessing whether treatment discontinuation scenarios curtailing the impact of treatment on PFS and OS outcomes at 2-, 3-, 4-, 5- and 10-years were plausible. It was commented that the cut-off points presented and those used in previous UK HTA submissions were not informed by any data and were instead scenarios for exploring uncertainty. Furthermore, the estimated long-term survival expectations averaged across responses to the questionnaire aligned with the estimates predicted by the gompertz distribution without any adjustment. Therefore, it was considered that the base case should not apply treatment discontinuation cut-offs. However, these should be explored in scenarios across a range of cut-off points and for both brigatinib and ceritinib.

In line with the ceritinib NICE and SMC submissions it was concluded that ToT should be modelled as the difference between median PFS and median ToT as the observed differences are clinically justifiable; 1.53 months using the brigatinib ALTA data. Clinical justification was that brigatinib and ceritinib are both treat to progression therapies, where progression is initially picked up on a scan and then patients would be re-scanned 6-weeks later for confirmation of progressive disease leading to treatment discontinuation or change. This aligns with the observed difference in median outcomes.

The list of ITCs for inclusion in the model was presented to the panel. For OS, it was confirmed that the meta-analysis using all available data should inform the base case, with the naïve indirect comparison and individual MAICs comprising scenario analyses. For PFS INV, it was confirmed that the MAIC using all available brigatinib data (pooled across ALTA and Study 101) should be used in the base case with the data for ceritinib from ASCEND-2; it was recognised that PFS INV was not reported in ASCEND-5, as such only one data source was available for this outcome for ceritinib. Additionally, the list of prognostic factors and treatment effect modifiers impacting survival as identified through the clinician questionnaire was presented to the panel. The nine selected variables were considered appropriate and relevant.

The four utility analyses using the ALTA HRQL data were presented to the experts at the advisory board; (1) response (defined by responding, stable and progressed disease) and ORR, (2) response (defined by pre-progression and progressed disease) and ORR, (3) response (defined by responding, stable and progressed disease) and BoR and (4) response (defined by pre-progression and progressed disease) and BoR. All response data were defined based on RECIST v1.1. These analyses are explained in more detail in Section B.3.4.1.

Experts commented that the utility analysis should reflect the model structure; the model is driven by two living health states (pre-progression and progressed disease). Therefore, analyses should consider utility as a function of pre-progression and progressed disease in the base case. Furthermore, based on case precedence for ceritinib, the ORR outcomes should be considered in the base case. The number of observations contributing to progressed disease estimates were presented to the experts. Based on the lack of data and case precedence with ceritinib, it was agreed that the literature should inform the progressed disease estimate in the base case – with scenarios considering the impact of using the ALTA utility analyses.

Clinicians considered that all adverse events (grades 1-4) should be considered within the economic modelling as patients with ALK+ advanced NSCLC are treated for a long time which increases the impact of adverse events on HRQL and cost outcomes. Furthermore, adverse events occurring in <5% of patients may be important drivers of HRQL and cost outcomes and so should be considered in the modelling. In the base case, the economic model considers all grade 3/4 adverse events; grade 1/2 adverse events were not included due to the number of categories which may over complicate the model. Furthermore, as ceritinib is the comparator to brigatinib, this submission aims to align with the case precedence observed in the ceritinib NICE submission where all grade 3/4 adverse events were included. The proportion of patients experiencing a dose reduction or dose interruption due to adverse events was higher in the ceritinib studies compared with the ALTA trial (

Table 28). Therefore, exclusion of grade 1/2 adverse events is a conservative assumption as it is likely that ceritinib causes more of these events; this was supported by clinical opinion at the advisory board. It was further commented that, often, clinicians preferred not to treat patients with ceritinib due to the adverse event profile.

The averaged estimates from the semi-structured interviews for pre-progression and progressed disease resource use were presented to the panel. Additional resource use requirements identified at the advisory board were: a pharmacist required at each visit to the oncologist, 25% of patients in progressed disease would receive radiotherapy and denosumab would be used for a proportion of patients instead of bisphosphonate. These responses are captured in Appendix I. The clinicians agreed with all other resource use estimates collected via the interviews.

Estimated life years and QALYs associated with ceritinib were validated against published estimates in patients with ALK+ advanced NSCLC post-crizotinib (Table 58). No studies were identified in the economic SLR presenting economic outcomes associated with brigatinib. Therefore, the modelled outcomes cannot be compared with the literature.

The efficacy outcomes for ceritinib reported in this submission are generally higher than other cost-effectiveness models. This submission makes use of both the ASCEND-2 and ASCEND-5 data for ceritinib for OS (PFS INV outcomes unavailable from ASCEND-5), whereas the NICE submission for ceritinib only considers ASCEND-2. The median OS from ASCEND-5 is 18.1 months vs. 14.9 months from ASCEND-2. Therefore, pooling data across these sources we would expect to see life years and QALYs increase.

Table 58: Comparison of life years and QALYs in patients treated with ceritinib across papers identified in the economic SLR

Study	Year	Life years	QALYs
This submission		1.91	1.29
Carlson *et al.* (58, 60)	2017, 2016	1.67	0.98
Hurry *et al.* (61)	2016	1.61	0.86
National Institute for Health and Care Excellence (NICE) TA395 (ceritinib) (86)	2016	1.77	1.08
Balu *et al*. (65)	2015	NR	2.49
Zhou et al. (66)	(2015a)	1.77	0.94
Zhou et al. (67)	(2015b)	1.61	0.86
Abbreviations: QALY, quality adjusted life year; SLR, systematic literature review			

B.3.11 Interpretation and conclusions of economic evidence

We have developed a health economic model to assess the cost-effectiveness of brigatinib reflecting previous models and HTAs for ALK+ NSCLC medicines. To date, no published data exist on the incremental cost-effectiveness of brigatinib. Therefore, it is not possible to validate or compare these results with previous analyses. The modelled population from ALTA and the subgroup from Study 101 match the anticipated indication for which brigatinib will be available: the treatment of adults with ALK+ advanced NSCLC previously treated with crizotinib. In line with the NICE scope, ceritinib is the only comparator to brigatinib for this indication.(86) The main strengths of this evaluation are as follows:

- Data for both brigatinib and ceritinib were derived from large clinical trials specifically designed for ALK+ advanced NSCLC.
- Parametric survival curves that were used to extrapolate efficacy data were selected based on a comprehensive assessment of goodness of fit, internal and external validations (see Section B.3.3.5). Scenario analyses explore the impact of other data sources and parametric curve choices.
- The uncertainty associated with relative efficacy inputs for ceritinib relative to brigatinib is explored in scenario analyses which demonstrate the limited variability in results.
- Brigatinib short-medium term clinical results predicted by the model are comparable to those observed in the ALTA and Study 101 clinical trials. The long-term outcomes predicted by the model for brigatinib align with expectations across six UK clinicians (see Section B.3.3.5). This gives reassurance that the predicted benefits of brigatinib are being accurately modelled.
- The utility data for the progression-free health state was derived from the ALTA trial using a published, validated mapping algorithm (Section B.3.4). The HRQL data

showed that patient's HRQL was clearly maintained above baseline over the treatment period with brigatinib

- Extensive sensitivity and scenario analyses explore the assumptions and uncertainty associated with different data sources and different methods. The analyses conducted clearly show that there is a great stability around the ICERs generated by the cost-effectiveness analyses, which gives confidence in determining the most-plausible ICER for decision making purposes (see Section B.3.7)

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

First, the analysis is based on the data cut with a median follow up of 18.6 months (Feb 2017 extraction); data with 24.3 months of follow-up is now available (Sept 2017 extraction). Unfortunately, these data became available with insufficient time to update this submission and ensure a high-quality statistical analysis. The data from the September 2017 data cut is presented in the clinical sections and is compared with model predictions in Section B.3.3.5 and B.3.10. And will be available for the time of the ERG clarification questions.

Second, the lack of an active comparator RCT or efficacy data on comparators from a head-to-head study with brigatinib. However, the uncertainty associated with relative efficacy estimates derived across single arm trials is explored through different statistical ITCs applied to the data and scenarios considering the impact of these different methods on results; results were shown to be relatively stable to variations in ITC increasing confidence in the plausibility of the ICER.

Third, there is a lack of long-term efficacy data such that validation of long-term model predictions has been based on UK clinician's expectations rather than observed data. These long-term predictions are unknown and, as such, scenario analyses explore curtailing the treatment benefit associated with brigatinib and ceritinib at 2-, 3-, 4-, 5- and 10-years.

Fourth, the HRQL captured within the ALTA clinical trial was measured using the EORTC-QLQ-C30 which was then mapped to the EQ-5D to elicit utility values for use in this submission. This tool did not prove to be sensitive to analyses and did not reflect the positive improvements seen by patients in terms of reduced tumour burden and intracranial responses.

Lastly, the lack of trial-based utility values for the progressed disease health state results in non-robust utility decrements associated with progressed disease when using the ALTA clinical trial data. Therefore, the base case analysis assumes generalisability of published data to the clinical trial data used. However, this is not uncommon in NICE appraisals of treatments in oncology.

Conclusion

There are limited treatment options available to patients with ALK+ advanced NSCLC who progress on or are intolerant to crizotinib. In England and Wales, only ceritinib is available at this stage in the pathway. There remains unmet need to improve PFS in patients who

progress on crizotinib when the current approved target therapy (ceritinib) only offers a range of median PFS between 5.4 and 7.2 months.

Furthermore, UK clinicians present at an advisory board held by Takeda advised that ceritinib is associated with considerable toxicities in practice. These are not reflected by the clinical trial data nor the economic model. Brigatinib addresses these unmet needs by offering patients an extended PFS of over 1-year, potent intracranial responses and through a good safety profile both in the clinical trials and supported by UK clinicians. Brigatinib has also been shown to offer an extended OS with a median survival of 34.1 months from the September 2017 ALTA data cut.

Brigatinib is an innovative targeted therapy and has been shown to confer benefits in patients who have brain metastasis (most patients will have brain metastases in this setting). Patients treated with brigatinib only require one tablet daily offering a reduced tablet burden compared with ceritinib. Brigatinib has shown that it can also prolong survival without a detrimental impact on HRQL; the adverse events associated with brigatinib are manageable and do not lead to a deterioration in HRQL in most patients.

Brigatinib also fulfils the end-of-life criteria advocated by NICE (see Section B.2.13.3).

A positive recommendation for brigatinib will provide patients and clinicians with an additional treatment option in a setting with limited choice and high unmet need**.**

B.4 References

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B.5 Appendices

Appendix C: Summary of product characteristics (draft)

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality-of-life studies

Appendix I: Cost and healthcare resource identification, measurement and valuation

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Checklist of confidential information

Appendix L: Additional appendices

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Single technology appraisal

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

Dear [redacted],

The Evidence Review Group, Peninsula Technology Assessment Group (PenTAG), and the technical team at NICE have looked at the submission received on 6 April 2018 from Takeda. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

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

Please provide your written response to the clarification questions by **5pm** on **Monday 14 May 2018**. Your response and any supporting documents should be uploaded to NICE Docs.

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

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

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

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

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

Yours sincerely

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Encl. checklist for confidential information

Section A: Clarification on effectiveness data

A1. Section B.2.9.2 (page 52) states that "For time-to-event outcomes, IPD [individual patient data] of OS [overall survival] and PFS [progression-free survival] from both ASCEND-2 and ASCEND-5 (ceritinib arm only) were reconstructed using an algorithm proposed by Guyot et al. (2012).(44)"

- Was there any missing information in this reconstruction that might have affected reproducibility (for example, missing numbers at risk and/or missing total numbers) as described by Guyot et al.?
- Was the same reconstructed curve (for ceritinib) also used in the matching-adjusted indirect comparison (MAIC) analysis?

A2. Section D.1.1.9.2 (appendix D) states that "weights obtained from the MAIC analysis were carried through into the Cox regression model"

- How did the variance estimates of the hazard ratio from the Cox regression incorporate the MAIC weights (e.g. using a 'sandwich' estimator)?
- Was this done in R (e.g. with the survival package)?

A3. Section B.2.9.3 states that "Standard pairwise meta-analyses were also conducted on MAIC data to estimate an overall pooled estimate …"; and Section D.1.1.9.2 (appendix D) states that "Bayesian meta-analysis methods were then applied to synthesise the naïve-HRs and MAIC-HRs …"

Are the meta-analysis results shown in Figure 16 of the company submission (also Table 4 of the submission summary) for the hazard ratios:

- from the Bayesian meta-analysis (posterior means and credible intervals), or,
- from the 'standard' (non-Bayesian) meta-analysis (maximum likelihood estimates and confidence intervals)?
- If these are not the Bayesian results, where are they shown?

A4. In the meta-analysis of the two MAIC analyses (i.e. the meta-analysis of pooled brigatinib compared to ASCEND-2 and pooled brigatinib compared to ASCEND-5), there appears to be double counting of the brigatinib patients. Please provide further justification or a reference to support the appropriateness of the meta-analysis of the two MAIC analyses.

Section B: Clarification on cost-effectiveness data

NICE National Institute for Health and Care Excellence

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B1. Please state the source for the terminal care cost estimate (£1,705.53) included in section B.3.5.3.2, Table 51.

B2. Please explain why the ICER derived from the probabilistic sensitivity analysis is so different to the ICER from the deterministic analysis?

Section C: Textual clarifications and additional points

C1. Request 1:

- Please provide all code used to analyse the parameters used in the model.
- As a minimum, please provide the code used for analysis after the estimation of MAIC weights, particularly for the generation of the adjusted Kaplan-Meier curve and the Cox regression.

C2. Request 2:

- Please supply the individual patient level dataset underlying the MAIC analyses of the base case model.

14th May 2018

Helen Knight
Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

Dear Helen

Please find below responses to the ERG and NICE technical team clarification requests. As discussed in the teleconference on the 1st May, a response to question B2 is no longer required, and the IPD requested has been uploaded to NICE docs as a separate file.

If there any further clarifications required, please do get in touch.

Sincerely

[redacted]
Takeda UK

Takeda Pharmaceuticals UK
Building 3, Glory Park,
Glory Park Avenue, Wooburn Green, BUCKS HP10 0DF

List of Abbreviations

ERG	Evidence Review Group
PenTAG	Peninsula Technology Assessment Group
NICE	National Institute for Health and Care Excellence
IPD	Individual patient data
OS	Overall survival
PFS	Progression free survival
MAIC	Matching-adjusted indirect comparison
HR	Hazard ratio
SE	Standard error

Please find below responses by Takeda to each of the questions raised by The Evidence Review Group, Peninsula Technology Assessment Group (PenTAG) and the technical team at NICE.

Section A: Clarification on effectiveness data

A1. Section B.2.9.2 (page 52) states that "For time-to-event outcomes, IPD [individual patient data] of OS [overall survival] and PFS [progression-free survival] from both ASCEND-2 and ASCEND-5 (ceritinib arm only) were reconstructed using an algorithm proposed by Guyot et al. (2012)."

- Was there any missing information in this reconstruction that might have affected reproducibility (for example, missing numbers at risk and/or missing total numbers) as described by Guyot et al.?

- Was the same reconstructed curve (for ceritinib) also used in the matching-adjusted indirect comparison (MAIC) analysis?

Response: For both ASCEND-2 and ASCEND-5 trial, the reported number at risk at various time points were used to increase the accuracy. The same reconstructed data for ceritinib were then used in the MAIC analysis**.** Both studies reported numbers of patients at risk at two monthly intervals and there were no missing numbers at risk.

A2. Section D.1.1.9.2 (appendix D) states that "weights obtained from the MAIC analysis were carried through into the Cox regression model"

- How did the variance estimates of the hazard ratio from the Cox regression incorporate the MAIC weights (e.g. using a 'sandwich' estimator)?

- Was this done in R (e.g. with the survival package)?

Response: The standard model-based variance estimate was used. Table 1 lists the estimated standard errors using both model based and sandwich estimator. The sandwich estimator tends to provide a slightly higher estimated standard error for most cases, with the exception of ASCEND-5 when incorporating the MAIC weights. The magnitude of the difference between the two estimators varies depending on the data used.

The Cox regression analyses with and without the MAIC weights for both model-based and sandwich estimator were conducted using the `survival` package in R (`coxph()`). The R code can be found in response to C1. The 95% confidence intervals for the naïve-HR and MAIC-HR reported in Figure 16 (B.2.9.4.1 Overall survival page 60) and 20 (B.2.9.4.2Progression-free survival page 64) in the submission were extracted directly from the Cox regression output provided by R (`summary(model.name)$conf.int`).

Table 1: Variance estimates using model based and sandwich estimate

Overall survival	**HR**	**SE (model based)**	**SE (sandwich estimator)**
ASCEND-2 vs. ALTA			
Naïve	2.14	0.24	0.23
Full	2.40	0.29	0.35
Reduced	2.41	0.29	0.35
ASCEND-2 vs. pooled ALTA/Study 101			
Naïve	2.16	0.22	0.21
Full/ Reduced	2.28	0.27	0.33
ASCEND-5 vs. ALTA			
Naïve	2.09	0.23	0.22
Full	2.77	0.37	0.33
Reduced	2.52	0.29	0.28
ASCEND-2 vs. pooled ALTA/Study 101			
Naïve	2.07	0.22	0.21
Full/ Reduced	1.94	0.25	0.26
Progression-free survival	**HR**	**SE (model based)**	**SE (sandwich estimator)**
ASCEND-2 vs. ALTA			
Naïve	2.57	0.18	0.17
Full	2.71	0.21	0.24
Reduced	2.71	0.21	0.24
ASCEND-2 vs. pooled ALTA/Study 101			
Naïve	2.56	0.17	0.16
Full/ Reduced	2.59	0.20	0.23
ASCEND-5 vs. ALTA			
Naïve	3.49	0.19	0.19
Full	4.75	0.31	0.28
Reduced	4.31	0.24	0.24

HR = hazard ratio, SE = standard error

A3. Section B.2.9.3 states that "Standard pairwise meta-analyses were also conducted on MAIC data to estimate an overall pooled estimate …"; and Section D.1.1.9.2 (appendix D) states that "Bayesian meta-analysis methods were then applied to synthesise the naïve-HRs and MAIC-HRs …"

Are the meta-analysis results shown in Figure 16 of the company submission (also Table 4 of the submission summary) for the hazard ratios:

- from the Bayesian meta-analysis (posterior means and credible intervals), or,
- from the 'standard' (non-Bayesian) meta-analysis (maximum likelihood estimates and confidence intervals)?
- If these are not the Bayesian results, where are they shown?

Response: All evidence synthesis was conducted using a Bayesian framework. The results were reported using the posterior median and credible intervals. The standard pairwise meta-analysis in the submission refers to standard Bayesian pairwise meta-analysis- i.e. only Bayesian analyses were conducted.

A4. In the meta-analysis of the two MAIC analyses (i.e. the meta-analysis of pooled brigatinib compared to ASCEND-2 and pooled brigatinib compared to ASCEND-5), there appears to be double counting of the brigatinib patients. Please provide further justification or a reference to support the appropriateness of the meta-analysis of the two MAIC analyses.

Response: The standard MAIC approach adjusts for cross-study difference between two studies. In the case where data are available from multiple single-arm studies, it is a pragmatic approach to conduct the evidence synthesis in two steps. Step 1: use the MAIC approach to adjust for cross-study difference between the comparator studies (ASCEND-2 and ASCEND-5) and brigatinib studies (ALTA/pooled data). As a result, this allows estimating the relative treatment effect of ceritinib vs. brigatinib under a trial setting. Step 2: synthesise the relative treatment effects estimated from step 1. The same brigatinib patients were used in the population adjustment. As the ASCEND-2 and ASCEND-5 studies were not identical, this resulted two sets of adjusted brigatinib data.

Section B: Clarification on cost-effectiveness data

B1. Please state the source for the terminal care cost estimate (£1,705.53) included in section B.3.5.3.2, Table 51.

Response: The ERG and NICE confirmed that a response to this question was no longer required during the teleconference on the 1st May 2018.

B2. Please explain why the ICER derived from the probabilistic sensitivity analysis is so different to the ICER from the deterministic analysis?

Response: Differences between the probabilistic ICER and the deterministic ICER are driven by the choice of and uncertainty associated with the OS parametric curve. If the uncertainty associated with the OS parametric curve is removed in the probabilistic analysis i.e. constant coefficients are considered, probabilistic results are shown to approximate the deterministic results.

Within the model, the probabilistic analysis samples the parametric curve fit to the OS data based on the AIC statistics. This process is repeated for each iteration. The gompertz distribution is not normally distributed, but right-skewed (positive skewness). Therefore, on average, sampling the Gompertz parameters is more likely to shift the OS curve up and estimate improved survival. This skews the probabilistic ICER in favour of brigatinib, contributing to the difference in the probabilistic results compared with the deterministic results.

The difference between the probabilistic ICER and the deterministic ICER is further pronounced if the selected curve is the gompertz for all iterations, which aligns with expectations given the rationale above

Section C: Textual clarifications and additional points

C1. Request 1:

- Please provide all code used to analyse the parameters used in the model.
- As a minimum, please provide the code used for analysis after the estimation of MAIC weights, particularly for the generation of the adjusted Kaplan-Meier curve and the Cox regression.

Response:

The code for the estimation of MAIC weights (including the generation of the adjusted KM curve and Cox regressions) is provided below.

MAIC analysis

```
if(!require(dplyr)) {install.packages("dplyr"); library(dplyr)}
if(!require(tidyr)) {install.packages("tidyr"); library(tidyr)}
if(!require(wakefield)) {install.packages("wakefield"); library(wakefield)}
if(!require(ggplot2)) {install.packages("ggplot2"); library(ggplot2)}
if(!require(sandwich)) {install.packages("sandwich"); library(sandwich)}
if(!require(survival)) {install.packages("sandwich"); library(survival)}

### Initial setup
```

```
objfn <- function(a1, X){
  sum(exp(X %*% a1))
}

gradfn <- function(a1, X){
  colSums(sweep(X, 1, exp(X %*% a1), "*"))
}

### covariates
#AGE_FINAL_NUM = age (continuous years)
#GENDER_MALE_FINAL_NUM = gender (1=female, 2=male)
#ECOG_2plus_FINAL_NUM = ECOG (1=0-1, 2=2+)
#BRAINMETS_FINAL_NUM = presence of brain metastases (0=No, 1=Yes)
#CHEMO_FINAL_NUM = prior chemo (0=No, 1=Yes)
#LASTCRZ_FINAL_NUM = last treatment was crizotinib (0=No, 1=Yes)
#NPRREG3plus_FINAL_NUM = number of prior regimens (0=1-2, 1=3+)
#SMOKE_NEVER_FINAL_NUM = smoking history (0=former/current, 1=Never)

cov1<-
c("AGE_FINAL_NUM","GENDER_MALE_FINAL_NUM","ECOG_2plus_FINAL_NUM",
      "BRAINMETS_FINAL_NUM","CHEMO_FINAL_NUM","LASTCRZ_FINAL_NUM",
      "NPRREG3plus_FINAL_NUM")

cov2<-
c("AGE_FINAL_NUM","GENDER_MALE_FINAL_NUM","ECOG_2plus_FINAL_NUM",
      "BRAINMETS_FINAL_NUM","CHEMO_FINAL_NUM","LASTCRZ_FINAL_NUM")

cov3<-
c("AGE_FINAL_NUM","GENDER_MALE_FINAL_NUM","ECOG_2plus_FINAL_NUM",
          "BRAINMETS_FINAL_NUM","CHEMO_FINAL_NUM","LASTCRZ_FINAL_NUM",
          "NPRREG3plus_FINAL_NUM","SMOKE_NEVER_FINAL_NUM")

covariates<-cov1 #change this accordingly to select the relevant covariates

### Load in datasets
dat1<-read.csv("ALTA.csv") #ALTA
dat2<-read.csv("Study 101.csv") #pooled

#data1_final<-rbind(dat1,dat2)   ### if using pooled data
data1_final<-dat1   ### if using ALTA data

###load in comparator data (reconstructed IPD)
data2<-read.csv("ASCEND2 OS.csv")  #change this accordingly

### select names for comparator data depending on loading in OS or PFS
colnames(data2)<-c("id","TM2DTH","DTHFLN","Trt") # OS
#colnames(data2)<-c("id","PFStime_INVSYS","PFSevent_INVSYS","Trt")   # PFS
data2$Trt<-2
```

```
### WEIGHTS calculation
#load in reported summary baseline characteristics
bc<-read.csv("comparator baseline characteristics NICE.csv")

### change to select correct row of bc per comparator
bc<-bc[1,]

# Centred EMs
# k=row in the AD dataset
X.EM.0 <-  t(apply(data1_final[,covariates],1,'-',as.numeric(bc[,covariates])))

opt1 <- optim(par =rep(0,length(covariates)),   fn = objfn, gr = gradfn, X = X.EM.0, method =
"BFGS")

a1 <- opt1$par

wt <- exp(X.EM.0 %*% a1)

# Effective sample size
ESS<-sum(wt)^2/sum(wt^2)

### Cox regression
### select outcome below
s<-rbind(data1_final[,c("TM2DTH","DTHFLN","Trt", "id")],data2)     # OS
#s<-rbind(data1_final[,c("PFStime_INVSYS","PFSevent_INVSYS","Trt", "id")],data2)    #
PFSINV

s[which(s$Trt==1),"TM2DTH"]<-s[which(s$Trt==1),"TM2DTH"]/7  #convert from daily to
weekly
s[which(s$Trt==2),"TM2DTH"]<-s[which(s$Trt==2),"TM2DTH"]*(365.25/7/12) #convert from
monthly to weekly
# s[which(s$Trt==1),"PFStime_INVSYS"]<-s[which(s$Trt==1),"PFStime_INVSYS"]/7
#convert from daily to weekly
# s[which(s$Trt==2),"PFStime_INVSYS"]<-
s[which(s$Trt==2),"PFStime_INVSYS"]*(365.25/7/12) #convert from monthly to weekly

### naïve-HR and MAIC-HR
coxN<-coxph(Surv(s[,1],s[,2])~s[,3],weights=rep(1,dim(s)[1]))

s_wt<-c(wt,rep(1,dim(data2)[1]))
coxM<-coxph(Surv(s[,1],s[,2])~s[,3],weights = s_wt) #model based
coxM_S<-coxph(Surv(s[,1],s[,2])~s[,3]+cluster(s[,4]),weights = s_wt) # sandwich estimator
```

C2. Request 2:

- Please supply the individual patient level dataset underlying the MAIC analyses of the base case model.

Response: The IPD are provided as requested- please see separate zip file ('IPD to NICE' data in csv format).

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Brigatinib for treating ALK-positive advanced non-small-cell lung cancer after crizotinib [ID1328]: Addendum of updated evidence for the consideration of the NICE Appraisal Committee

Submitted by Takeda UK Ltd.

Submitted 14 May 2018

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List of Abbreviations

AIC	Akaike information criterion
ALK+	Anaplastic lymphoma kinase positive
BoR	Best overall response
BIC	Bayesian information criterion
CEAC	Cost effectiveness acceptability curve
CMs	Concomitant medications
ECOG	Eastern Cooperative Oncology Group
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30
EQ-5D-3L	EuroQol 5-dimensions 3-levels
ESS	Effective sample size
FE	Fixed effects
HR	Hazard ratio
HRQL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient data
INV	Investigator
IRC	Independent review committee
ITC	Indirect treatment comparison
LYG	Life year gained
MAIC	Matching-adjusted indirect comparison
NICE	National Institute for Health and Care Excellence
NSCLC	Non-small cell lung cancer
OS	Overall survival
ORR	Objective/overall response rate
OR	Odds Ratio
PFS	Progression free survival
PS	Performance status
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
RE	Random effects
ToT	Time on treatment
TKI	Tyrosine kinase inhibitor
WTP	Willingness to pay threshold

1. Executive summary

Brigatinib is a potent, oral, tyrosine kinase inhibitor (TKI) developed for the treatment of anaplastic lymphoma kinase rearranged (ALK+), non-small-cell lung cancer (NSCLC), a genetically defined subgroup. Takeda submitted to NICE on 6th April 2018 a dossier to address the decision problem defined in the final NICE scope of February 2018: an evaluation of the clinical and cost-effectiveness of brigatinib (Alunbrig®), for the treatment of anaplastic lymphoma kinase positive (ALK+) advanced non-small cell lung cancer (NSCLC) after crizotinib.[1]

Clinical evidence for the efficacy and safety of brigatinib arise predominantly from the ALTA study, a phase II, open-label, non-comparator trial examining the efficacy and safety of brigatinib in patients who had a diagnosis of ALK+ locally advanced or metastatic NSCLC and have experienced progression on crizotinib.[2] Supportive evidence comes from Study 101, a phase I/II, single arm, open-label, multi-cohort trial examining the efficacy and safety of brigatinib in ALK-rearranged NSCLC and other malignancies which includes a sub-group of patients eligible for the proposed indication.[3]

The primary analyses of the pivotal ALTA trial of brigatinib occurred initially from data extraction in February and May 2016, for investigator and IRC-assessed outcomes, respectively. This was followed by a further data cut-off in February 2017 and finally updated most recently with a September 2017 data cut.[4] The original NICE submission considered the main published data from May 2016 and the February 2017 updated data cut, the latter of which informed subsequent indirect treatment comparisons (ITCs), survival analyses and other clinical parameters populating the economic model. Efficacy data from the most recent September 2017 data extraction were presented in the clinical sections (section B.2.6) of the submission of 6th April 2018, although due to time constraints these data were not made available in time for incorporation into the statistical analyses and inclusion in the economic model of the original submission.

This addendum of updated evidence is in support of the original evidence presented in the submission and includes updated statistical analyses, updated inputs to the economic model and the updated cost effectiveness results, based on the most recent September 2017 data. This is accompanied by an updated model, file name: “Brigatinib NICE model_updated Sept data”. Updated inputs within the model are highlighted yellow and are in the “OS”, “PFSINV”, “PFSIRC”, “ToT”, “CODA”, “HRQL”, “AEs” and “Parameters” sheets. Note there were no changes in the methods used for these analyses from those reported in the original submission dossier. Therefore, only the updated inputs and results are presented in this addendum.

The deterministic base case incremental cost-effectiveness ratio (ICER) for brigatinib compared with ceritinib based on the September 2017 data cut is £54,311 and the probabilistic ICER is £67,540. These are compared with ICERs of £61,062 and £53,898 - deterministic and probabilistic, respectively - presented in the original submission using the February 2017 data cut. The updated inputs benefit from an additional 5.7 months of follow-up which translates into more robust estimates incorporating reduced uncertainty.

This updated evidence has been presented for review for NICE and the Evidence Review Group. As the updated data provides more robust estimates, we consider that these data should be considered by the Appraisal Committee for decision making purposes.

2. Updated indirect and mixed treatment comparisons

2.1 Overview

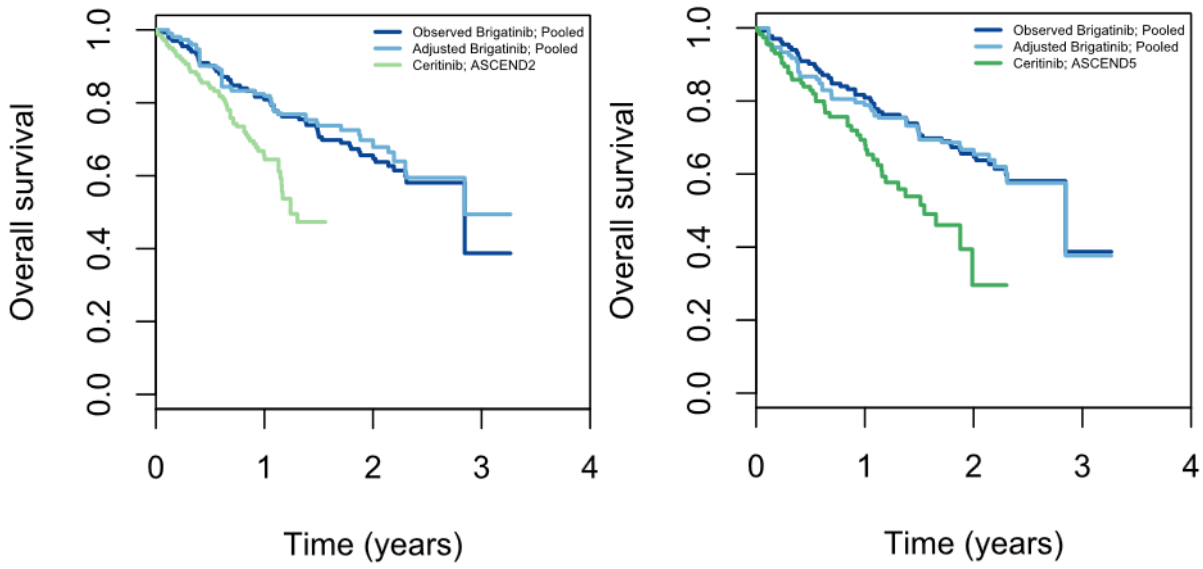
The ITCs reported in the original submission dossier used the February 2017 data cut from the ALTA trial. These ITCs have been updated using the September 2017 data cut, with updated results reported below. Please note there were no changes in the methods used for these statistical analyses from those reported in the original submission dossier (Section B.2.9), dated 6th April 2018, and clarified in the response submitted on the 14th May 2018. Therefore, only the updated results are presented in this addendum.

The results of the updated ITCs consistently show more favourable results for brigatinib across relative overall survival (OS), progression free survival (PFS) and response outcomes. This indicates that the original model submitted to NICE using the February 2017 data cut may underestimate the relative efficacy of brigatinib compared with ceritinib. The impact of the updated ITCs on the cost-effectiveness is presented in Section 4.

2.1.1 Overall Survival (update of Section B.2.9.4.1)

The pooled ALTA/Study 101 brigatinib observed and matching-adjusted indirect comparison (MAIC) Kaplan-Meier curves of OS are presented in Figure 1 along with the ceritinib Kaplan-Meier curve based on reconstructed individual patient-level data (IPD) from ASCEND-2 and ASCEND-5.

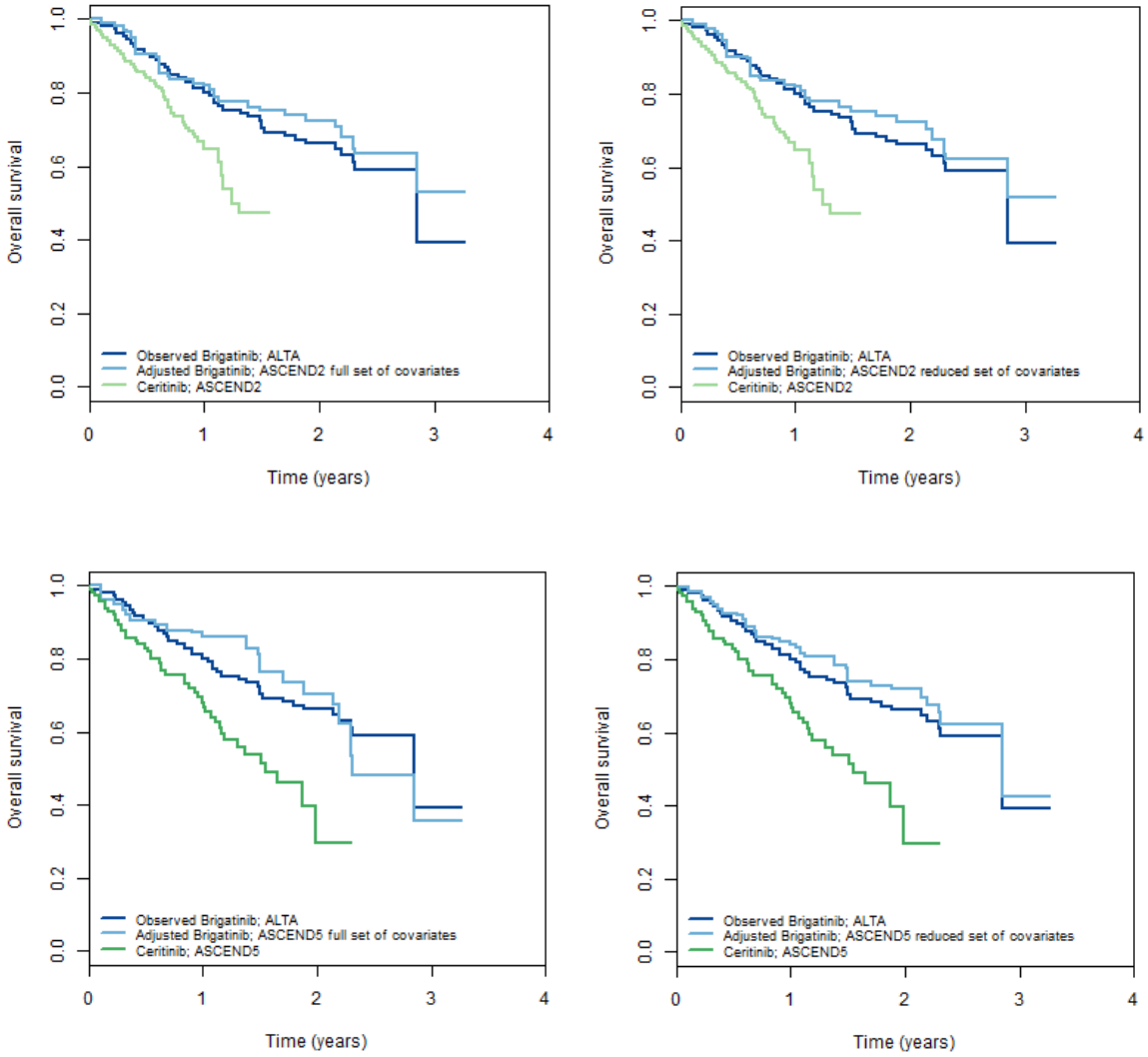
Figure 1: Observed and MAIC Kaplan-Meier curves of OS based on pooled ALTA/Study 101 data and reconstructed ceritinib OS data from ASCEND-2 and ASCEND-5 (update of Figure 14)



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

The ALTA brigatinib observed and MAIC Kaplan-Meier curves of OS are presented in Figure 2 along with the ceritinib Kaplan-Meier curve based on reconstructed IPD from ASCEND-2 and ASCEND-5.

Figure 2: Observed and MAIC Kaplan-Meier curves of OS based on ALTA data and reconstructed ceritinib data from ASCEND-2 and ASCEND-5 (update of Figure 15)



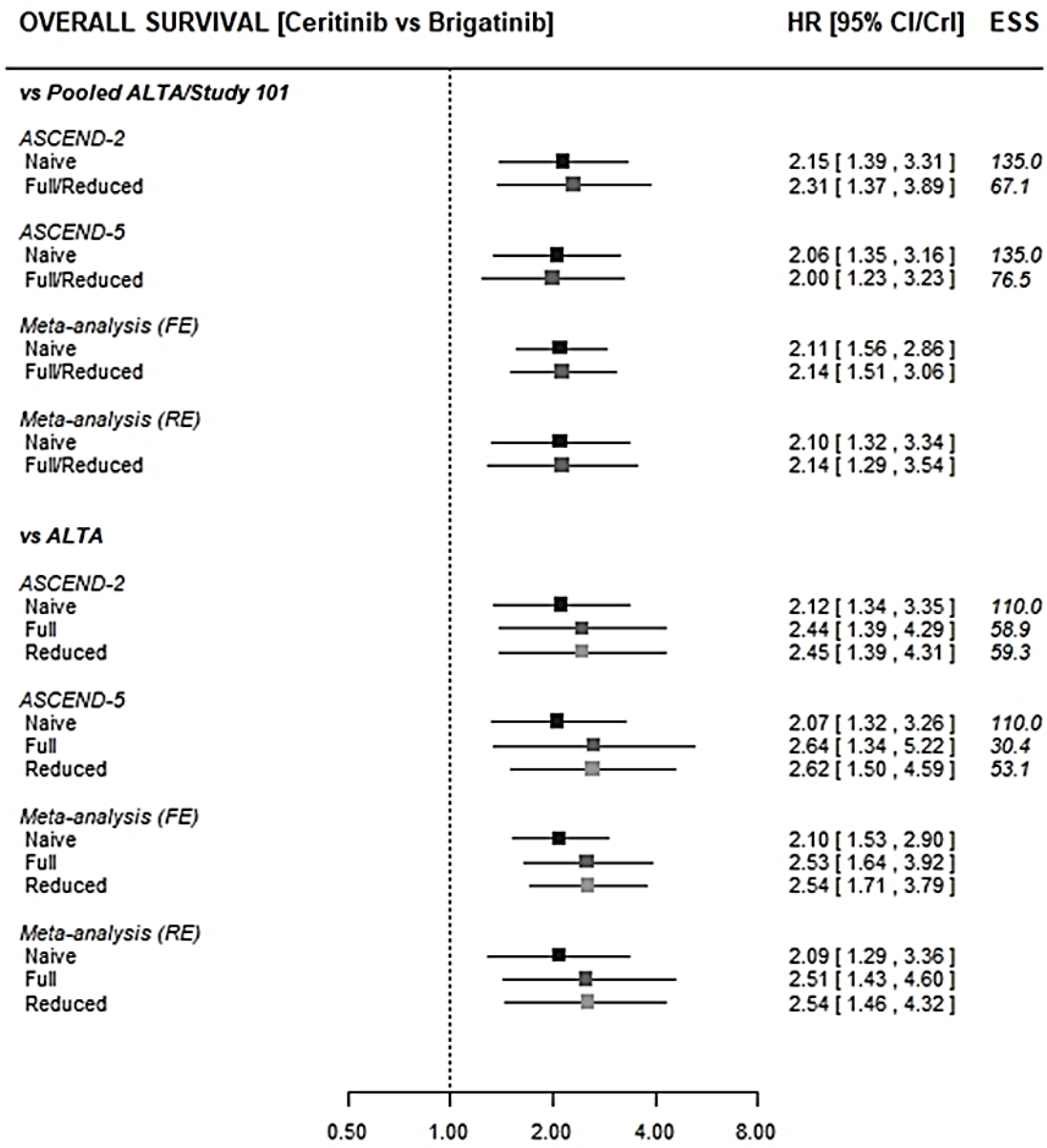
Abbreviations: MAIC, matching-adjusted indirect comparison; OS, overall survival

The MAIC Kaplan-Meier data were utilised within univariate Cox regression models to estimate a MAIC hazard ratio (HR). Since there are multiple estimates of relative efficacy due to two sources of ceritinib data, a pairwise meta-analysis was conducted, synthesising the MAIC-HRs to obtain an overall pooled HR to represent comparative efficacy between brigatinib and ceritinib. A summary of the naïve-HRs and MAIC-HRs ceritinib versus brigatinib are presented in Figure 3 along with the respective effective sample size (ESS) and estimates from the pairwise meta-analyses. HRs less than 1 favours ceritinib and HRs greater than 1 favour brigatinib. Note these methods are in line with the original NICE submission dossier (Section B.2.9).

Compared with the HRs estimated using the February 2017 data cut (as presented in the original submission, Section B.2.9.4), the estimates for the MAICs and the meta-analyses have improved in favour of brigatinib using the September 2017 data cut. In the base case

model, the HR derived from the meta-analysis of the fully covariate-adjusted MAICs using RE and pooled brigatinib data was considered for OS. This HR was 2.09 (95% CI: 1.26, 3.46) for ceritinib vs. brigatinib using the February 2017 data cut and using the September data cut this estimate is now 2.14 (95% CI: 1.29, 3.54).

Figure 3: Summary of ITC results – overall survival (update of Figure 16)

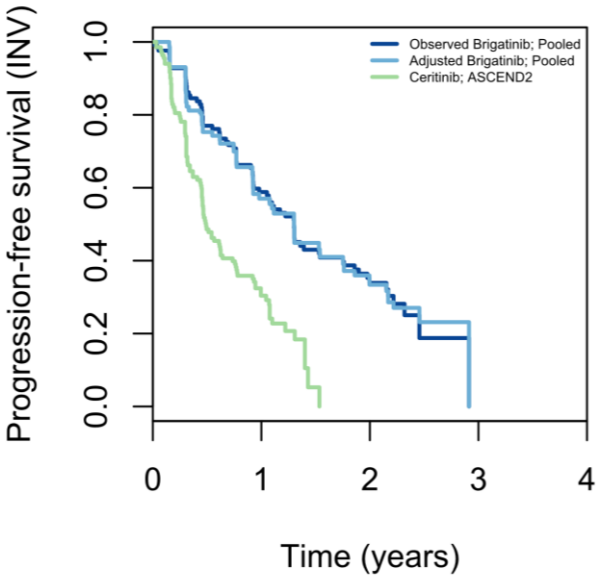


Abbreviations: CI, confidence interval; CrI, credible interval; ESS, effective sample size; FE, fixed-effect; HR, hazard ratio; RE, random-effects. Notes: Naïve estimates denote comparison without adjusting for prognostic factors. Full MAIC estimates denote analysis adjusting for all prognostic factors 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

2.1.2 Progression-free survival (update of Section B.2.9.4.2)

The pooled ALTA/Study 101 brigatinib observed and MAIC Kaplan-Meier curves of PFS INV (investigator assessed) are presented in Figure 4 along with the ceritinib Kaplan-Meier curve based on reconstructed IPD from ASCEND-2. These data are unavailable from ASCEND-5 which assessed PFS by IRC.

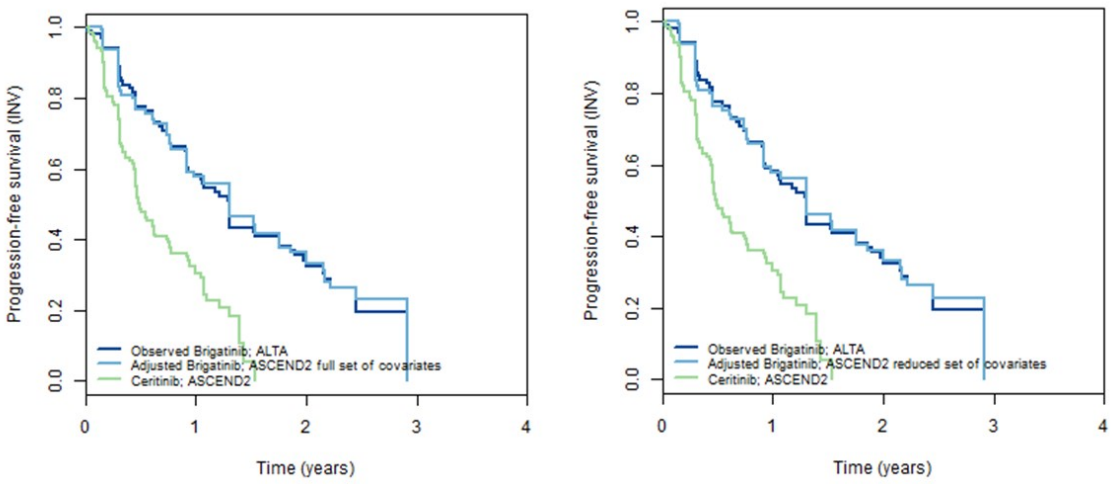
Figure 4: Observed and MAIC Kaplan-Meier curves for progression-free survival (INV-assessed) based on pooled ALTA/Study 101 and reconstructed ASCEND-2 (update of Figure 17)



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

The ALTA brigatinib observed/unadjusted and MAIC Kaplan-Meier curves of PFS (INV) are presented in Figure 5 along with the ceritinib curve based on reconstructed IPD from ASCEND-2 only (because PFS was assessed by IRC in ASCEND-5).

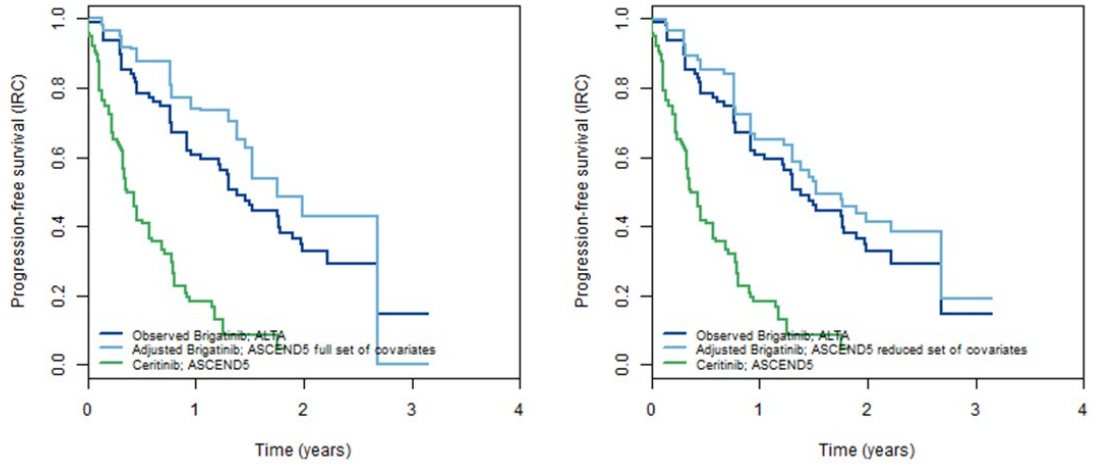
Figure 5: **Observed and MAIC Kaplan-Meier curves for progression-free survival (INV-assessed) based on ALTA and reconstructed ASCEND-2 (update of Figure 18)**



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

The ALTA brigatinib (observed/unadjusted) and MAIC Kaplan-Meier curves of PFS (IRC) are presented in Figure 6 along with the ceritinib curve based on reconstructed IPD from ASCEND-5.

Figure 6: **Observed and MAIC Kaplan-Meier curves for progression-free survival (IRC-assessed) based on ALTA and reconstructed ASCEND-5 (update of Figure 19)**



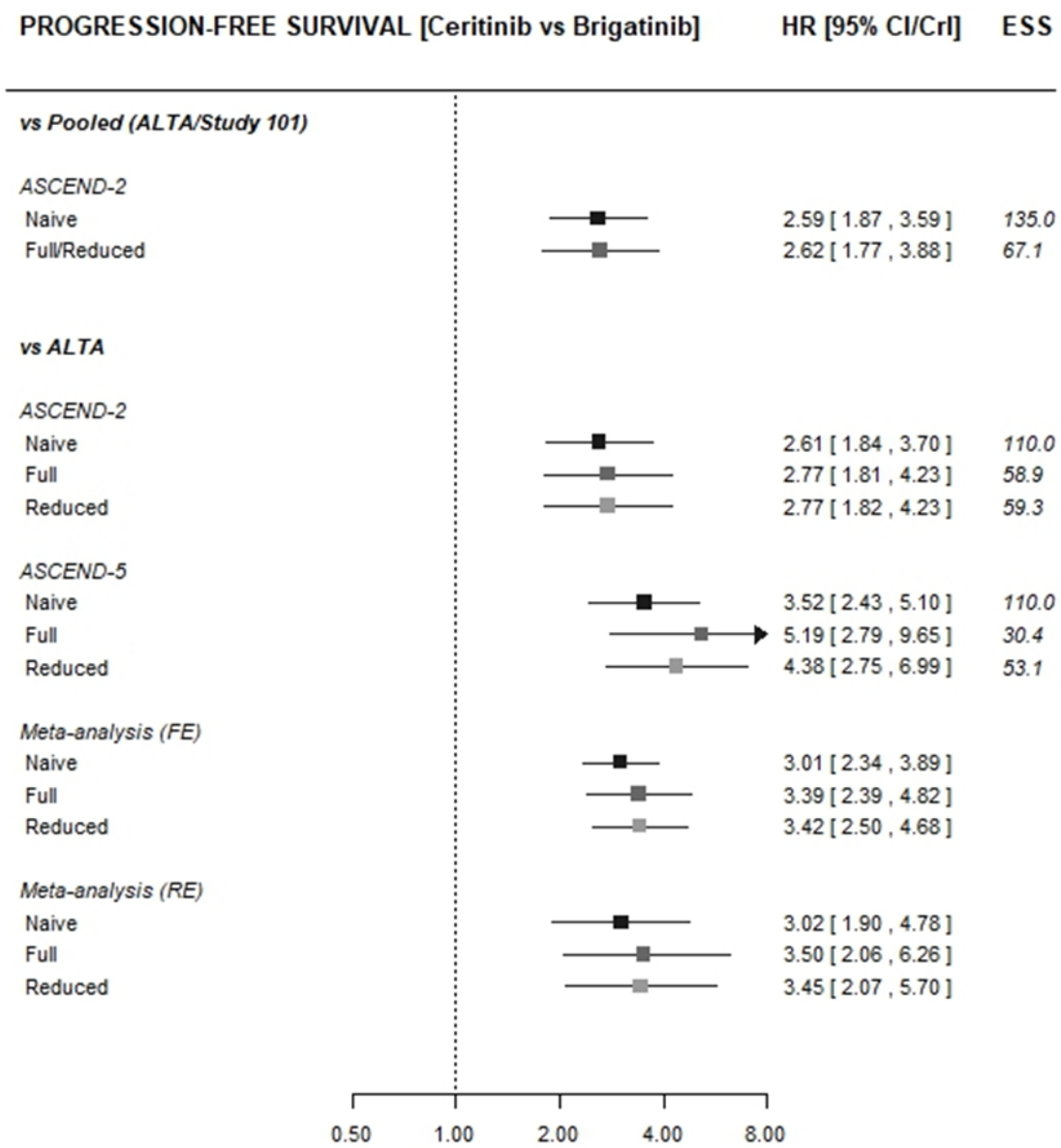
Abbreviations: IRC, independent review committee; MAIC, matching-adjusted indirect comparison

A summary of the naïve-HRs and MAIC-HRs ceritinib versus brigatinib are presented in Figure 7 (HR less than 1 favours ceritinib and HR greater than 1 favours brigatinib), along with the respective ESS as well as the pooled estimates obtained from the pairwise meta-analysis.

In the base case model, the HR derived from the fully covariate adjusted MAIC using pooled brigatinib data was considered for PFS. Compared with the HRs estimated using the February 2017 data cut (as presented in the original submission), the estimates for all the

ITCs considering the relative PFS outcomes have improved in favour of brigatinib using the September 2017 data cut. In the base case model, the estimated HR was 2.59 (95% CI: 1.75, 3.82) for ceritinib vs. brigatinib using the February 2017 data cut and using the September data cut this estimate is now 2.62 (95% CI: 1.77, 3.88).

Figure 7: Summary of ITC results – progression-free survival (update of Figure 20)



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.

2.1.3 Response (update of Section B.2.9.4.3)

Similar to PFS, objective/overall response rates (ORR) was measured either by INV or IRC-assessment, and the ALTA data were used accordingly dependent on what measure was reported in the comparator study under evaluation. ORR is defined as those patients achieving either complete or partial response to the treatment. The corresponding ORR data are presented in Table 1; this includes the observed (ALTA) and MAIC brigatinib data, as well as the observed ceritinib data from ASCEND-2 and ASCEND-5. The relative measure is represented by an odds ratio (OR) for ceritinib versus brigatinib (ORs less than 1 favours brigatinib and OR greater than 1 favours ceritinib).

Compared with the odds ratios estimated using the February 2017 data cut (as presented in the original submission), the estimates for all the ITCs considering the relative response have improved in favour of brigatinib when using the September 2017 data cut based on one additional responder for INV-assessed and two additional responders for IRC-assessed.

Table 1: Summary of ITC results – objective/overall response rates (update of Table 22)

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.

3. Updated cost-effectiveness inputs

3.1 Clinical parameters and variables (update of Section B.3.3)

The clinical parameters and variables reported in the original submission dossier used the February 2017 data cut from the ALTA trial (median follow-up of 18.6 months). These parameters have been updated using the September 2017 data cut (median follow-up of 24.3 months), with updated extrapolated outcomes, ITCs and adverse events reported below. The updated inputs benefit from an additional 5.7 months of follow-up which translates into more robust estimates incorporating reduced uncertainty.

Please note there were no changes in the methods used for these statistical analyses from those reported in the original submission dossier (Section B.3.3 and Appendix L), dated 6th April 2018. Therefore, only the updated inputs are presented in this addendum.

3.1.1 Extrapolated outcomes (update of section B.3.3.2)

Sections 3.1.2, 3.1.3 and 3.1.4 report the updated inputs used in the base case economic model for OS, PFS and time on treatment (ToT), respectively. Appendices 6.2.1, 6.2.2, 6.2.3 and 6.2.4 present the updated inputs used in scenario analyses associated with ALTA only OS, PFS INV, PFS IRC and ToT, respectively. PFS IRC and ToT were not reported in Study 101.

3.1.2 Overall survival (pooled data) (update of section B.3.3.2.1)

The pooled data for OS were obtained from pooling the observed brigatinib data from ALTA and Study 101 (n=135). Table 2 summarises the Akaike Information Criterion (AIC) and Bayes Information Criterion (BIC) values for each parametric survival distribution. The statistical goodness-of-fit indicates that all the models fit the observed data well; the AIC values are less than or equal to 5 points between the models. BIC penalizes on the number of parameters used in a model, this suggests that the exponential distribution is the best fitting model. The empirical hazard plot associated with the pooled OS data is presented in Figure 8. The Kaplan-Meier curve and fitted parametric distributions are presented in Figure 9.

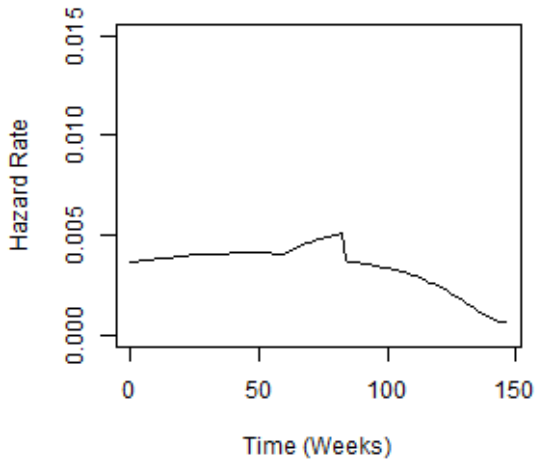
The visual inspection of the fitted curves suggests that all models fit the observed data well. However, the observed data are immature and provide no information relevant to the long-term predictions.

Table 2: Goodness-of-fit statistics for OS, pooled data using the September 2017 data-cut from the ALTA trial (update of Table 33)

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

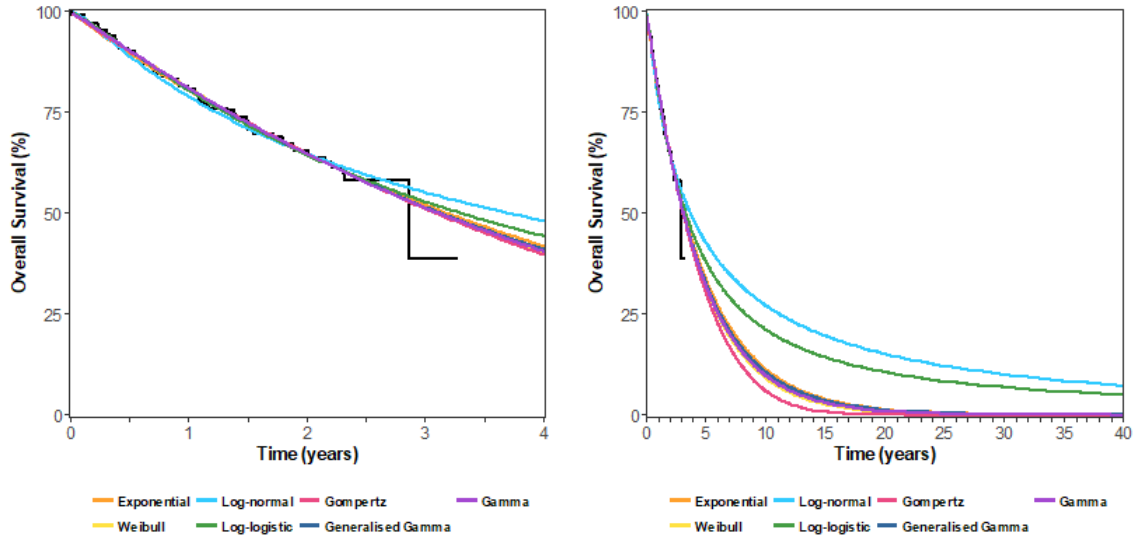
Model	AIC	BIC
Weibull	664.24	670.05
Gompertz	664.34	670.15
Exponential	662.43	665.34
Abbreviations: AIC, Akaike information criterion; BIC, Bayes information criterion; OS, overall survival		

Figure 8: Empirical hazard plot for OS, pooled data using the September 2017 data-cut from the ALTA trial (update of Figure 22)



Abbreviations: OS, overall survival

Figure 9: Kaplan-Meier curve and fitted parametric distributions for OS, pooled data using the September 2017 data-cut from the ALTA trial (update of Figure 23)



Abbreviations: OS, overall survival

Table 3 provides the extrapolated long-term brigatinib survival rates for 3-years, 5-years, 10-years and 20-years associated with each parametric curve and compares these estimates with experts' judgements on clinical plausibility (see original submission Section B.3.3.5 and B.3.10 for full details of expert elicitation). The Gompertz, followed by the Weibull, provide the long-term estimates that align most closely with what would be expected in clinical practice.

Table 4 presents the long-term extrapolated survival estimated for brigatinib for each of the parametric curves and compares these estimates with the observed median and mean. Based on assessing both internal and external validity, the Gompertz distribution was determined to be the most appropriate model in the base case for the OS pooled data. This parametric curve choice is in line with the curve selected to predict OS using the February 2017 data cut in the original submission and continues to be supported by the data available when estimated using the September 2017 data cut.

Table 3: Extrapolated long-term survival rates for brigatinib, pooled data using the September 2017 data-cut from the ALTA trial (update of Table 34)

	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%

Table 4: Extrapolated long-term survival outcomes for brigatinib, pooled data using the September 2017 data-cut from the ALTA trial (update of Table 35)

	Predicted median (months)	Predicted mean over trial period (months)	Predicted mean over lifetime (months)	Median from pooled data (months)	Mean from pooled data (months)
Generalised gamma	37.72	21.79	53.12	34.1	27.5
Gamma	37.72	21.80	51.75		
Log-normal	45.08	21.53	82.21		

	Predicted median (months)	Predicted mean over trial period (months)	Predicted mean over lifetime (months)	Median from pooled data (months)	Mean from pooled data (months)
Log-logistic	39.56	21.72	71.56		
Weibull	37.72	21.81	50.95		
Gompertz	37.72	21.79	46.83		
Exponential	38.64	21.69	54.19		

In the base case, the model assumes a continued treatment benefit associated with OS and PFS for brigatinib and ceritinib. Therefore, the extrapolated curves presented above for OS and below for PFS INV are used for the duration of the model time horizon.

3.1.3 Progression-free survival investigator assessed (pooled data) (update of Section B.3.3.2.2)

The pooled data for PFS INV were obtained from the observed brigatinib data from ALTA and and Study 101 (n=135). Table 5 summarises AIC and BIC values for each parametric survival distribution. The statistical goodness-of-fit indicates that all the models fit the observed data well; the AIC values are less than 5 points between the models (with the exception of the log normal). BIC suggests that the exponential distribution is the best fitting model. However, the empirical hazard plot indicates that the hazard rate may not be constant over time (see

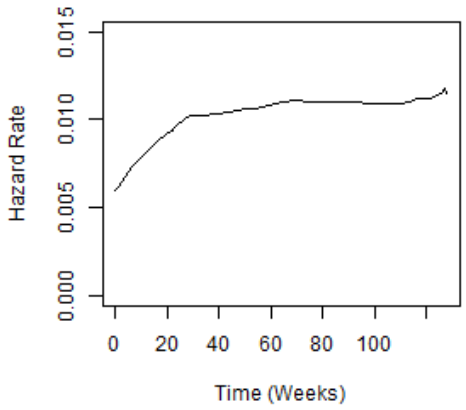
Figure 10); hence the exponential distribution may not be appropriate.

Table 5: Goodness-of-fit statistics for PFS INV-assessed, pooled data using the September 2017 data-cut from the ALTA trial (update of Table 36)

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; INV, investigator; PFS, progression-free survival

Figure 10: Empirical hazard for PFS INV-assessed, pooled data using the September 2017 data-cut from the ALTA trial (update of Figure 24)



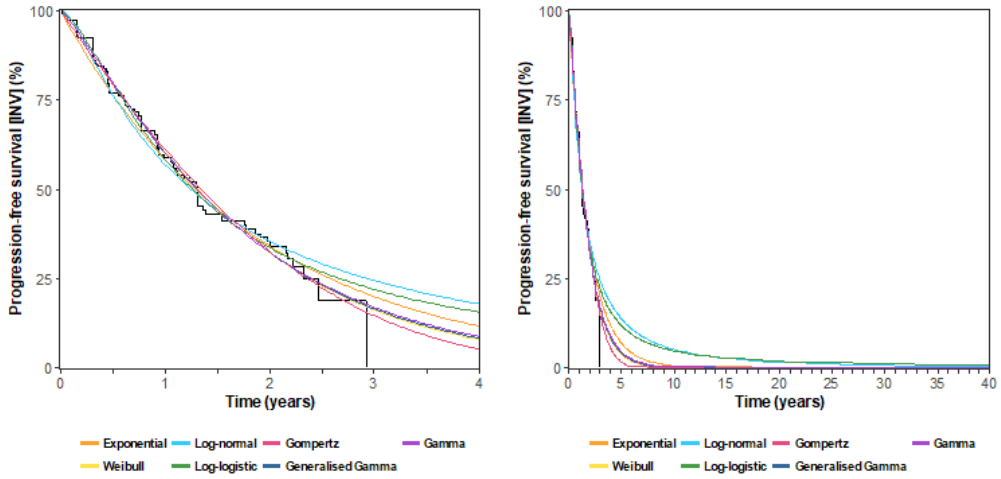
Abbreviations: INV, investigator; PFS, progression-free survival

The Kaplan-Meier curve and fitted parametric distributions are presented in

Figure 11. The visual inspection of the fitted curves suggests that the Weibull, gamma, exponential and Gompertz fit the observed data well. Table 6 provides the long-term extrapolated estimates of brigatinib associated with PFS INV for each of the parametric curves in the model compared with the observed median and mean. Based on assessing both internal and external validity, the Gompertz distribution was selected in the base case for the PFS INV outcome. This is aligned with the distribution applied to the OS pooled data – as such, the OS and PFS investigator assessed curves follow the same shape and extrapolated curves do not cross, avoiding clinically implausible outcomes.

This parametric curve choice is also in line with the curve selected to estimate PFS INV using the February 2017 data cut in the original submission and continues to be supported by the data available when estimated using the September 2017 data cut.

Figure 11: Kaplan-Meier curve and fitted parametric distributions for PFS INV-assessed, pooled data using the September 2017 data-cut from the ALTA trial (update of Figure 25)



Abbreviations: INV, investigator; PFS, progression-free survival

Table 6: Extrapolated long-term PFS INV-assessed outcomes for brigatinib, pooled data using the September 2017 data-cut from the ALTA trial (update of Table 37)

	Predicted median	Predicted mean over trial period	Predicted mean over lifetime	Median from pooled data	Mean from pooled data
Generalised gamma	16.56	14.00	20.50	15.61	17.62
Gamma	15.64	13.98	20.75		
Log-normal	15.64	13.61	28.98		
Log-logistic	15.64	13.84	27.70		
Weibull	16.56	14.03	20.30		
Gompertz	16.56	14.05	19.27		
Exponential	15.64	13.63	22.15		

Abbreviations: INV, investigator; PFS, progression-free survival

3.1.4 Time on treatment (ToT) (update of Section B.3.3.2.3)

In the base case, the model assumes that patients treated with brigatinib and ceritinib receive treatment for 1.53 months beyond progression. This is calculated by the difference in median ToT and median PFS observed in the ALTA clinical trial from the September 2017 data cut. The median PFS associated with ALTA is 15.62 months and the median ToT is 17.15 months, resulting in a difference of 1.53 months. This aligns with the difference in median ToT and median PFS observed with the February 2017 data cut.

3.1.5 Indirect treatment comparisons (ITCs) (update of Section B.3.3.3)

Sections 2.1.1, 2.1.2 and 2.1.3 present the results of the updated ITCs for ceritinib vs. brigatinib for relative OS, PFS and response outcomes, respectively. The updated economic analysis uses the inverse of these results for OS and PFS in the base case – i.e. brigatinib vs. ceritinib – presented in Sections 3.1.5.1 and 3.1.5.2, respectively.

Appendix 6.2.5 presents the odds ratios associated with the relative efficacy scenario relevant to response outcomes applied in scenario analyses.

3.1.5.1 Overall survival (OS) (update of Section B.3.3.3.1)

Table 7 presents the HRs for brigatinib relative to ceritinib for OS associated with each combination of ITC method, covariate list, brigatinib data source and ceritinib data source.

Table 7: HRs for brigatinib vs. ceritinib associated with OS using the September 2017 data-cut from the ALTA trial (update of Table 38)

Method	Covariate list	Brigatinib data source	Ceritinib data source	HR brigatinib vs. ceritinib
Naïve ITC	NA	ALTA	ASCEND-2	0.47
MAIC	Full	ALTA	ASCEND-2	0.41
MAIC	Reduced	ALTA	ASCEND-2	0.41
Naïve ITC	NA	Pooled (ALTA and Study 101)	ASCEND-2	0.47
MAIC	Full	Pooled (ALTA and Study 101)	ASCEND-2	0.43
MAIC	Reduced	Pooled (ALTA and Study 101)	ASCEND-2	0.43
Naïve ITC	NA	ALTA	ASCEND-5	0.48
MAIC	Full	ALTA	ASCEND-5	0.38
MAIC	Reduced	ALTA	ASCEND-5	0.38
Naïve ITC	NA	Pooled (ALTA and Study 101)	ASCEND-5	0.48
MAIC	Full	Pooled (ALTA and Study 101)	ASCEND-5	0.50
MAIC	Reduced	Pooled (ALTA and Study 101)	ASCEND-5	0.50
FE meta-analysis of naïve ITC	NA	ALTA	ASCEND-2 and ASCEND-5	0.39
RE meta-analysis of naïve ITC	NA	ALTA	ASCEND-2 and ASCEND-5	0.40
FE meta-analysis of MAICs	Full	ALTA	ASCEND-2 and ASCEND-5	0.48
RE meta-analysis of MAICs	Full	ALTA	ASCEND-2 and ASCEND-5	0.48
FE meta-analysis of MAICs	Reduced	ALTA	ASCEND-2 and ASCEND-5	0.39

Method	Covariate list	Brigatinib data source	Ceritinib data source	HR brigatinib vs. ceritinib
RE meta-analysis of MAICs	Reduced	ALTA	ASCEND-2 and ASCEND-5	0.39
FE meta-analysis of naïve ITC	NA	Pooled (ALTA and Study 101)	ASCEND-2 and ASCEND-5	0.47
RE meta-analysis of naïve ITC	NA	Pooled (ALTA and Study 101)	ASCEND-2 and ASCEND-5	0.47
FE meta-analysis of MAICs	Full	Pooled (ALTA and Study 101)	ASCEND-2 and ASCEND-5	0.47
RE meta-analysis of MAICs (base case)	Full	Pooled (ALTA and Study 101)	ASCEND-2 and ASCEND-5	0.48
FE meta-analysis of MAICs	Reduced	Pooled (ALTA and Study 101)	ASCEND-2 and ASCEND-5	0.47
RE meta-analysis of MAICs	Reduced	Pooled (ALTA and Study 101)	ASCEND-2 and ASCEND-5	0.47

Abbreviations: FE, fixed effects; HR, hazard ratio; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; NA, not applicable; OS, overall survival; RE, random effects

3.1.5.2 Progression free survival (PFS) (update of Section B.3.3.3.2)

Table 8 presents the HRs for brigatinib relative to ceritinib for PFS associated with each combination of ITC method, covariate list, brigatinib data source, ceritinib data source and PFS assessment.

Table 8: HRs for brigatinib vs. ceritinib associated with progression-free survival (PFS) using the September 2017 data-cut from the ALTA trial (update of Table 39)

Method	Covariate list	Brigatinib data source	Ceritinib data source	PFS assessment	HR brigatinib vs. ceritinib
Naïve ITC	NA	ALTA	ASCEND-2	INV	0.38
MAIC	Full	ALTA	ASCEND-2	INV	0.36
MAIC	Reduced	ALTA	ASCEND-2	INV	0.36
Naïve ITC	NA	Pooled (ALTA and Study 101)	ASCEND-2	INV	0.39
MAIC (base case)	Full	Pooled (ALTA and Study 101)	ASCEND-2	INV	0.38
MAIC	Reduced	Pooled (ALTA and Study 101)	ASCEND-2	INV	0.38
Naïve ITC	NA	ALTA	ASCEND-5	IRC	0.28
MAIC	Full	ALTA	ASCEND-5	IRC	0.19
MAIC	Reduced	ALTA	ASCEND-5	IRC	0.23
FE meta-analysis of naïve ITC	NA	ALTA	ASCEND-2 and ASCEND-5	Pooled	0.29
RE meta-analysis of naïve ITC	NA	ALTA	ASCEND-2 and ASCEND-5	Pooled	0.29
FE meta-analysis of MAICs	Full	ALTA	ASCEND-2 and ASCEND-5	Pooled	0.33
RE meta-analysis of MAICs	Full	ALTA	ASCEND-2 and ASCEND-5	Pooled	0.33
FE meta-analysis of MAICs	Reduced	ALTA	ASCEND-2 and ASCEND-5	Pooled	0.29
RE meta-analysis of MAICs	Reduced	ALTA	ASCEND-2 and ASCEND-5	Pooled	0.29

Abbreviations: FE, fixed effects; HR, hazard ratio; INV, investigator; IRC, independent review committee; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; NA, not applicable; PFS, progression-free survival; RE, random effects

3.1.6 Adverse events (update of Section B.3.3.4)

Appendix 6.2.6 presents the adverse events included in the economic analysis based on the updated September 2017 data cut of the ALTA trial and the calculated incidence rate. In total, 67 different adverse events have been included (there had been 60 in the previous data cut). The average treatment exposure was reported as 84-weeks. Appendix 6.2.7 reports the unit costs applied to each adverse event in the economic analysis. Note no unit

costs were changed for adverse events included in the original submission dossier. Unit costs associated with the additional adverse events are presented in Appendix 6.2.7.

3.2 Health-related quality of life (update of Section B.3.4)

3.2.1 Health-related quality-of-life data from clinical trials (update of Section B.3.4.1)

Health-related quality of life (HRQL) analyses have been updated using the September 2017 data cut, with updated results reported below. The updated data benefit from an additional 5.7 months of follow-up which translates into more robust estimates of HRQL incorporating reduced uncertainty; the number of records available for analysis increased by 298 to 2,010 (compared with 1,712 using the February 2017 data cut).

Please note there were no changes in the methods used for these statistical analyses from those reported in the original submission dossier (Section B.3.3.4), dated 6th April 2018. Therefore, only the updated results are presented in this addendum.

3.2.1.1 Mapping from EORTC-QLQ-C30 to EQ-5D (update of Section B.3.4.1.1)

The mapping algorithm used to convert EORTC QLQ-C30 into EQ-5D-3L utility values is one published by Longworth *et al*. (2014).[5] A summary of utility values after the mapping procedure is presented in Table 9. These methods are in line with those presented in Section B.3.4.1.1 of the original submission dossier. The estimates below remain as per the original submission (to 2dp).

Table 9: Summary of mapped utility values (update of Table 42)

	Number of patients	Number of records	Mean (SD)	Range	Median [Q1-Q3]
Overall EQ-5D score (across a maximum of 35 cycles)	103	2010	0.752 (0.194)	[-0.297, 0.959]	0.784 [0.683, 0.899]
Baseline EQ-5D score	103	103	0.712 (0.22)	[-0.246, 0.951]	0.764 [0.652, 0.861]

Abbreviations: Q1, lower quartile; Q3, upper quartile; SD, standard deviation.

3.2.2 HRQL analyses (update of Section B.3.4.1.2)

The covariates included and methods used in the updated HRQL analyses were the same as reported in the original submission dossier (Section B.3.4.1.2) and so are not reported in this addendum. Results from the four updated regression models are presented in Table 10.

Table 10: HRQL regression results (update of Table 44)

	HRQL model 1		HRQL model 2		HRQL model 3		HRQL model 4	
Covariate	**Mean**	**SE**	**Mean**	**SE**	**Mean**	**SE**	**Mean**	**SE**
Number of patients	99				101			
Number of records	642				2006			
Intercept	0.581	0.093	0.572	0.087	0.546	0.085	0.552	0.0703
Overall response [4 categories] (ref=Complete response)								
Partial response	-0.011	0.038	NA					
Progressive disease	-0.071	0.039			NA			
Stable disease	-0.010	0.040						
Overall response [2 categories] (ref=Progression-free)								
Progressive disease			-0.061	0.016				
Best overall response [4 categories] (ref=Confirmed complete response)								
Partial response (confirmed/unconfirmed)					0.007	0.052		
Progressive disease	NA		NA		-0.172	0.071	NA	
Stable disease					0.012	0.053		
Best overall response [2 categories] (ref=Progression-free)								
Progressive disease					NA		-0.181	0.051
Baseline EQ-5D score (continuous)	0.452	0.066	0.453	0.066	0.514	0.056	0.513	0.056
ECOG PS (ref=0-1)								
2	-0.137	0.058	-0.138	0.058	-0.062	0.047	-0.060	0.047
Experience of 1+ grade 3/4 AE (ref=No)								
Yes	-0.068	0.032	-0.068	0.031	-0.065	0.027	-0.065	0.027
Age (years)	-0.002	0.001	-0.002	0.001	-0.002	0.001	-0.002	0.001

	HRQL model 1		HRQL model 2		HRQL model 3		HRQL model 4	
Gender (ref=Female) Male	-0.012	0.027	-0.012	0.027	-0.020	0.023	-0.020	0.023
Presence of brain metastases (ref=No) Yes	-0.083	0.047	-0.084	0.047	-0.096	0.039	-0.095	0.039
Presence of liver metastases (ref=No) Yes	0.031	0.037	0.032	0.037	0.034	0.031	0.032	0.030
Presence of bone metastases (ref=No) Yes	-0.0005	0.036	-0.0005	0.035	0.007	0.030	0.006	0.029
Number of metastatic sites (continuous)	0.019	0.015	0.019	0.014	0.013	0.012	0.013	0.012
Receipt of prior chemotherapy (ref=No) Yes	-0.004	0.032	-0.005	0.032	-0.005	0.026	-0.005	0.026
Presence of active brain lesions (ref=No) Yes	0.042	0.040	0.043	0.040	0.056	0.032	0.055	0.033
Time since prior crizotinib therapy to receipt of brigatinib (months)	-0.005	0.006	-0.005	0.006	-0.002	0.005	-0.002	0.005
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; HRQL, health related quality of life; NA, not applicable; SE, standard error.								

Resulting utility values by response status (based on a mean of covariates approach) are presented in Table 11. These mean utility scores are then applied in the economic model.

Table 11: Mean utility values by response category (update of Table 45)

	Overall response (4 categories)	Overall response (2 categories)	Best overall response (4 categories)	Best overall response (2 categories)
Complete response	0.757	NA	0.729	NA
Partial (confirmed/unconfirmed) response	0.746		0.737	
Stable disease	0.746		0.741	
Progressive disease	0.686		0.557	
Progression-free	NA	0.747	NA	0.738
Progressed		0.686		0.556
Abbreviations: NA, not applicable.				

3.2.3 Adverse events (update of Section B.3.4.3)

With the updated September data, the utility decrement associated with experience of at least one grade 3/4 adverse event, based on the base case HRQL model (model 2), is -0.0678. The utility decrement has been multiplied by the per-cycle probability of a grade 3/4 adverse event and by the weighted number of cycles of duration of grade 3/4 adverse events obtained from the ALTA data. Where the mean duration of an adverse event was unavailable in the ALTA data set, the average of the reported durations of adverse events was assumed. This was the case for 13 of the 67 adverse events. Appendix 6.2.6 presents the mean cycles of duration for each adverse event. The utility decrements associated with adverse events per cycle are -0.0048 and -0.0076 for brigatinib and ceritinib, respectively.

3.2.4 Health-related quality-of-life data used in the cost-effectiveness analysis (update of Section B.3.4.4)

Within the model, base case data are taken from the HRQL analyses on the ALTA data for pre-progression and from Chouaid *et al.* (2013)[6] for progressed disease. Table 12 presents the mean covariates and the coefficients used in the base case estimation for pre-progression utility values. Table 13 then summarises the utility values used in the cost-effectiveness analysis.

Table 12: Mean covariates, base case intercept and coefficients (update of Table 46)

	Mean covariate	Estimate
Intercept	NA	0.5722
Baseline EQ-5D-3L score	0.71	0.4530
Progressed	NA	-0.0610
ECOG PS	9.09%	-0.1375
≥1 grade 3/4 adverse event	NA	-0.0678

	Mean covariate	Estimate
Age	54.79	-0.0020
Gender (male)	38.38%	-0.0123
Presence of brain metastases = yes	68.69%	-0.0840
Presence of liver metastases = yes	21.21%	0.0318
Presence of bone metastases = yes	33.33%	-0.0005
Number of metastatic sites	3.36	0.0187
Receipt of prior chemotherapy = yes	72.73%	-0.0045
Presence of active brain lesions = yes	51.52%	0.0427
Time since prior crizotinib therapy	0.73	-0.0049
Abbreviations: ECOG, Eastern Cooperative Oncology Group; EQ-5D-3L, EuroQol 5-dimensions 3-levels; NA, not applicable; PS, performance score		

Table 13: Summary of utility values used in the cost-effectiveness analysis (update of Table 47)

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)[6] (-0.15). This is in line with the NICE Methods Guide 2013[7] and the NICE submission for ceritinib [TA395].[8] 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		

3.3 Concomitant medications (update of section B.3.5.2.3)

Appendix 6.2.8 presents the updated list of concomitant medications (CMs) included in the economic analysis based on the September 2017 data-cut from the ALTA trial. A total of 42 CMs were included.

Section 6.2.8 of the appendix also presents the dosing information and costs associated with each CM. The drug cost per cycle (28-days) assuming no drug wastage and the proportion of patients receiving each CM derived from the September data-cut are also presented. Note no dosing or cost inputs were changed for CMs included in the original submission dossier. Dosing and cost inputs associated with new CMs are highlighted in bold.

The total cost per model cycle in the updated model is £57.49.

4. Updated cost-effectiveness results

4.1.1 Base-case results (update of Section B.3.7)

4.1.1.1 Base-case incremental cost-effectiveness analysis results (update of Section B.3.7.1)

The base case results for brigatinib compared with ceritinib are shown in Table 14. Results were subject to discounting at a rate of 3.5% per annum. Brigatinib is associated with a gain of 1.58 incremental life years and 1.12 incremental quality adjusted life years (QALYs) per patient, and an increase in overall costs of £61,097 per patient. Based on list prices for brigatinib and ceritinib, the ICER is £54,311 per additional QALY gained. This is compared with an ICER of £61,062 presented in the original submission using the February 2017 data cut.

Appendix 6.1 provides the updated clinical outcomes and disaggregated life years, QALYs and costs.

Table 14: Base-case results (update of Table 53)

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

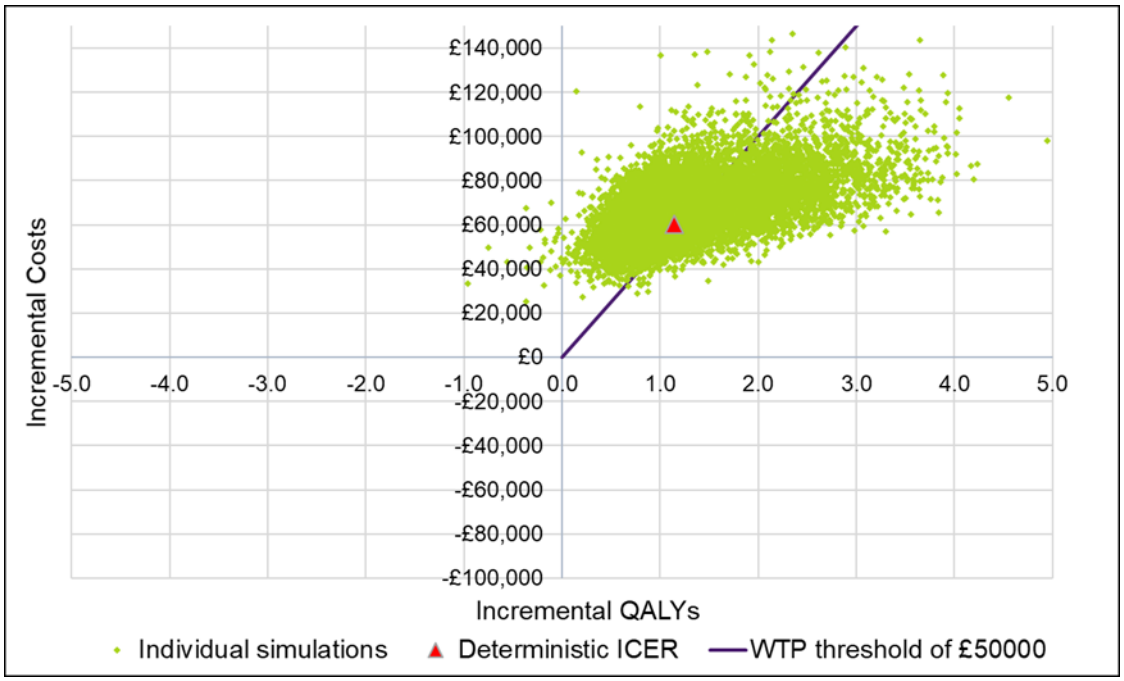
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life year

4.1.2 Sensitivity analyses (update of Section B.3.8)

4.1.2.1 Probabilistic sensitivity analysis (update of Section B.3.8.1)

The results of 10,000 probabilistic sensitivity analysis (PSA) iterations are presented in Figure 12 (cost-effectiveness plane) and Figure 13 (cost-effectiveness acceptability curve (CEAC)). Mean probabilistic incremental QALYs gained from brigatinib were 1.30 (SD: 0.69). Mean probabilistic incremental costs were £67,540 (SD: £14,270). The resulting probabilistic ICER from 10,000 iterations was £51,882.

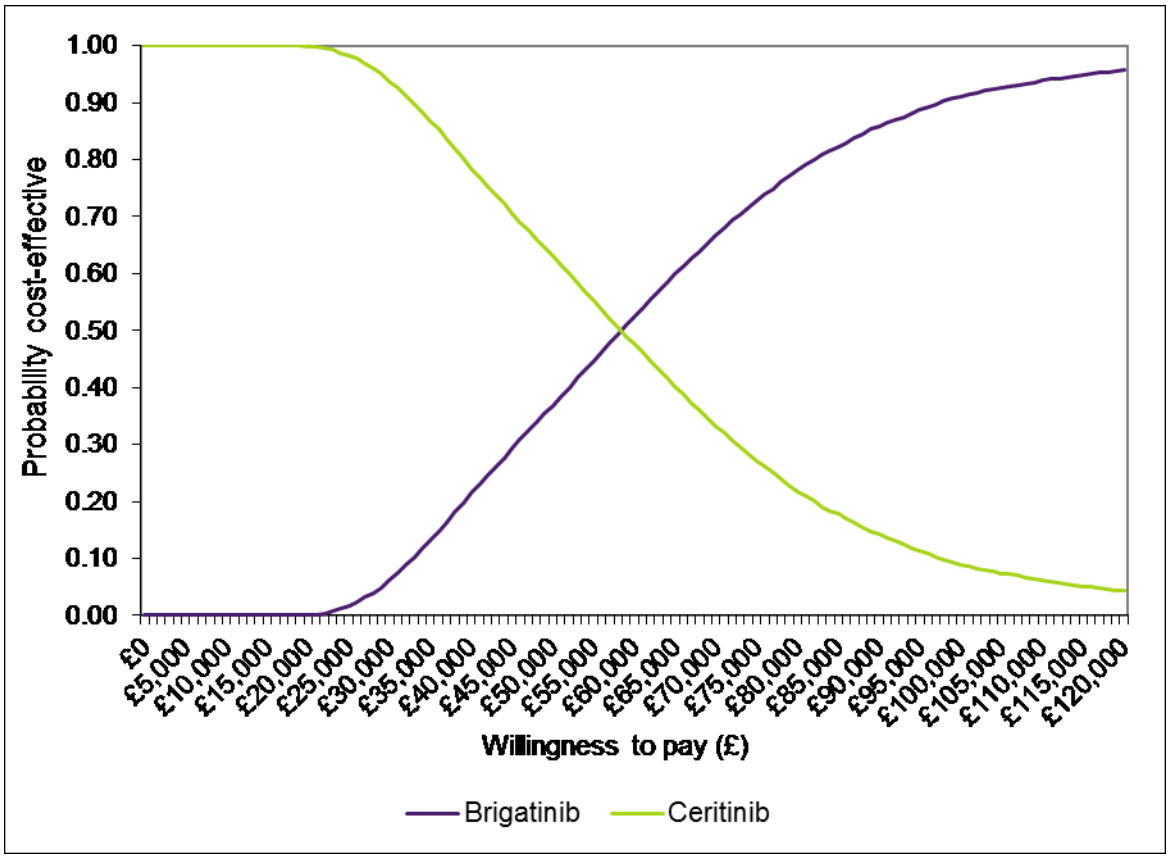
Figure 12: Cost-effectiveness plane from 10,000 iterations with uncertainty in OS and PFS curve selection accounted for (update of Figure 26)



Abbreviations: ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality adjusted life year; WTP, willingness-to-pay threshold.

Based on these 10,000 PSA iterations and the list price for brigatinib and ceritinib, the CEAC (Figure 13) suggests that there is a 36.87% likelihood of brigatinib being cost-effectiveness at a willingness-to-pay (WTP) of £50,000 per QALY (end of life threshold permitted by NICE).

Figure 13: CEAC with uncertainty in OS and PFS selection accounted for (update of Figure 27)



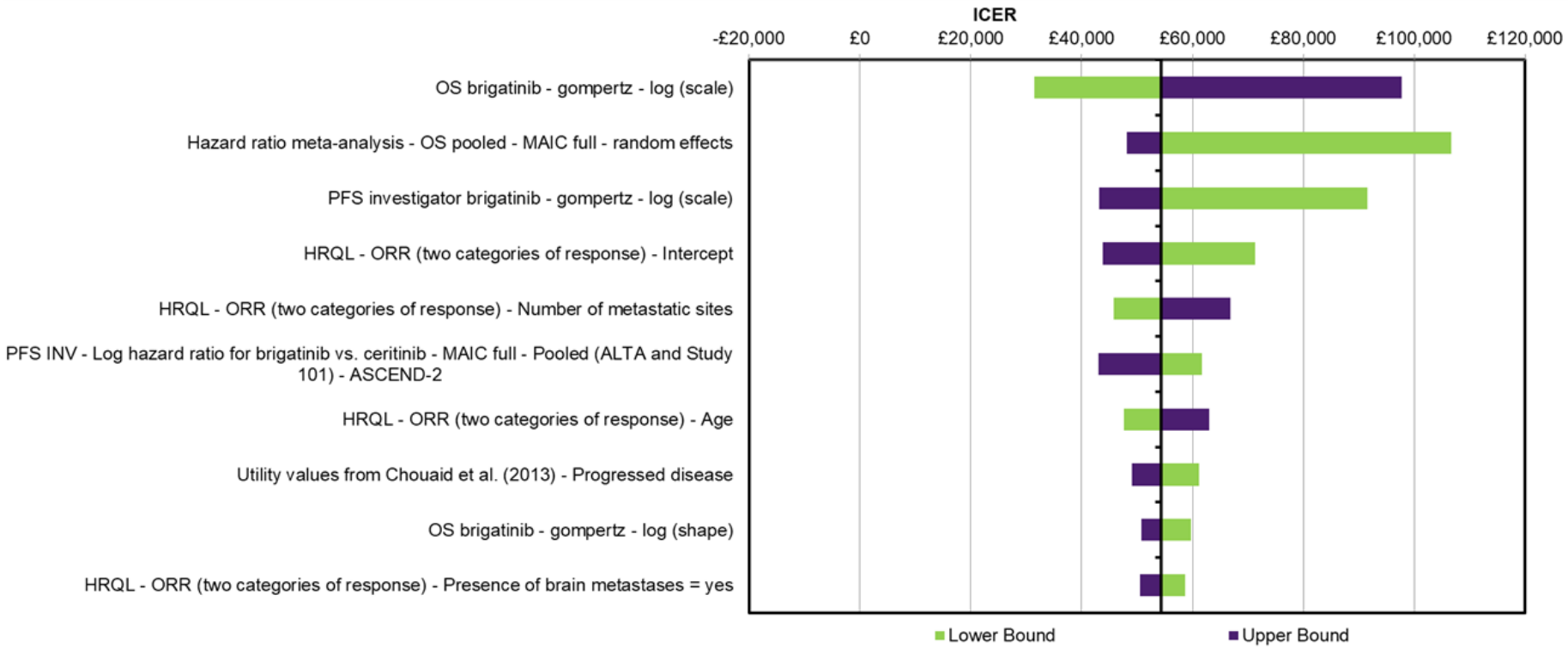
Abbreviations: CEAC, cost-effectiveness acceptability curve; OS, overall survival; PFS, progression-free survival

4.1.2.2 Deterministic sensitivity analysis (update of Section B.3.8.2)

Figure 14 presents a tornado diagram with the ten most influential parameters shown in descending order of ICER sensitivity.

Table 15 displays this information in a tabular format. The variables with the greatest impact on model outcomes were the parameters associated with brigatinib OS and PFS estimation, the HR applied for OS and PFS for ceritinib relative to brigatinib and utility values applied to the health states. The model is relatively insensitive to remaining parameters.

Figure 14: Tornado diagram (update of Figure 28)



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

Table 15: Numerical results of one-way sensitivity analysis (update of Table 54)

Parameter	Lower Bound	Upper Bound	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	£48,419.27
HRQL - ORR (two categories of response) - Intercept	£71,272	£43,870	£27,402.61
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
Abbreviations: HR, hazard ratio; HRQL, health-related quality of life; ICER, incremental cost-effectiveness ratio; INV, investigator assessed; MAIC, matching-adjusted indirect comparison; ORR, overall response rate; OS, overall survival; PFS, progression-free survival			

4.1.2.3 Scenario analysis (update of Section B.3.8.3)

The results from each of the scenario analyses are given in Table 16.

Table 16: Scenario analyses results (update of Table 56)

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%

Scenario	Incremental costs	Incremental QALYs	ICER	Difference from base case ICER
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				
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%

Scenario	Incremental costs	Incremental QALYs	ICER	Difference from base case ICER
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%
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	£61,097	1.1249	£54,311	0.00%

Scenario	Incremental costs	Incremental QALYs	ICER	Difference from base case ICER
101) - ASCEND-2				
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%
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	£61,097	1.1035	£55,368	1.95%

Scenario	Incremental costs	Incremental QALYs	ICER	Difference from base case ICER
et al. (2013) for progressed disease				
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

5. References

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6. Appendices

6.1 Update of Appendix J

6.1.1 Clinical outcomes from the model

Table 17 compares the updated clinical and base case model outcomes for the three main outcome measures: OS, PFS and ToT.

Table 17: Comparison of the clinical outcomes with the base case model outcomes (update of Table 30)

	Brigatinib		**Ceritinib**	
Outcome	**Clinical trial result**	**Model result**	**Clinical trial result**	**Model result**
Median outcomes (months)				
OS	Pooled = NA ALTA (Feb 2017) = 27.57 ALTA (Sept 2017) = 34.14	37.72	ASCEND-2 = 14.9 (95% CI: 13.5-NE) ASCEND-5 = 18.1 (95% CI: 13.4-23.9)	18.40
PFS INV	Pooled (Feb 2017) = 15.61 Pooled (Sept 2017) = 15.61 ALTA (Feb 2017) = 15.62 ALTA (Sept 2017) = 15.61	16.56	ASCEND-2 = 5.7 (95% CI: 5.4-7.6) ASCEND-5 = 6.7 (95% CI: 4.4-7.9)	7.36
ToT	ALTA (Feb 2017) = 17.15 ALTA (Sept 2017) = 17.15	17.48	NR	7.36
Mean outcomes (months)				
OS	Pooled (Feb 2017) = 24.31 Pooled (Sept 2017) = 27.50 ALTA (Feb 2017) = 24.11 Pooled (Sept 2017) = 27.68	46.83	NR	24.34
PFS INV	Pooled (Feb 2017) = 16.57 Pooled (Sept 2017) = 17.62 ALTA (Feb 2017) = 16.49 ALTA (Sept 2017) = 17.58	19.27	NR	8.84
ToT	ALTA (Feb 2017) = 17.81 ALTA (Sept 2017) = 19.20	20.81	NR	10.37

Abbreviations: CI, confidence interval; INV, investigator; NE, not evaluable; OS, overall survival; PFS, progression free survival; ToT, time on treatment

Markov traces

Markov traces are presented for brigatinib and ceritinib in Figure 15 and Figure 16, respectively.

Figure 15: Markov trace for patients treated with brigatinib (update of Figure 19)

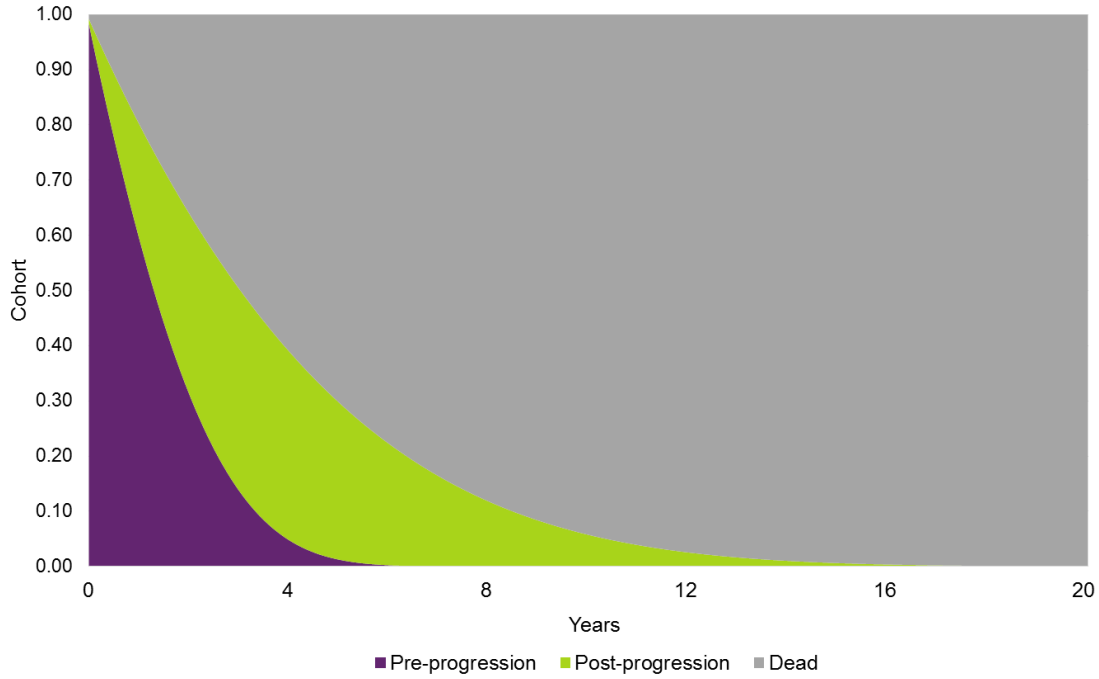
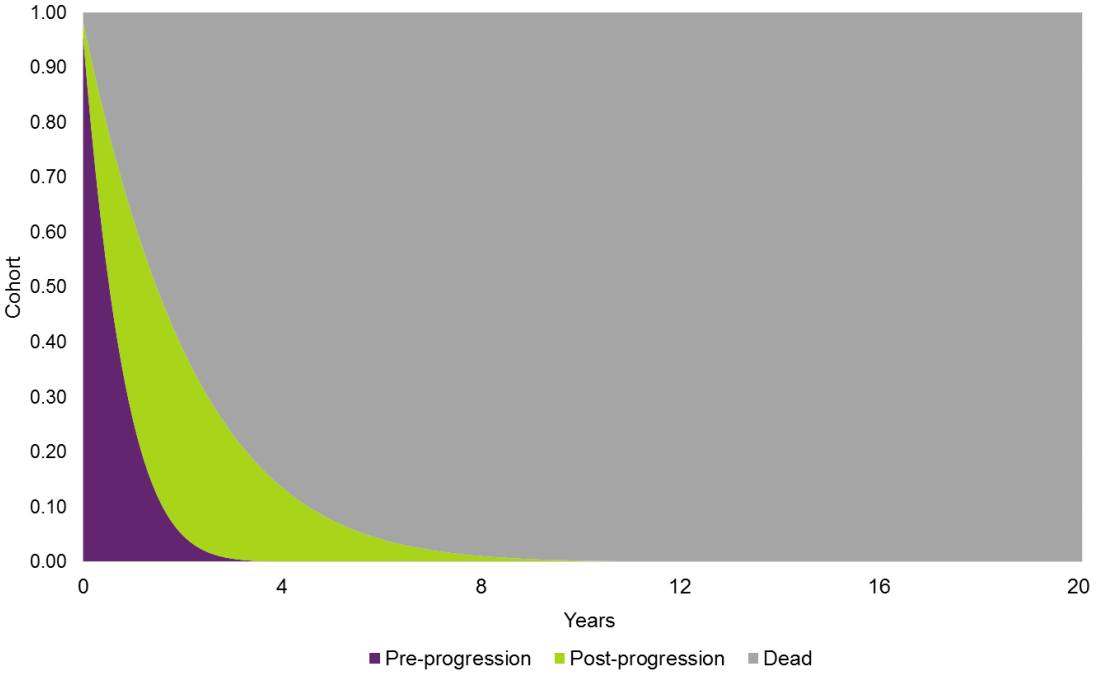
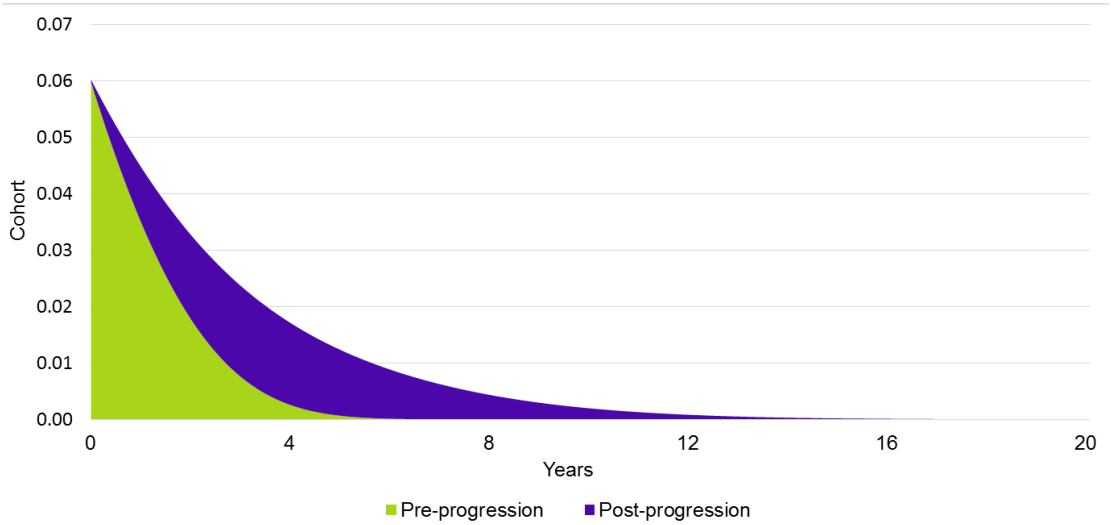


Figure 16: Markov trace for patients treated with ceritinib (update of Figure 20)



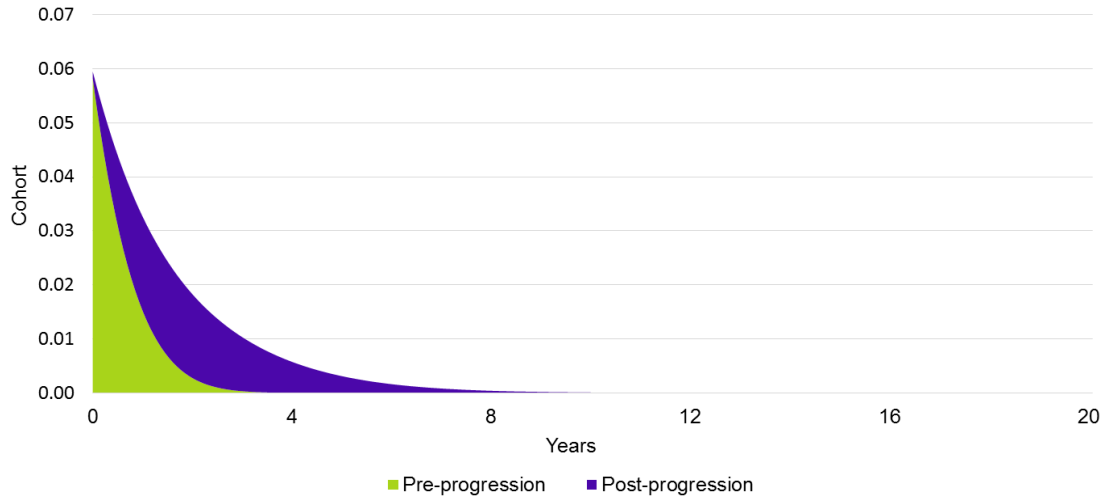
The accumulation of QALYs over time is shown in Figure 17 and Figure 18 for brigatinib and ceritinib, respectively. QALYs were subject to discounting at a rate of 3.5% per annum.

Figure 17: Accumulation of QALYs for patients treated with brigatinib (update of Figure 21)



Abbreviations: QALY, quality-adjusted life years

Figure 18: Accumulation of QALYs for patients treated with ceritinib (update of Figure 22)



Abbreviations: QALY, quality-adjusted life years

6.1.2 Disaggregated results of the base-case incremental cost-effectiveness analysis (update of Appendix J.1.2)

Life years

The total discounted life years gained by patients in each health state are shown in

Table **18**. Life years are discounted at an annual rate of 3.5%.

Table 18: Life years associated with brigatinib and ceritinib

Outcome	Brigatinib	Ceritinib	Increment	% Increment
Pre-progression	1.54	0.72	0.82	51.67%
Progressed disease	1.95	1.19	0.77	48.33%

QALYs

The total discounted QALYs gained by patients in each health state are shown in Table 19. These values are from the base case where QALYs are calculated using utilities obtained from a regression equation using the ALTA patient level data for pre-progression and Chouaid et al. (2013) for the progressed disease decrement. QALYs are discounted at an annual rate of 3.5%.

Table 19: QALYs associated with brigatinib and ceritinib

Outcome	Brigatinib	Ceritinib	Increment	Absolute increment	% Absolute increment
Pre-progression	1.22	0.57	0.63	0.65	57.26%
Progressed disease	1.24	0.76	0.40	0.48	42.61%
Adverse events	-0.0079	-0.0064	-0.0056	0.0015	0.13%
Abbreviations: QALY, quality-adjusted life years					

Costs

The total discounted costs accrued by patients in each health state are shown in Table 20. Costs are discounted at an annual rate of 3.5%. Most of the costs incurred by patients treated with brigatinib are accrued in the pre-progression health state, as the majority of patients discontinue treatment following disease progression. This is evident in Table 21, showing the summary of predicted resource use by category of cost in the base case analysis, where the costs incurred by brigatinib patients are primarily driven by drug costs.

Table 20: Total discounted costs by health state

	Brigatinib	Ceritinib	Increment	Absolute increment	% Absolute Increment
Pre-progression	£98,025	£42,093	£55,932	£55,932	91.55%
Progressed disease	£19,514	£14,246	£5,268	£5,268	8.62%
Terminal care costs	£1,490	£1,594	-£104	£104	0.17%
Total costs	£119,029	£57,932			

Table 21: Disaggregated total discounted costs

	Brigatinib	Ceritinib	Increment	Absolute Increment	% Absolute Increment
Treatment	£93,680	£42,052	£51,628	£51,628	84.50%
Concomitant medications	£1,231	£627	£604	£604	0.99%
Resource use - pre-progression	£6,863	£3,373	£3,489	£3,489	5.71%
Resource use - post-progression	£13,079	£7,956	£5,123	£5,123	8.39%
Terminal care	£1,490	£1,594	-£104	£104	0.17%
Adverse events	£2,687	£2,331	£356	£356	0.58%
Total costs	£119,029	£57,932			

6.2 Update of Appendix L

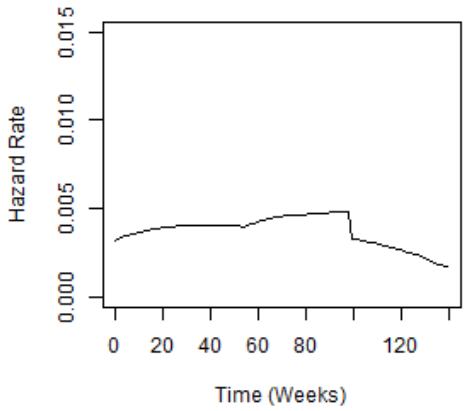
6.2.1 Overall survival (ALTA) (update of Appendix L.5.1.1a)

The ALTA data for OS were from the observed brigatinib data from ALTA (n=110). Table 22 summarises AIC and BIC values for each parametric survival distribution and Figure 19 presents the empirical hazard plot for OS using the ALTA data. The Kaplan-Meier curve and fitted parametric distributions are presented in Figure 20.

Table 22: Goodness-of-fit statistics for overall survival (OS), September 2017 data-cut ALTA (update of Table 35)

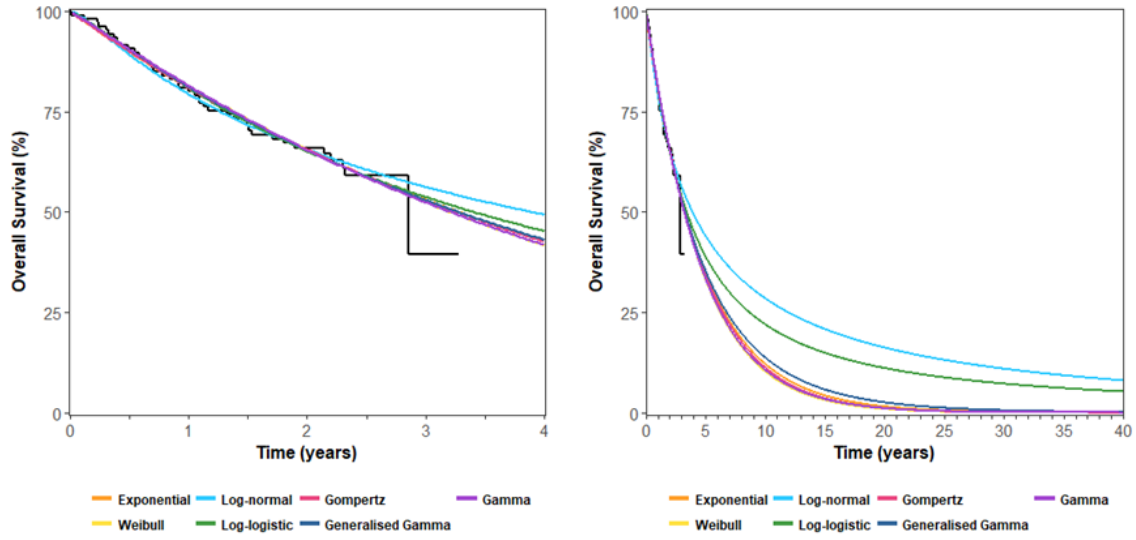
Model	AIC	BIC
Generalised gamma	526.27	534.37
Gamma	524.34	529.74
Log normal	526.88	532.28
Log logistic	524.11	529.52
Weibull	524.36	529.76
Gompertz	524.46	529.86
Exponential	522.46	525.16
Abbreviations: AIC, Akaike information criterion; BIC, Bayes information criterion; OS, overall survival		

Figure 19: Empirical hazard plot for OS, September 2017 data-cut ALTA (update of Figure 23)



Abbreviations: OS, overall survival

Figure 20: Kaplan-Meier curve and fitted parametric distributions for OS, September 2017 data-cut ALTA (update of Figure 24)



Abbreviations: OS, overall survival

6.2.2 Progression-free survival investigator assessed (ALTA) (update of Appendix L.5.1.1b)

The ALTA data for PFS INV were obtained from the observed brigatinib data from ALTA (n=110). Table 23 summarises AIC and BIC values for each parametric survival distribution and Figure 21 presents the empirical hazard plot for PFS INV using the ALTA data. The Kaplan-Meier curve and fitted parametric distributions are presented in

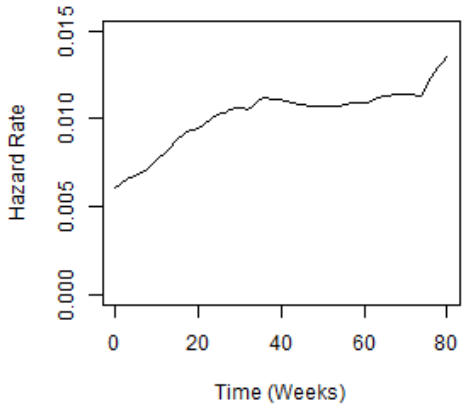
Figure 22.

Table 23: Goodness-of-fit statistics for PFS INV-assessed, September 2017 data-cut ALTA (update of Table 36)

Model	AIC	BIC
Generalised gamma	712.59	720.69
Gamma	710.61	716.01
Log normal	718.12	723.52
Log logistic	712.22	717.62
Weibull	710.62	716.02
Gompertz	711.42	716.82
Exponential	711.64	714.34

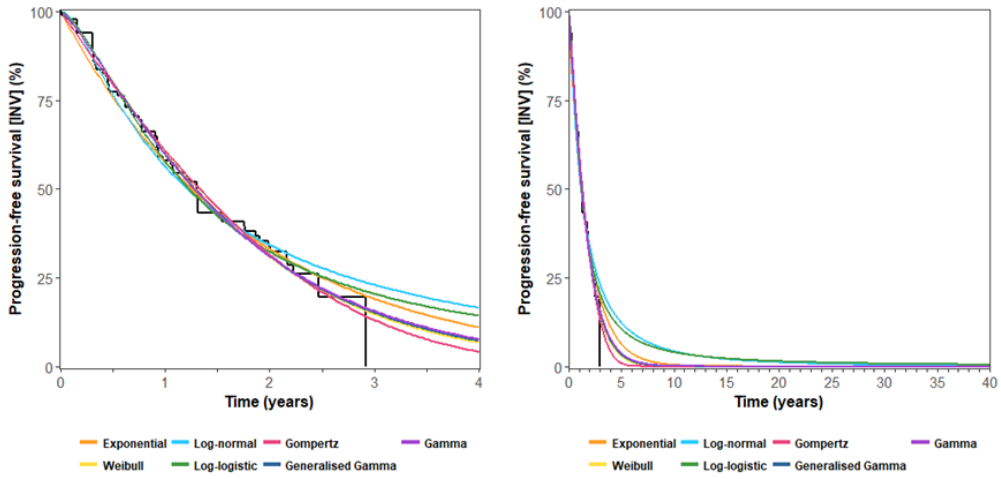
Abbreviations: AIC, Akaike information criterion; BIC, Bayes information criterion; INV, investigator; PFS, progression-free survival

Figure 21: Empirical hazard for PFS INV-assessed, September 2017 data-cut ALTA (update of Figure 25)



Abbreviations: INV, investigator; PFS, progression-free survival

Figure 22: **Kaplan-Meier curve and fitted parametric distributions for PFS INV-assessed, September 2017 data-cut ALTA (update of Figure 26)**



Abbreviations: INV, investigator; PFS, progression-free survival

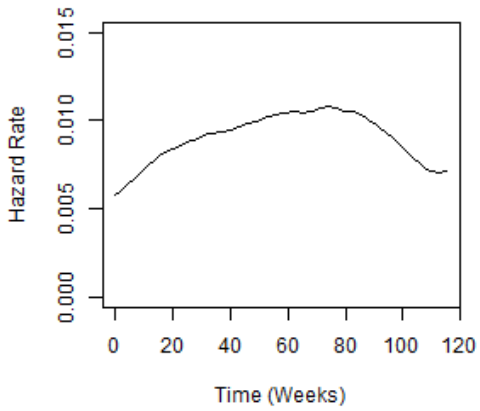
6.2.3 Progression-free survival (PFS) independent review committee (IRC) assessed (ALTA) (update of Appendix L.5.1.2)

The ALTA data for PFS IRC were obtained from the observed brigatinib data from ALTA (n=110). Table 24 summarises AIC and BIC values for each parametric survival distribution and Figure 23 presents the empirical hazard plot for PFS IRC using the ALTA data. The Kaplan-Meier curve and fitted parametric distributions are presented in Figure 24.

Table 24: **Goodness-of-fit statistics for PFS IRC-assessed, September 2017 data-cut ALTA (update of Table 37)**

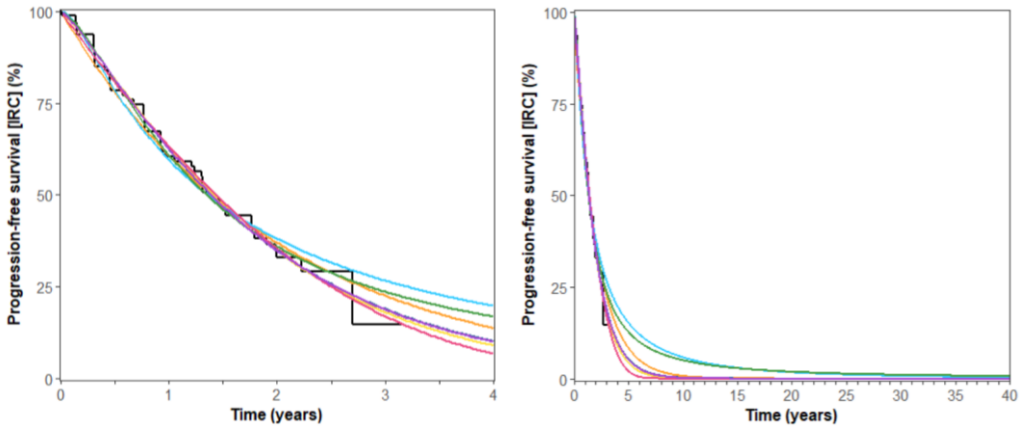
Model	AIC	BIC
Generalised gamma	613.72	621.82
Gamma	611.72	617.12
Log normal	617.32	622.72
Log logistic	612.53	617.93
Weibull	611.81	617.21
Gompertz	612.75	618.15
Exponential	612.09	614.79
Abbreviations: AIC, Akaike information criterion; BIC, Bayes information criterion; IRC, independent review committee; PFS, progression-free survival		

Figure 23: Empirical hazard for PFS IRC-assessed, September 2017 data-cut ALTA (update of Figure 27)



Abbreviations: IRC, independent review committee; PFS, progression-free survival

Figure 24: Kaplan-Meier curve and fitted parametric distributions for PFS IRC-assessed, September 2017 data-cut ALTA (update of Figure 28)



Abbreviations: IRC, independent review committee; PFS, progression-free survival

6.2.4 Time on treatment (ALTA) (update of Appendix L.5.1.3)

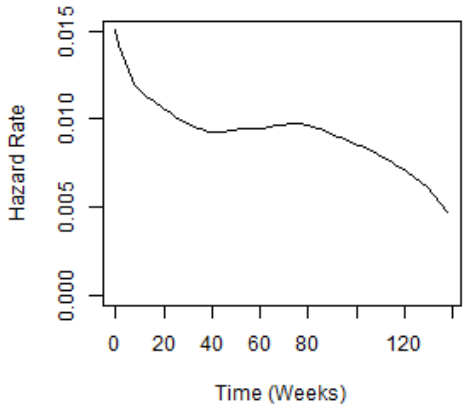
The ALTA data for ToT were obtained from the observed brigatinib data from ALTA (n=110). Table 25 summarises AIC and BIC values for each parametric survival distribution and Figure 25 presents the empirical hazard plot for OS using the ALTA data. The Kaplan-Meier curve and fitted parametric distributions are presented in Figure 26.

Table 25: Goodness-of-fit statistics for ToT, September 2017 data-cut ALTA (update of Table 38)

Model	AIC	BIC
Generalised gamma	877.91	886.01
Gamma	877.06	882.46
Log normal	893.17	898.57
Log logistic	884.30	889.70

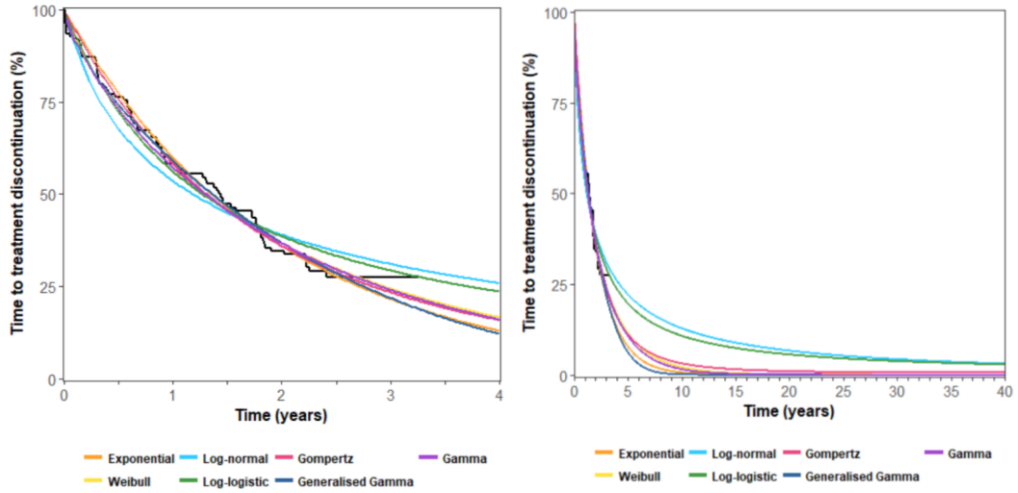
Model	AIC	BIC
Weibull	877.85	883.25
Gompertz	880.49	885.89
Exponential	878.93	881.63
Abbreviations: AIC, Akaike information criterion; BIC, Bayes information criterion; ToT, time on treatment		

Figure 25: Empirical hazard for ToT, September 2017 data-cut ALTA (update of Figure 29)



Abbreviations: ToT, time on treatment

Figure 26: Kaplan-Meier curve and fitted parametric distributions for ToT, September 2017 data-cut ALTA (update of Figure 30)



Abbreviations: ToT, time on treatment

6.2.5 Indirect treatment comparisons (update of Appendix L.5.2)

6.2.5.1 Response (update of Appendix L.5.2.10)

Scenario analyses explore the impact of four categories of response based on ORR and best overall response (BoR) (complete response, partial response, stable disease and progressive disease) in the pre-progression health state on HRQL. To apply these scenarios

within the model, the proportion of patients in each of the response categories for brigatinib and ceritinib is required. These estimates are available for brigatinib from ALTA for ORR INV, ORR IRC, BoR INV and BoR IRC.

The relative efficacy for ceritinib compared with brigatinib is obtained from ITCs. Table 26 presents the odds ratios for brigatinib relative to ceritinib for response associated with each combination of ITC method, covariate list, brigatinib data source, ceritinib data source and ORR assessment. BoR data were unavailable from ASCEND-2 and ASCEND-5. Therefore, all comparative efficacy estimates were based on ORR. Scenario analyses consider the impact on results of the different methods of ITCs for response. To utilise all the brigatinib data and all the ceritinib data, meta-analyses of the individual MAICs were conducted. The results of these meta-analyses are presented in Table 26.

Table 26: Odds ratios for brigatinib vs. ceritinib associated with response using the September 2017 data-cut from the ALTA trial (update of Table 39)

Method	Covariate list	Brigatinib data source	Ceritinib data source	Response assessment	Odds ratio brigatinib vs. ceritinib
Naïve ITC	NA	ALTA	ASCEND-2	ORR INV	2.06
MAIC	Full	ALTA	ASCEND-2	ORR INV	1.85
MAIC	Reduced	ALTA	ASCEND-2	ORR INV	1.91
Naïve ITC	NA	ALTA	ASCEND-5	ORR IRC	2.01
MAIC	Full	ALTA	ASCEND-5	ORR IRC	2.62
MAIC	Reduced	ALTA	ASCEND-5	ORR IRC	1.92
FE meta-analysis of naïve ITC	NA	ALTA	ASCEND-2 and ASCEND-5	Pooled	2.10
RE meta-analysis of naïve ITC	NA	ALTA	ASCEND-2 and ASCEND-5	Pooled	2.12
FE meta-analysis of MAICs	Full	ALTA	ASCEND-2 and ASCEND-5	Pooled	2.03
RE meta-analysis of MAICs	Full	ALTA	ASCEND-2 and ASCEND-5	Pooled	2.03
FE meta-analysis of MAICs	Reduced	ALTA	ASCEND-2 and ASCEND-5	Pooled	1.91
RE meta-analysis of MAICs	Reduced	ALTA	ASCEND-2 and ASCEND-5	Pooled	1.90

Abbreviations: FE, fixed effects; INV, investigator assessed; IRC, independent review committee; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; NA, not applicable; ORR, overall response rate; RE, random effects

6.2.6 Adverse event rates (update of appendix L.5.3)

The probabilities of experiencing grade 3/4 adverse events per cycle for brigatinib and ceritinib are presented in Table 27. Probabilities associated with adverse events introduced by the September 2017 data cut are highlighted in **bold**.

Table 27: Per-cycle probabilities of experiencing grade 3/4 adverse events; September 2017 data-cut from the ALTA trial (update of Table 40)

Grade 3/4 adverse events	Average duration (days)	Brigatinib			Ceritinib cycle probability
		No. of events	Rate	Cycle probability	
Anaemia	32	2	0.0114	0.0009	0.0014
Appendicitis	4	2	0.0114	0.0009	0.0009*
Asthenia	NA	1	0.0057	0.0004	0.0054
Behcet's syndrome	**NA**	**1**	**0.0057**	**0.0004**	**0.0004***
Cardiac failure	**NA**	**1**	**0.0057**	**0.0004**	**0.0004***
Cardiac arrhythmia	2	3	0.0170	0.0013	0.0013*
Cataract	78	2	0.0114	0.0009	0.0009*
Cellulitis	12	1	0.0057	0.0004	0.0004*
Clostridium difficile colitis	**36**	**1**	**0.0057**	**0.0004**	**0.0004***
Coagulation	7	1	0.0057	0.0004	0.0004*
Cognitive disorder	NA	2	0.0114	0.0009	0.0009*
Confusional state	5	2	0.0114	0.0009	0.0009*
Decreased appetite	18	2	0.0114	0.0009	0.0032
Dermatitis allergic	8	1	0.0057	0.0004	0.0004*
Device occlusion	5	1	0.0057	0.0004	0.0004*
Diabetes mellitus	NA	1	0.0057	0.0004	0.0004*
Dysarthria	8	1	0.0057	0.0004	0.0004*
Dyspepsia	11	1	0.0057	0.0004	0.0004*
Dyspnoea	13	3	0.0170	0.0013	0.0063
Electrocardiogram QT prolonged	4	3	0.0170	0.0013	0.0013*
Food poisoning	2	1	0.0057	0.0004	0.0004*
Generalised tonic-clonic seizure	**1**	**1**	**0.0057**	**0.0004**	**0.0004***
Haemoptysis	3	1	0.0057	0.0004	0.0004*
Haemorrhagic anaemia	1	1	0.0057	0.0004	0.0004*
Hepatic function abnormal	NA	1	0.0057	0.0004	0.0004*
Hydronephrosis	5	1	0.0057	0.0004	0.0004*
Hyperglycaemia	**2**	**1**	**0.0057**	**0.0004**	**0.0018**
Hyperlipaseamia	8	1	0.0057	0.0004	0.0004*
Hypertension	22	17	0.0966	0.0074	0.0074*
Hyponatraemia	23	7	0.0398	0.0030	0.0030*
Hypophosphataemia	**NA**	**1**	**0.0057**	**0.0004**	**0.0014***
Hypoxia	190	4	0.0227	0.0017	0.0017*
Infusion site thrombosis	26	1	0.0057	0.0004	0.0004*
Intermittent claudication	NA	1	0.0057	0.0004	0.0004*
Jaundice cholestasis	4	1	0.0057	0.0004	0.0004*
Laboratory results (including neutropenia, hypokalaemia pericardial effusion and hypophosphatemia)	17	55	0.3124	0.0239	0.0620
Liver disorder	11	11	0.0625	0.0048	0.0048*
Macular oedema	36	1	0.0057	0.0004	0.0004*
Malignant pleural effusion	7	4	0.0227	0.0017	0.0017*
Meningitis bacterial	**13**	**1**	**0.0057**	**0.0004**	**0.0004***
Muscular weakness		1	0.0057	0.0004	0.0004*
Nausea/vomiting/diarrhoea/constipation	18	1	0.0057	0.0004	0.0226

Grade 3/4 adverse events	Average duration (days)	Brigatinib			Ceritinib cycle probability
		No. of events	Rate	Cycle probability	
Nervous system disorder	NA	1	0.0057	0.0004	0.0004*
Osteoarthritis	NA	1	0.0057	0.0004	0.0004*
Osteonecrosis	42	1	0.0057	0.0004	0.0004*
Pain	25	14	0.0795	0.0061	0.0032
Pancreatic disorder	9	4	0.0227	0.0017	0.0017*
Paraesthesia	1	2	0.0114	0.0009	0.0009*
Peripheral artery stenosis	37	1	0.0057	0.0004	0.0004*
Peripheral sensory neuropathy	85	1	0.0057	0.0004	0.0004*
Photosensitivity reaction	19	1	0.0057	0.0004	0.0004*
Pleural effusion	61	1	0.0057	0.0004	0.0004*
Pneumonia	13	14	0.0795	0.0061	0.0023
Pulmonary embolism	155	3	0.0170	0.0013	0.0013*
Pyrexia	1	1	0.0057	0.0004	0.0027
Radiation necrosis	7	1	0.0057	0.0004	0.0004*
Respiratory infection	4	1	0.0057	0.0004	0.0004*
Simple partial seizures	2	2	0.0114	0.0009	0.0009*
Skin infection	**54**	**1**	**0.0057**	**0.0004**	**0.0004***
Subcutaneous abscess	46	1	0.0057	0.0004	0.0004*
Swelling/rash	12	6	0.0341	0.0026	0.0026*
Syncope	3	2	0.0114	0.0009	0.0009*
Tooth abscess	8	1	0.0057	0.0004	0.0004*
Tooth socket haemorrhage	**6**	**1**	**0.0057**	**0.0004**	**0.0004***
Tuberculosis pleurisy	NA	1	0.0057	0.0004	0.0004*
Urosepsis	6.00	1	0.0057	0.0004	0.0004*
Weight decreased / fatigue / general health deterioration / dehydration	NA	1	0.0057	0.0004	0.0140

Abbreviations: NA, not available

*Data unavailable for ceritinib and so assumed equal to brigatinib

Notes: Inputs which have been updated based on the September 2017 data cut are highlighted in bold.

6.2.7 Adverse event costs (update of Appendix L.5.5)

Table 28 presents the unit costs used in the model for each included adverse event. Note no unit costs were changed for adverse events included in the original submission dossier. Unit costs associated with additional adverse events included based on the September 2017 data cut are highlighted in **bold**.

Table 28: Unit costs associated with grade 3/4 adverse events (update of Table 43)

Adverse event	Cost of adverse event	Source
Anaemia	£1,170.78	*NHS Reference Costs 2016/17; Total HRGs, Haemolytic anaemia with CC score 0-2 and 3+, SA03G, SA03H.*
Appendicitis	£3,149.58	*NHS Reference Costs 2016/17; Total HRGs, Appendicetomy procedures, 19 years and over, with CC score 0 and 1-2, FF37C and FF37D.*
Asthenia	£1,574.27	*NHS Reference Costs 2016/17; Total HRGs, Nutritional disorders with interventions, with CC score 0-1 and 2+*

Adverse event	Cost of adverse event	Source
		and nutritional disorders without interventions with CC score 0-1, 2-5 and 6+, FD04B, FD04A, FD04E, FD04D and FD04C.
Behcet's syndrome	**£837.42**	***NHS Reference Costs 2016/17; Total HRGs, Other Red Blood Cell Disorders, with CC score 14+, 10-13, 6-9, 2-5, 0-1, SA09G, SA09H, SA09J, and SA09K***
Cardiac failure	**£1,445.48**	***NHS Reference Costs 2016/17; Total HRGs, Cardiac Arrest, with CC score 9+, 5-9, 0-4, EB05A, EB05B, and EB05C***
Cardiac arrhythmia	£1,243.30	*NHS Reference Costs 2016/17; Total HRGs, Arrhythmia or conduction disorders, with CC score 7-9, EB07C.*
Cataract	£1,143.18	*NHS Reference Costs 2016/17; Total HRGs, Complex, cataract or lens procedures with CC score 0-1 and 2+, very major, cataract or lens procedures, with CC score 0-1 and 2+, intermediate, cataract or lens procedures with CC score 0-1 and 2+, BZ30B, BZ30A, BZ31B, BZ31A, BZ32B and BZ32A.*
Cellulitis	£3,208.00	*NHS Reference Costs 2016/17; Total HRGs, Skin disorders with interventions with CC score 0-3, 4-7, 8-11 and 12+, JD07D, JD07C, JD07B and JD07A.*
Clostridium difficile colitis	**£3,763.15**	***NHS Reference Costs 2016/17; Total HRGs, Gastrointestinal Infections with Single Intervention, with CC score 5+, 2-4, 0-1, FZ36J, FZ36K, and FZ36L***
Coagulation	£882.74	*NHS Reference Costs 2016/17; Total HRGs, Coagulation defect with CC score 2-4, SA02H.*
Cognitive disorder	£1,499.34	*NHS Reference Costs 2016/17; Total HRGs, Tendency to fall, senility or other conditions affecting cognitive functions, with multiple interventions and Tendency to fall, senility or other conditions affecting cognitive functions, with single intervention with CC score 0-2 and 3+ and Tendency to fall, senility or other conditions affecting cognitive functions, without interventions with CC score 0-1, 2-3, 4-5 and 6+, WH09A, WH09C, WH09B, WH09G, WH09F, WH09E and WH09D.*
Confusional state	£1,831.88	*NHS Reference Costs 2016/17; Total HRGs, Cerebral degenerations or miscellaneous disorders of nervous system, with CC score 0-4, 5-7, 8-10, 11-13 and 14+, AA25G, AA25F, AA25E, AA25D and AA25C. .*
Decreased appetite	£1,574.27	*NHS Reference Costs 2016/17; Total HRGs, Nutritional disorders with interventions, with CC score 0-1 and 2+ and nutritional disorders without interventions with CC score 0-1, 2-5 and 6+, FD04B, FD04A, FD04E, FD04D and FD04C.*
Dermatitis allergic	£457.48	*NHS Reference Costs 2016/17; Total HRGs, Allergy or adverse allergic reaction, WH05Z.*
Device occlusion	£593.85	*NHS Reference Costs 2016/17; Total HRGs, Admission related to the fitting, adjustment or management of device with interventions and without interventions, WH18A, WH18B.*
Diabetes and hyperglycaemia	£1,103.81	*NHS Reference Costs 2016/17; Total HRGs, Diabetes with hypoglycaemic disorders, with CC score 0-2, 3-4, 5-7 and 8+, 0-1, 2-4, 5-7 and 8+, KB01F, KB01E, KB01D, KB01C, KB02K, KB02J, KB02H and KB02G.*
Dysarthria	£2,840.06	*NHS Reference Costs 2016/17; Total HRGs, Motor Neuron Disease with CC score 0-1, 2-4, 5-7 and 8+, AA28F, AA28E, AA28D and AA28C.*

Adverse event	Cost of adverse event	Source
Dyspepsia	£3,663.31	*NHS Reference Costs 2016/17; Total HRGs, Non-malignant gastrointestinal tract disorders with multiple interventions with CC score 0-2, 3-4, 5-7 and 8+ and with single intervention with CC score 0-2, 3-4, 5-8 and 9+, FD10D, FD10C, FD10B, FD10A, FD10H, FD10G, FD10F and FD10E.*
Dyspnoea	£680.16	*NHS Reference Costs 2016/17; Total HRGs, Other respiratory disorders with multiple interventions, with single intervention with CC score 0-4 and 5+ and without interventions with CC score 0-4, 5-10 and 11+, DZ19H, DZ19K, DZ19J, DZ19N, DZ19M and DZ19L.*
Electrocardiogram QT prolonged	£133.43	*NHS Reference Costs 2016/17; Total HRGs, Electrocardiogram monitoring or stress testing, EY51Z.*
Food poisoning	£610.99	*NHS Reference Costs 2016/17; Total HRGs, Poisoning diagnosis with multiple interventions, with single interventions with CC score 0-1 and 2+ and without interventions with CC score 0-1 and 2+, WH04A, WH04C, WH04B, WH04E and WH04D.*
Generalised tonic-clonic seizure/cerebrovascular accident/embolic stroke	**£3,278.79**	***NHS Reference Costs 2016/17; Total HRGs, Stroke, with CC score 16+, 13-15, 10-12, 7-9, 4-6, 0-3, AA35A, AA35B, AA35C, AA35D, AA35E, and AA35F***
Haemoptysis	£1,057.56	*NHS Reference Costs 2016/17; Total HRGs, Other haematological or splenic disorders with CC score 0-2, 3-5 and 6+, SA08J, SA08H and SA08G.*
Haemorrhagic anaemia	£837.42	*NHS Reference Costs 2016/17; Total HRGs, Other red blood cell disorders with CC score 0-1, 2-5, 6-9, 10-13 and 14+, SA09L, SA09K, SA09J, SA09H and SA09G.*
Hepatic function abnormal	£2,387.96	*NHS Reference Costs 2016/17; Total HRGs, Liver failure with multiple interventions, with single intervention and without interventions with CC score 0-4 and 5+, GC01C, GC01D, GC01F and GC01E.*
Hydronephrosis	£4,114.98	*NHS Reference Costs 2016/17; Total HRGs, Chronic kidney disease with interventions with CC score 0-2, 3-5 and 6+ and general renal disorders with interventions with CC score 0-2, 3-5 and 6+, LA08J, LA08H, LA08G, LA09L, LA09K and LA09J.*
Hyperglycaemia	**£1,053.80**	***NHS Reference Costs 2016/17; Total HRGs, Diabetes with Hyperglycaemic Disorders, with CC Score 8+, 5-7, 2-4, 0-1, KB02G, KB02H, KB02J, and KB02K***
Hyperlipaseamia	£4,396.99	*NHS Reference Costs 2016/17; Total HRGs, Non-malignant hepatobiliary or pancreatic disorders with multiple interventions with CC score 0-3, 4-8 and 9+, with single interventions with CC score 0-3, 4-8 and 9+, GC17C, GC17B, GC17A, GC17F, GC17E, GC17D.*
Hypertension	£713.21	*NHS Reference Costs 2016/17; Total HRGs, Hypertension, EB04Z.*
Hyponatraemia	£1,574.27	*NHS Reference Costs 2016/17; Total HRGs, Nutritional disorders with interventions, with CC score 0-1 and 2+ and nutritional disorders without interventions with CC score 0-1, 2-5 and 6+, FD04B, FD04A, FD04E, FD04D and FD04C.*
Hypophosphataemia	£879.50	*NHS Reference Costs 2016/17; Total HRGs, Other Endocrine Disorders with CC Score 4+, 2-3, 0-1, KA08A, KA08B, and KA08C*

Adverse event	Cost of adverse event	Source
Hypoxia	£156.10	*NHS Reference Costs 2016/17; Total HRGs, Oxygen assessment and monitoring, DZ38Z.*
Infusion site thrombosis	£613.54	*NHS Reference Costs 2016/17; Total HRGs, deep vein thrombosis with CC score 0-2, 3-5, 6-8, 9-11 and 12+, YQ51E, YQ51D, YQ51C, YQ51B and YQ51A.*
Intermittent claudication	£1,002.41	*NHS Reference Costs 2016/17; Total HRGs, Musculoskeletal signs or symptoms with CC score 0-3, 4-7, 8-11 and 12+, HD26G, HD26F, HD26E and HD26D.*
Jaundice cholestasis	£923.06	*NHS Reference Costs 2016/17; Total HRGs, Non-obstructive jaundice with CC score 0-4 and 5+, GC18B and GC18A.*
Laboratory results (including neutropenia, hypokalaemia pericardial effusion and hypophosphatemia)	£164.19	*NHS Reference Costs 2016/17; Total Outpatient Attendances Medical Oncology 370 and DAPs, Haematology DAPS05.*
Liver disorder	£2,387.96	*NHS Reference Costs 2016/17; Total HRGs, Liver failure with multiple interventions, with single intervention and without interventions with CC score 0-4 and 5+, GC01C, GC01D, GC01F and GC01E.*
Macular oedema	£603.01	*NHS Reference Costs 2016/17; Total HRGs, Non-surgical ophthalmology with interventions BZ24D and macular oedema drugs, band 1, XD55Z.*
Malignant pleural effusion	£1,776.89	*NHS Reference Costs 2016/17; Total HRGs, Pleural effusion with multiple interventions with CC score 0-5, 6-10 and 11+, with single intervention with CC score 0-5, 6-10 and 11+ and without interventions with CC score 0-5, 6-10 and 11+, DZ16K, DZ16J, DZ16H, DZ16N, DZ16M, DZ16L, DZ16R, DZ16Q and DZ19P.*
Meningitis bacterial	**£9,786.81**	***NHS Reference Costs 2016/17; Total HRGs, Spinal Infection with Interventions, with CC Score 6+, 0-5, HC31H and HC31J***
Muscular weakness	£1,002.41	*NHS Reference Costs 2016/17; Total HRGs, Musculoskeletal signs or symptoms with CC score 0-3, 4-7, 8-11 and 12+, HD26G, HD26F, HD26E and HD26D.*
Nausea/vomiting/diarrhoea/constipation	£3,663.31	*NHS Reference Costs 2016/17; Total HRGs, Non-malignant gastrointestinal tract disorders with multiple interventions with CC score 0-2, 3-4, 5-7 and 8+ and with single intervention with CC score 0-2, 3-4, 5-8 and 9+, FD10D, FD10C, FD10B, FD10A, FD10H, FD10G, FD10F and FD10E.*
Nervous system disorder	£1,831.88	*NHS Reference Costs 2016/17; Total HRGs, Cerebral degenerations or miscellaneous disorders of nervous system, with CC score 0-4, 5-7, 8-10, 11-13 and 14+, AA25G, AA25F, AA25E, AA25D and AA25C. .*
Osteoarthritis	£678.27	*NHS Reference Costs 2016/17; Total HRGs, Rehabilitation for inflammatory arthritis VC20Z and inflammatory, spine, joint or connective tissue disorders with CC score 0-2, 3-4, 5-6, 7-8, 9-11 and 12+, HD23J, HD23H, HD23G, HD23F, HD23E and HD23D.*
Osteonecrosis	£1,305.16	*NHS Reference Costs 2016/17; Total HRGs, Non-inflammatory, bone or joint disorders with CC score 0-1, 2-4, 5-7, 8-11 and 12+, HD24H, HD24G, HD24F, HD24E, HD24D.*
Pain	£1,138.33	*NHS Reference Costs 2016/17; Total HRGs, Unspecified pain with CC score 0 and 1+, WH08B, WH08A.*

Adverse event	Cost of adverse event	Source
Pancreatic disorder	£1,469.75	*NHS Reference Costs 2016/17; Total HRGs, Non-malignant hepatobiliary or pancreatic disorders without interventions with CC score 2-4, GC17J.*
Paraesthesia	£1,277.41	*NHS Reference Costs 2016/17; Total HRGs, Muscular, balance, cranial or peripheral nerve disorders, epilepsy or head injury with CC score 0-2, 3-5, 6-8, 9-11, 12-14 and 15+, AA26H, AA26G, AA26F, AA26E, AA26D and AA26C.*
Peripheral artery stenosis	£1,704.87	*NHS Reference Costs 2016/17; Total HRGs, Other acquired cardiac conditions with CC score 0-2, 3-5, 6-8, 9-12 and 13+. EB14E, EB14D, EB14C, EB14B and EB14A.*
Peripheral sensory neuropathy	£1,277.41	*NHS Reference Costs 2016/17; Total HRGs, Muscular, balance, cranial or peripheral nerve disorders, epilepsy or head injury with CC score 0-2, 3-5, 6-8, 9-11, 12-14 and 15+, AA26H, AA26G, AA26F, AA26E, AA26D and AA26C.*
Photosensitivity reaction	£88.96	*NHS Reference Costs 2016/17; Total HRGs, Photodynamic therapy JC46Z and Phototherapy or photochemotherapy, 13 years and over JC47A.*
Pleural effusion	£1,776.89	*NHS Reference Costs 2016/17; Total HRGs, Pleural effusion with multiple interventions with CC score 0-5, 6-10 and 11+, with single intervention with CC score 0-5, 6-10 and 11+ and without interventions with CC score 0-5, 6-10 and 11+, DZ16K, DZ16J, DZ16H, DZ16N, DZ16M, DZ16L, DZ16R, DZ16Q and DZ19P.*
Pneumonia	£4,195.65	*NHS Reference Costs 2016/17; Total HRGs, Lobar, atypical or viral pneumonia with multiple interventions with CC score 0-8, 9-13 and 14+ and with single intervention with CC score 0-7, 8-12 and 13+.*
Pulmonary embolism	£1,432.27	*NHS Reference Costs 2016/17; Total HRGs, Pulmonary embolus with interventions with CC score 0-8 and 9+ and without interventions with CC score 0-2, 3-5, 6-8, 9-11 and 12+.*
Pyrexia	£947.54	*NHS Reference Costs 2016/17; Total HRGs, Fever of unknown origin with interventions with CC score 0-3 ad 4+ and without interventions with CC score 0-3 and 4+, WJ07B, WJ07A, WJ07D and WJ07C.*
Radiation necrosis	£1,898.42	*NHS Reference Costs 2016/17; Total HRGs, Infections or other complications of procedures with multiple interventions with CC score 0-1 and 2+, with single intervention with CC score 0-1 and 2+ and without interventions with CC score 0-1, 2-3 and 4+, WH07B, WH07A, WH07D, WH07C, WH07G, WH07F and WH07E.*
Respiratory infection	£3,761.42	*NHS Reference Costs 2016/17; Total HRGs, Unspecified acute lower respiratory infection with interventions with CC score 0-8 and 9+, DZ22L and DZ22K.*
Simple partial seizures	£1,831.88	*NHS Reference Costs 2016/17; Total HRGs, Cerebral degenerations or miscellaneous disorders of nervous system, with CC score 0-4, 5-7, 8-10, 11-13 and 14+, AA25G, AA25F, AA25E, AA25D and AA25C. .*
Skin infection	**£3,208.00**	***NHS Reference Costs 2016/17; Total HRGs, Skin disorders with interventions with CC score 0-3, 4-7, 8-11 and 12+, JD07D, JD07C, JD07B and JD07A.***
Subcutaneous abscess	£3,208.00	*NHS Reference Costs 2016/17; Total HRGs, Skin disorders with interventions with CC score 0-3, 4-7, 8-11 and 12+, JD07D, JD07C, JD07B and JD07A.*
Swelling/rash	£3,208.00	*NHS Reference Costs 2016/17; Total HRGs, Skin disorders with interventions with CC score 0-3, 4-7, 8-11*

Adverse event	Cost of adverse event	Source
		and 12+, JD07D, JD07C, JD07B and JD07A.
Syncope	£893.76	*NHS Reference Costs 2016/17; Total HRGs, Syncope or collapse with CC score 0-3, 4-6, 7-9, 10-12 and 13+, EB08E, EB08D, EB08C, EB08B and EB08A.*
Tooth abscess	£270.62	*NHS Reference Costs 2016/17; Total HRGs, Major dental procedures 19 years and over CD01A, Intermediate dental procedures 19 years and over CD02A and minor dental procedures 19 years and over CD03A.*
Tooth socket haemorrhage	**£661.91**	***NHS Reference Costs 2016/17; Total HRGs, Major dental procedures 19 years and over CD01A, Intermediate dental procedures 19 years and over CD02A and minor dental procedures 19 years and over CD03A.***
Tuberculosis pleurisy	£422.71	*NHS Reference Costs 2016/17; Total HRGs, Pleurisy with CC score 0-2 and 3+.*
Urosepsis	£2,085.20	*NHS Reference Costs 2016/17; Total HRGs, Sepsis with multiple interventions with CC score 0-4, 5-8 and 9+, with single intervention with CC score 0-4, 5-8 and 9+ and without interventions with CC score 0-4, 5-8 and 9+, WJ06C, WJ06B, WJ06A, WJ06F, WJ06E, WJ06D, WJ06J, WJ06H and WJ06G.*
Weight decreased/fatigue/general health deterioration/dehydration	£0.00	*NHS Reference Costs 2016/17; Total HRGs, Nutritional disorders with interventions, with CC score 0-1 and 2+ and nutritional disorders without interventions with CC score 0-1, 2-5 and 6+, FD04B, FD04A, FD04E, FD04D and FD04C.*
Notes: Inputs which have been updated based on the September 2017 data cut are highlighted in bold.		

6.2.8 Concomitant medications (update of Appendix L.5.4)

Table 29 presents the dosing information and costs associated with each CM. Inputs which have been updated based on the September 2017 data cut are highlighted in bold. Table 30 presents the drug cost per cycle (28-days) assuming no drug wastage and the proportion of patients receiving each CM.

Table 29: CMs dose and costs (update of Table 41)

CM	Dosing information	Cost per pack	Number of units in a pack	Dose per unit	Source
Paracetamol	**Paracetemol, 0.5-1g every 4-6 hours, maximum 4g per day. Assume 2g per day**	**£0.40**	**100**	**500**	**eMIT, DDM003, accessed March 2018**
Oxycodone	**Oxycodone hydrochloride, 10-200mg every 12 hours. Assumed 105mg per day**	**£18.43**	**56**	**40**	**eMIT, DDG305, accessed March 2018**
Targin	**Oxycodone with naloxone, 10/5mg-40/20mg every 12 hours. Assumed 20mg/10mg every 12 hours**	**£84.62**	**56**	**20**	**BNF, accessed March 2018; https://bnf.nice.org.uk/medicinal-forms/oxycodone-with-naloxone.html**
Acetaminophen	**Assumed paracetemol**	**£0.40**	**100**	**500**	**Assumption**
Morphine	**Morphine, 20-60mg daily. Assumed 40mg daily**	**£10.04**	**56**	**20**	**eMIT, DDG191, accessed March 2018**
Tramadol	**Tramadol hydrochloride, immediate-release medicine, 50-400mg per day. Assumed 200mg per day**	**£0.79**	**100**	**50**	**eMIT, DDG212, accessed March 2018**
Gabapentin	**Gabapentin, 0.3-3.6g per day. Assumed 2g daily**	**£1.98**	**100**	**400**	**eMIT, DDH034, accessed March 2018**
Lyrica	**Pregabalin, 150-600mg daily. Assumed 150mg daily**	**£96.60**	**84**	**25**	**BNF, accessed March 2018; https://bnf.nice.org.uk/medicinal-forms/pregabalin.html**
Tylenol	**Assumed paracetemol**	**£0.40**	**100**	**500**	**Assumption**
Augmentin	**Co-amoxiclav, 250/125mg - 500/125mg every 8 hours. Assumed 250/125mg**	**£2.25**	**21**	**250**	**eMIT, DEC033, accessed March 2018**
Amoxicillin	Amoxicillin 350mg capsule/packsize 21, 500mg x3 a day	£0.43	21	500	eMIT, accessed February 2018
Ceftriaxone	**Ceftriaxone, 1-2g daily. Assumed 1g**	**£0.59**	**1**	**1000**	**eMIT, DEA299, accessed March 2018**
Keflex	**Assumed amoxicillin**	**£0.43**	**21**	**500**	**Assumption**
Omeprazole	**Omeprazole, 20mg once daily**	**£0.45**	**28**	**20**	**eMIT, DAI012, accessed March 2018**
Pantoprazole	**Pantoprazole, 40mg twice daily**	**£0.53**	**28**	**40**	**eMIT, DAC000, accessed March 2018**
Famotidine	**Famotidine, 20-40mg once daily. Assumed 20mg**	**£21.94**	**28**	**20**	**BNF, accessed March 2018; https://bnf.nice.org.uk/medicinal-forms/famotidine.html**
Omeprazol	**Assumed omeprazole**	**£0.45**	**28**	**20**	**Assumption**
Ranitidine	**Ranitidine, 300mg once daily**	**£0.62**	**30**	**300**	**eMIT, DAE014, accessed March 2018**
Pantoprazol	**Assumed pantoprazole**	**£0.53**	**28**	**40**	**Assumption**

CM	Dosing information	Cost per pack	Number of units in a pack	Dose per unit	Source
Dexamethasone	Dexamethasone 2mg tablets/packsize 100, 8mg daily	£47.01	100	2	eMIT, DFN010, accessed February 2018
Prednisolone	Prednisolone 5mg tablets/packsize 28, 15mg daily (5-25mg)	£0.31	28	5	eMIT, DFN040, accessed February 2018
Prednisone	Lodotra 5mg modified-release tablets, 15mg daily (10-20mg)	£26.70	30	5	BNF, accessed February 2018; https://www.medicinescomplete.com/mc/bnf/current/PHP4378-prednisone.htm
Soldesam	Assumed dexamethasone	£47.01	100	2	Assumption
Medrol	Assumed methylprednisolone	£6.19	30	4	Assumption
Methylprednisolone	Medrone 4mg tablets, 20mg daily (2-40mg daily)	£6.19	30	4	BNF, accessed February 2018; https://www.medicinescomplete.com/mc/bnf/current/PHP4371-methylprednisolone.htm
Clexane	**Enoxaparin sodium, 20-40mg daily. Assumed 20mg**	**£20.86**	**10**	**20**	**BNF, accessed March 2018; https://bnf.nice.org.uk/medicinal-forms/enoxaparin-sodium.html**
Lorazepam	Lorazepam 1mg tablets (scored)/packsize 28, 2mg daily	£0.94	28	1	eMIT, DDA111, accessed February 2018
Zolpidem	Zolpidem 10mg tablets/packsize 28, 10mg daily	£0.47	28	10	eMIT, DDA034, accessed February 2018
Midazolam	**Midazolam, 30-200micrograms/kg/hour. Assumed 100micrograms/kg/hour for one day per cycle**	**£5.42**	**1**	**50**	**eMIT, DOA064, accessed March 2018**
Ibuprofen	Ibuprofen 200mg tables/packsize 84, 600mg daily	£0.47	84	200	eMIT, DJA157, accessed February 2018
Naproxen	Naproxen 500mg tablets/packsize 56, 500mg daily	£2.94	56	500	eMIT, DKA056, accessed February 2018
Metoclopramide	Assumed metoclopramide hydrochloride	£0.66	28	10	Assumption
Calcium	Renacet 475mg tablets, 1 x3 daily	£9.71	200	475	BNF, accessed February 2018; https://www.medicinescomplete.com/mc/bnf/current/PHP104228-calcium-acetate.htm
Multivitamin	**Vitamins with minerals and trace elements, one**	**£25.44**	**90**	**1**	**BNF, accessed March 2018;**

CM	Dosing information	Cost per pack	Number of units in a pack	Dose per unit	Source
	capsule daily				**https://bnf.nice.org.uk/medicinal-forms/vitamins-with-minerals-and-trace-elements.html**
Vitamin D3	**Vitamins with minerals and trace elements, one capsule daily**	**£26.44**	**90**	**1**	**BNF, accessed March 2018; https://bnf.nice.org.uk/medicinal-forms/vitamins-with-minerals-and-trace-elements.html**
Lasix	**Furosemide, 40-80mg daily. Assumed 60mg**	**£0.09**	**28**	**20**	**eMIT, DBB085, accessed March 2018**
Hydrocortisone	Hydrocortisone 20mg tablets, 20mg daily	£39.99	30	20	eMIT, DFC057, accessed March 2018
Folic acid	Folic acid 5mg tables, 5mg daily	£0.21	28	5	eMIT, DIA040, accessed March 2018
Prochlorperzine	Prochlorperazine 5mg tablets, 5-10mg (assumed 5mg) 2-3 daily (assumed 2)	£0.30	28	5	eMIT, DDF010, accessed March 2018
Ondansetron	Ondansetron 4mg tablets, 8mg twice daily for five days (assumed per cycle)	£0.73	30	4	eMIT, DDF028, accessed March 2018
Loperamide	**Loperamide 2mg capsules, 4-16mg daily (assumed 8mg)**	**£0.48**	**30**	**2**	**eMIT, DAK002, accessed March 2018**
Keppra	**Levetiracetam, 0.25-1.5g twice daily. Assumed 500mg twice daily**	**£6.22**	**60**	**500**	**eMIT, DDH108, accessed March 2018**

Abbreviations: BNF, British National Formulary; CM, concomitant medications; eMIT, electronic marketing information tool; mg, milligram; NHS, National Health Service; PSSRU, Personal Social Services Research Unit
Notes: Inputs which have been updated based on the September 2017 data cut are highlighted in bold.

Table 30: CMs cycle costs (update of Table 42)

CMs	Drug cost per cycle (28-days)	Proportion receiving CM	Total cost per cycle (28-days)
Paracetamol	**£0.45**	**19.09%**	**£0.09**
Oxycodone	**£48.38**	**5.45%**	**£2.64**
Targin	**£84.62**	**6.36%**	**£5.38**
Acetaminophen	**£0.45**	**6.36%**	**£0.03**
Morphine	**£10.04**	**7.27%**	**£0.73**
Tramadol	**£0.88**	**5.45%**	**£0.05**
Gabapentin	**£2.77**	**5.45%**	**£0.15**
Lyrica	**£193.20**	**8.18%**	**£15.81**
Tylenol	**£0.45**	**6.36%**	**£0.03**
Augmentin	**£9.00**	**10.91%**	**£0.98**
Amoxicillin	£1.72	10.00%	£0.17
Ceftriaxone	**£16.52**	**6.36%**	**£1.05**
Keflex	**£1.72**	**6.36%**	**£0.11**

CMs	Drug cost per cycle (28-days)	Proportion receiving CM	Total cost per cycle (28-days)
Omeprazole	**£0.45**	**6.36%**	**£0.03**
Pantoprazole	**£1.06**	**5.45%**	**£0.06**
Famotidine	**£21.94**	**5.45%**	**£1.20**
Omeprazol	**£0.45**	**6.36%**	**£0.03**
Ranitidine	**£0.58**	**7.27%**	**£0.04**
Pantoprazol	**£1.06**	**6.36%**	**£0.07**
Dexamethasone	£52.65	12.73%	£6.70
Prednisolone	£0.93	7.27%	£0.07
Prednisone	£74.76	6.36%	£4.76
Soldesam	£52.65	7.27%	£3.83
Medrol	£28.89	6.36%	£1.84
Methylpredinsolone	£28.89	6.36%	£1.84
Clexane	**£58.41**	**8.18%**	**£4.78**
Lorazepam	£1.88	7.27%	£0.14
Zolpidem	£0.47	6.36%	£0.03
Midazolam	**£5.42**	**5.45%**	**£0.30**
Ibuprofen	£0.47	7.27%	£0.03
Naproxen	£1.47	6.36%	£0.09
Metoclopramide	£1.98	10.91%	£0.22
Calcium	£4.08	8.18%	£0.33
Multivitamin	**£7.91**	**8.18%**	**£0.65**
Vitamin D3	**£8.23**	**7.27%**	**£0.60**
Lasix	**£0.27**	**6.36%**	**£0.02**
Hydrocortisone	£37.32	5.45%	£2.04
Folic acid	£0.21	5.45%	£0.01
Prochlorperzine	£0.60	6.36%	£0.04
Ondansetron	£0.49	7.27%	£0.04
Loperamide	**£1.79**	**5.45%**	**£0.10**
Keppra	**£5.81**	**7.27%**	**£0.42**
Abbreviations: CM, concomitant medication			

6.2.9 Parameters used in the model (update of Appendix L.5.6)

Table 31: Summary of variables applied in the economic model (update of Table 44)

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in original submission
Baseline characteristics - Baseline EQ-5D-3L score	0.71	Beta 95% CI: 0.66-0.75	HRQL – Section B.3.4, Health-related quality of life data from clinical trials, Table 46, Page 112
Baseline characteristics - ECOG PS 2+	0.09	Beta 95% CI: 0.05-0.14	
Baseline characteristics - Age	54.79	Normal 95% CI: 44.05-65.53	
Baseline characteristics - Gender (male)	0.38	Beta 95% CI: 0.34-0.43	
Baseline characteristics - Presence of brain metastases = yes	0.69	Beta 95% CI: 0.64-0.73	

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in original submission
Baseline characteristics - Presence of liver metastases = yes	0.21	Beta 95% CI: 0.17-0.26	
Baseline characteristics - Presence of bone metastases = yes	0.33	Beta 95% CI: 0.29-0.38	
Baseline characteristics - Number of metastatic sites	3.36	Normal 95% CI: 0.23-0.5	
Baseline characteristics - Receipt of prior chemotherapy = yes	0.73	Beta 95% CI: 0.68-0.77	
Baseline characteristics - Presence of active brain lesions = yes	0.52	Beta 95% CI: 0.47-0.56	
Baseline characteristics - Time since prior CRZ therapy	0.73	Normal 95% CI: 0.23-0.5	
OS brigatinib - generalised gamma - mu	5.42	Multivariate normal 95% CI: 5.06-5.78	
OS brigatinib - generalised gamma - sigma	0.00	Multivariate normal 95% CI: -0.64-0.63	
OS brigatinib - generalised gamma - Q	0.91	Multivariate normal 95% CI: 1.25-0.57	
OS brigatinib - exponential - log (scale)	-5.47	Multivariate normal 95% CI: -5.75--5.2	
OS brigatinib - Weibull - log (scale)	5.43	Multivariate normal 95% CI: 5.18-5.68	
OS brigatinib - Weibull - log (shape)	0.06	Multivariate normal 95% CI: 0-0.12	
OS brigatinib - log-normal - log (scale)	5.26	Multivariate normal 95% CI: 4.86-5.66	
OS brigatinib - log-normal - log (shape)	0.49	Multivariate normal 95% CI: 0.19-0.79	
OS brigatinib - log-logistic - log (scale)	5.14	Multivariate normal 95% CI: 4.9-5.39	
OS brigatinib - log-logistic - log (shape)	0.17	Multivariate normal 95% CI: 0.05-0.29	
OS brigatinib - gompertz - log (scale)	0.00	Multivariate normal 95% CI: -0.01-0.01	
OS brigatinib - gompertz - log (shape)	-5.54	Multivariate normal 95% CI: -5.39--5.7	
OS brigatinib - gamma - log (shape)	0.07	Multivariate normal 95% CI: -0.24-0.39	
OS brigatinib - gamma - log (rate)	-5.35	Multivariate normal 95% CI: -6.14--4.56	OS – Section B.3.3, Extrapolated outcomes
PFS investigator brigatinib - generalised gamma - mu	4.52	Multivariate normal 95% CI: 4.2-4.84	
PFS investigator brigatinib - generalised gamma - sigma	-0.14	Multivariate normal 95% CI: -0.18--0.1	
PFS investigator brigatinib - generalised gamma - Q	0.95	Multivariate normal 95% CI: 0.39-1.5	
PFS investigator brigatinib - exponential - log (scale)	-4.57	Multivariate normal 95% CI: -4.79--4.35	
PFS investigator brigatinib - Weibull - log (scale)	4.54	Multivariate normal 95% CI: 4.35-4.72	
PFS investigator brigatinib - Weibull - log (shape)	0.16	Multivariate normal 95% CI: 0-0.32	
PFS investigator brigatinib - log-	4.17	Multivariate normal	PFSINV – Section B.3.3, Extrapolated outcomes

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in original submission
normal - log (scale)		95% CI: 3.92-4.42	
PFS investigator brigatinib - log-normal - log (shape)	0.24	Multivariate normal 95% CI: 0.03-0.44	
PFS investigator brigatinib - log-logistic - log (scale)	4.18	Multivariate normal 95% CI: 3.99-4.37	
PFS investigator brigatinib - log-logistic - log (shape)	0.38	Multivariate normal 95% CI: 0.2-0.57	
PFS investigator brigatinib - gompertz - log (scale)	0.00	Multivariate normal 95% CI: 0-0.01	
PFS investigator brigatinib - gompertz - log (shape)	-4.79	Multivariate normal 95% CI: -4.69--4.88	
PFS investigator brigatinib - gamma - shape	0.23	Multivariate normal 95% CI: -0.04-0.49	
PFS investigator brigatinib - gamma - rate	-4.28	Multivariate normal 95% CI: -4.81--3.75	
PFS IRC brigatinib - generalised gamma - mu	4.56	Multivariate normal 95% CI: 4.2-4.91	
PFS IRC brigatinib - generalised gamma - sigma	-0.12	Multivariate normal 95% CI: -0.23--0.01	
PFS IRC brigatinib - generalised gamma - Q	0.86	Multivariate normal 95% CI: 0.34-1.39	
PFS IRC brigatinib - exponential - log (scale)	-4.65	Multivariate normal 95% CI: -4.92--4.38	
PFS IRC brigatinib - Weibull - log (scale)	4.60	Multivariate normal 95% CI: 4.38-4.82	
PFS IRC brigatinib - Weibull - log (shape)	0.18	Multivariate normal 95% CI: 0.01-0.35	
PFS IRC brigatinib - log-normal - log (scale)	4.26	Multivariate normal 95% CI: 3.96-4.56	PFSIRC – Appendix L.5.1, Extrapolated outcomes
PFS IRC brigatinib - log-normal - log (shape)	0.24	Multivariate normal 95% CI: -0.01-0.49	
PFS IRC brigatinib - log-logistic - log (scale)	4.25	Multivariate normal 95% CI: 4.03-4.47	
PFS IRC brigatinib - log-logistic - log (shape)	0.39	Multivariate normal 95% CI: 0.19-0.59	
PFS IRC brigatinib - gompertz - log (scale)	0.00	Multivariate normal 95% CI: 0-0.01	
PFS IRC brigatinib - gompertz - log (shape)	-4.86	Multivariate normal 95% CI: -4.75--4.96	
PFS IRC brigatinib - gamma - shape	0.25	Multivariate normal 95% CI: -0.06-0.56	
PFS IRC brigatinib - gamma - rate	-4.31	Multivariate normal 95% CI: -4.95--3.67	
ToT brigatinib - generalised gamma - mu	4.86	Multivariate normal 95% CI: 4.44-5.28	
ToT brigatinib - generalised gamma - sigma	-0.14	Multivariate normal 95% CI: -0.06--0.22	
ToT brigatinib - generalised gamma - Q	1.68	Multivariate normal 95% CI: 0.79-2.56	ToT – Appendix L.5.1, Extrapolated outcomes
ToT brigatinib - exponential - log (scale)	-4.62	Multivariate normal 95% CI: -4.84--4.4	
ToT brigatinib - Weibull - log (scale)	4.64	Multivariate normal 95% CI: 4.44-4.84	

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in original submission
ToT brigatinib - Weibull - log (shape)	-0.17	Multivariate normal 95% CI: -0.41-0.06	
ToT brigatinib - log-normal - log (scale)	4.12	Multivariate normal 95% CI: 3.75-4.49	
ToT brigatinib - log-normal - log (shape)	0.63	Multivariate normal 95% CI: 0.43-0.83	
ToT brigatinib - log-logistic - log (scale)	4.19	Multivariate normal 95% CI: 4-4.39	
ToT brigatinib - log-logistic - log (shape)	0.03	Multivariate normal 95% CI: -0.26-0.32	
ToT brigatinib - gompertz - log (scale)	0.00	Multivariate normal 95% CI: -0.01-0	
ToT brigatinib - gompertz - log (shape)	-4.52	Multivariate normal 95% CI: -4.43--4.6	
ToT brigatinib - gamma - shape	-0.25	Multivariate normal 95% CI: -0.52-0.01	
ToT brigatinib - gamma - rate	-4.95	Multivariate normal 95% CI: -5.55--4.35	
Weekly cost of ceritinib	960.31	Not varied 95% CI: 960.31-960.31	Costs – Section B.3.5, Intervention and comparators' cost and resource use, Table 48, Page 114
Costs of oncology outpatient visit (first)	219.19	95% CI:197.27 - 241.11	Costs – Section B.3.5, Health-state unit costs and resource use, Table 49, Page 117
Costs of oncology outpatient visit (subsequent)	172.67	95% CI:155.4 - 189.94	
Costs of pharmacist	44	95% CI:39.6 - 48.4	
Costs of GP visit	37	95% CI:33.3 - 40.7	
Costs of Cancer nurse	82.09	95% CI:73.88 - 90.3	
Costs of Complete blood count	3.06	95% CI:2.75 - 3.37	
Costs of Serum chemistry	1.13	95% CI:1.01 - 1.24	
Costs of CT scan	110.04	95% CI:99.04 - 121.05	
Costs of X-ray	29.78	95% CI:26.8 - 32.75	
Costs of Home oxygen	200.68	95% CI:100.49 - 122.82	Costs – Section B.3.5, Health-state unit costs and resource use, Table 50, Page 119
Costs of radiotherapy	130.85	95% CI:117.77 - 143.94	
Costs of Steroids (dexamethasone)	0.75	95% CI:0.68 - 0.83	
Costs of NSAIDs (aspirin)	0.04	95% CI:0.04 - 0.04	
Costs of Morphine (morphine sulphate)	5.78	95% CI:5.2 - 6.36	
Costs of Bisphosphonate (alendronic acid)	0.06	95% CI:0.05 - 0.06	
Costs of Denosumab	366	95% CI:329.4 - 402.6	
Costs of Dietitian	84.85	95% CI:76.36 - 93.33	
Cost of terminal care	11124	95% CI:10011.6 - 12236.4	
Frequency of oncology outpatient visits in pre-progression (first cycle)	2	Normal 95% CI: 1-3	Costs – Section B.3.5, Health-state unit costs and resource use, Table 49, Page 117
Frequency of oncology outpatient visits in pre-progression (subsequent cycles)	1	Normal 95% CI: 1-1	

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in original submission
Frequency of GP visits in pre-progression	0.25	Normal 95% CI: 0-1	
Frequency of Cancer nurses in pre-progression	0.42	Normal 95% CI: 0.1-1	
Frequency of Complete blood counts in pre-progression (first cycle)	2	Normal 95% CI: 1-3	
Frequency of Complete blood counts in pre-progression (subsequent cycles)	1	Normal 95% CI: 0.75-1	
Frequency of Serum chemistries in pre-progression (first cycle)	2	Normal 95% CI: 1-3	
Frequency of Serum chemistries in pre-progression (subsequent cycles)	1	Normal 95% CI: 0.75-1	
Frequency of CT scans in pre-progression	0.41	Normal 95% CI: 0.23-0.5	
Frequency of X-rays in pre-progression	0.55	Normal 95% CI: 0-0.75	
Frequency of Oncology outpatient visits in post-progression	1.13	Normal 95% CI: 0.91-1.35	Costs – Section B.3.5, Health-state unit costs and resource use, Table 50, Page 119
Frequency of GP visits in post-progression	0.28	Normal 95% CI: 0.23-0.34	
Frequency of Cancer nurses in post-progression	0.66	Normal 95% CI: 0.53-0.79	
Frequency of Complete blood counts in post-progression	0.6	Normal 95% CI: 0.48-0.72	
Frequency of Serum chemistry in post-progression	0.6	Normal 95% CI: 0.48-0.72	
Frequency of CT scans in post-progression	0.21	Normal 95% CI: 0.17-0.25	
Frequency of X-rays in post-progression	0.12	Normal 95% CI: 0.1-0.14	
Frequency of Home oxygens in post-progression	0.12	Normal 95% CI: 0.09-0.14	
Frequency of radiotherapy	0.25	Normal 95% CI: 0.2-0.3	
Frequency of Steroids (dexamethasone)s in post-progression	14	Normal 95% CI: 11.26-16.74	
Frequency of NSAIDs (aspirin)s in post-progression	5.88	Normal 95% CI: 4.73-7.03	
Frequency of Morphine (morphine sulphate) in post-progression	20.44	Normal 95% CI: 16.43-24.45	
Frequency of Bisphosphonate (alendronic acid) in post-progression	1.6	Normal 95% CI: 1.28-1.91	
Frequency of denosumab in post-progression	0.04	Normal 95% CI: 0.03-0.05	
Frequency of Dietitians in post-progression	0.42	Normal 95% CI: 0.34-0.5	
Dose intensity - brigatinib	0.89	Beta 95% CI: 0.87-0.91	Costs – Section B.3.5, Intervention and comparators'
Dose intensity - ceritinib	0.84	Beta 95% CI: 0.83-0.85	

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in original submission
Oral administration costs	170.75	Gamma 95% CI: 153.68-187.83	cost and resource use
Cycle cost of concomitant medications	57.24	Gamma 95% CI: 40.07-74.41	Costs – Section B.3.5, Intervention and comparators' cost and resource use, Appendix L.5.4
HRQL - ORR (four categories of response) - Intercept	0.58	95% CI: 0.4 - 0.76	HRQL – Section B.3.4.1, Health-related quality of life data from clinical trials, Table 44
HRQL - ORR (four categories of response) - Baseline EQ-5D-3L score	0.45	95% CI: 0.42 - 0.49	
HRQL - ORR (four categories of response) - ORR Investigator assessed - Partial response	-0.01	95% CI: -0.04 - 0.02	
HRQL - ORR (four categories of response) - ORR Investigator assessed - Progressive disease	-0.07	95% CI: -0.13 - -0.01	
HRQL - ORR (four categories of response) - ORR Investigator assessed - Stable disease	-0.01	95% CI: -0.08 - 0.06	
HRQL - ORR (four categories of response) - ECOG PS	-0.14	95% CI: -0.22 - -0.05	
HRQL - ORR (four categories of response) - ≥1 grade 3/4 adverse event	-0.07	95% CI: -0.11 - -0.03	
HRQL - ORR (four categories of response) - Age	0.00	95% CI: 0 - 0	
HRQL - ORR (four categories of response) - Gender (male)	-0.01	95% CI: -0.03 - 0.01	
HRQL - ORR (four categories of response) - Presence of brain metastases = yes	-0.08	95% CI: -0.16 - -0.01	
HRQL - ORR (four categories of response) - Presence of liver metastases = yes	0.03	95% CI: -0.07 - 0.13	
HRQL - ORR (four categories of response) - Presence of bone metastases = yes	0.00	95% CI: -0.08 - 0.07	
HRQL - ORR (four categories of response) - Number of metastatic sites	0.02	95% CI: 0.06 - -0.02	
HRQL - ORR (four categories of response) - Receipt of prior chemotherapy = yes	0.00	95% CI: 0.02 - -0.02	
HRQL - ORR (four categories of response) - Presence of active brain lesions = yes	0.04	95% CI: 0.13 - -0.05	
HRQL - ORR (four categories of response) - Time since prior CRZ therapy	0.00	95% CI: -0.01 - 0	
HRQL - ORR (two categories of response) - Intercept	0.57	95% CI: 0.4 - 0.74	
HRQL - ORR (two categories of	0.45	95% CI: 0.42 - 0.48	

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in original submission
response) - Baseline EQ-5D-3L score			
HRQL - ORR (two categories of response) - Progressed	-0.06	95% CI: -0.09 - -0.03	
HRQL - ORR (two categories of response) - ECOG PS	-0.14	95% CI: -0.22 - -0.05	
HRQL - ORR (two categories of response) - ≥1 grade 3/4 adverse event	-0.07	95% CI: -0.11 - -0.02	
HRQL - ORR (two categories of response) - Age	0.00	95% CI: 0 - 0	
HRQL - ORR (two categories of response) - Gender (male)	-0.01	95% CI: -0.03 - 0.01	
HRQL - ORR (two categories of response) - Presence of brain metastases = yes	-0.08	95% CI: -0.16 - -0.01	
HRQL - ORR (two categories of response) - Presence of liver metastases = yes	0.03	95% CI: -0.07 - 0.13	
HRQL - ORR (two categories of response) - Presence of bone metastases = yes	0.00	95% CI: -0.07 - 0.07	
HRQL - ORR (two categories of response) - Number of metastatic sites	0.02	95% CI: 0.06 - -0.02	
HRQL - ORR (two categories of response) - Receipt of prior chemotherapy = yes	0.00	95% CI: 0.01 - -0.02	
HRQL - ORR (two categories of response) - Presence of active brain lesions = yes	0.04	95% CI: 0.13 - -0.05	
HRQL - ORR (two categories of response) - Time since prior CRZ therapy	0.00	95% CI: -0.01 - 0	
HRQL - BOR (four categories of response) - Intercept	0.55	95% CI: 0.38 - 0.71	
HRQL - BOR (four categories of response) - Baseline EQ-5D-3L score	0.51	95% CI: 0.48 - 0.55	
HRQL - BOR (four categories of response) - BoR INV Partial Response	0.01	95% CI: 0 - 0.02	
HRQL - BOR (four categories of response) - BoR INV Progressive Disease	-0.17	95% CI: -0.26 - -0.09	
HRQL - BOR (four categories of response) - BoR INV Stable Disease	0.01	95% CI: -0.05 - 0.07	
HRQL - BOR (four categories of response) - ECOG PS	-0.06	95% CI: -0.11 - -0.01	
HRQL - BOR (four categories of response) - ≥1 grade 3/4 adverse event	-0.07	95% CI: -0.1 - -0.03	

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in original submission
HRQL - BOR (four categories of response) - Age	0.00	95% CI: 0 - 0	
HRQL - BOR (four categories of response) - Gender (male)	-0.02	95% CI: -0.04 - 0	
HRQL - BOR (four categories of response) - Presence of brain metastases = yes	-0.10	95% CI: -0.16 - -0.04	
HRQL - BOR (four categories of response) - Presence of liver metastases = yes	0.03	95% CI: -0.06 - 0.13	
HRQL - BOR (four categories of response) - Presence of bone metastases = yes	0.01	95% CI: -0.06 - 0.08	
HRQL - BOR (four categories of response) - Number of metastatic sites	0.01	95% CI: 0.05 - -0.03	
HRQL - BOR (four categories of response) - Receipt of prior chemotherapy = yes	-0.01	95% CI: 0.01 - -0.02	
HRQL - BOR (four categories of response) - Presence of active brain lesions = yes	0.06	95% CI: 0.13 - -0.02	
HRQL - BOR (four categories of response) - Time since prior CRZ therapy	0.00	95% CI: -0.01 - 0	
HRQL - BOR (two categories of response) - Intercept	0.55	95% CI: 0.41 - 0.69	
HRQL - BOR (two categories of response) - Baseline EQ-5D-3L score	0.51	95% CI: 0.49 - 0.54	
HRQL - BOR (two categories of response) - BoR INV Progressed disease	-0.18	95% CI: -0.26 - -0.1	
HRQL - BOR (two categories of response) - ECOG PS	-0.06	95% CI: -0.12 - 0	
HRQL - BOR (two categories of response) - ≥1 grade 3/4 adverse event	-0.07	95% CI: -0.11 - -0.02	
HRQL - BOR (two categories of response) - Age	0.00	95% CI: 0 - 0	
HRQL - BOR (two categories of response) - Gender (male)	-0.02	95% CI: -0.04 - 0	
HRQL - BOR (two categories of response) - Presence of brain metastases = yes	-0.10	95% CI: -0.16 - -0.03	
HRQL - BOR (two categories of response) - Presence of liver metastases = yes	0.03	95% CI: -0.05 - 0.11	
HRQL - BOR (two categories of response) - Presence of bone metastases = yes	0.01	95% CI: -0.05 - 0.07	
HRQL - BOR (two categories of response) - Number of metastatic	0.01	95% CI: 0.05 - -0.02	

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in original submission
sites			
HRQL - BOR (two categories of response) - Receipt of prior chemotherapy = yes	0.00	95% CI: 0 - -0.01	
HRQL - BOR (two categories of response) - Presence of active brain lesions = yes	0.06	95% CI: 0.14 - -0.03	
HRQL - BOR (two categories of response) - Time since prior CRZ therapy	0.00	95% CI: -0.01 - 0	
Utility values from Nafees et al. (2008) - Stable	0.65	Beta 95% CI: 0.61-0.7	Presented on "HRQL" sheet in model
Utility values from Nafees et al. (2008) - Progressive	-0.18	Beta 95% CI: 0.14-0.22	
Utility values from Nafees et al. (2008) - Response	0.02	Beta 95% CI: 0.01-0.03	
Utility values from Nafees et al. (2008) - Neutropenia	-0.09	Beta 95% CI: 0.06-0.12	
Utility values from Nafees et al. (2008) - Febrile neutropenia	-0.09	Beta 95% CI: 0.06-0.12	
Utility values from Nafees et al. (2008) - Fatigue	-0.07	Beta 95% CI: 0.04-0.11	
Utility values from Nafees et al. (2008) - Nausea and vomiting	-0.05	Beta 95% CI: 0.02-0.08	
Utility values from Nafees et al. (2008) - Diarrhoea	-0.05	Beta 95% CI: 0.02-0.08	
Utility values from Nafees et al. (2008) - Hair loss	-0.04	Beta 95% CI: 0.02-0.08	
Utility values from Nafees et al. (2008) - Rash	-0.03	Beta 95% CI: 0.01-0.06	
Utility values from Chouaid et al. (2013) - Progression free	0.74	Beta 95% CI: 0.69-0.79	
Utility values from Chouaid et al. (2013) - Progressed disease	0.59	Beta 95% CI: 0.42-0.75	
OS - Log HR for brigatinib vs. ceritinib - Naïve ITC - ALTA - ASCEND-2	-0.75	Normal 95% CI: -1.22 - -0.3	Efficacy – Section B.3.3, Indirect treatment comparisons
OS - Log HR for brigatinib vs. ceritinib - MAIC full - ALTA - ASCEND-2	-0.89	Normal 95% CI: -1.44 - -0.31	
OS - Log HR for brigatinib vs. ceritinib - MAIC reduced - ALTA - ASCEND-2	-0.90	Normal 95% CI: -1.44 - -0.32	
OS - Log HR for brigatinib vs. ceritinib - Naïve ITC - Pooled (ALTA and Study 101) - ASCEND-2	-0.76	Normal 95% CI: -1.2 - -0.34	
OS - Log HR for brigatinib vs. ceritinib - MAIC full - Pooled (ALTA and Study 101) - ASCEND-2	-0.84	Normal 95% CI: -1.34 - -0.3	
OS - Log HR for brigatinib vs. ceritinib - MAIC reduced - Pooled (ALTA and Study 101) - ASCEND-2	-0.84	Normal 95% CI: -1.34 - -0.3	
OS - Log HR for brigatinib vs.	-0.73	Normal 95% CI: -1.2 - -	

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in original submission
ceritinib - Naïve ITC - ALTA - ASCEND-5		0.28	
OS - Log HR for brigatinib vs. ceritinib - MAIC full - ALTA - ASCEND-5	-0.97	Normal 95% CI: -1.75 - -0.29	
OS - Log HR for brigatinib vs. ceritinib - MAIC reduced - ALTA - ASCEND-5	-0.96	Normal 95% CI: -1.49 - -0.36	
OS - Log HR for brigatinib vs. ceritinib - Naïve ITC - Pooled (ALTA and Study 101) - ASCEND-5	-0.72	Normal 95% CI: -1.16 - -0.3	
OS - Log HR for brigatinib vs. ceritinib - MAIC full - Pooled (ALTA and Study 101) - ASCEND-5	-0.69	Normal 95% CI: -1.14 - -0.18	
OS - Log HR for brigatinib vs. ceritinib - MAIC reduced - Pooled (ALTA and Study 101) - ASCEND-5	-0.69	Normal 95% CI: -1.14 - -0.18	
PFS INV - Log HR for brigatinib vs. ceritinib - Naïve ITC - ALTA - ASCEND-2	-0.96	95% CI: -1.29 - -0.59	Efficacy – Section B.3.3, Indirect treatment comparisons
PFS INV - Log HR for brigatinib vs. ceritinib - MAIC full - ALTA - ASCEND-2	-1.02	95% CI: -1.42 - -0.58	
PFS INV - Log HR for brigatinib vs. ceritinib - MAIC reduced - ALTA - ASCEND-2	-1.02	95% CI: -1.42 - -0.58	
PFS INV - Log HR for brigatinib vs. ceritinib - Naïve ITC - Pooled (ALTA and Study 101) - ASCEND-2	-0.95	95% CI: -1.26 - -0.62	
PFS INV - Log HR for brigatinib vs. ceritinib - MAIC full - Pooled (ALTA and Study 101) - ASCEND-2	-0.96	95% CI: -1.34 - -0.56	
PFS INV - Log HR for brigatinib vs. ceritinib - MAIC reduced - Pooled (ALTA and Study 101) - ASCEND-2	-0.96	95% CI: -1.34 - -0.56	
PFS IRC - Log HR for brigatinib vs. ceritinib - Naïve ITC - ALTA - ASCEND-5	-1.26	95% CI: -1.62 - -0.88	Efficacy – Section B.3.3, Indirect treatment comparisons
PFS IRC - Log HR for brigatinib vs. ceritinib - MAIC full - ALTA - ASCEND-5	-1.65	95% CI: -2.17 - -0.95	
PFS IRC - Log HR for brigatinib vs. ceritinib - MAIC reduced - ALTA - ASCEND-5	-1.48	95% CI: -1.93 - -1	
ORR INV - Log odds ratio for brigatinib vs. ceritinib - Naïve ITC - ALTA - ASCEND-2	0.72	95% CI: 0.18 - 1.2	Efficacy – Appendix L.5.2.1, Indirect treatment comparisons, Table 39
ORR INV - Log odds ratio for brigatinib vs. ceritinib - MAIC full - ALTA - ASCEND-2	0.61	95% CI: -0.01 - 1.16	
ORR INV - Log odds ratio for brigatinib vs. ceritinib - MAIC reduced - ALTA - ASCEND-2	0.65	95% CI: 0.03 - 1.2	

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in original submission
ORR IRC - Log odds ratio for brigatinib vs. ceritinib - Naïve ITC - ALTA - ASCEND-5	0.70	95% CI: 0.1 - 1.16	Efficacy – Appendix L.5.2.1, Indirect treatment comparisons, Table 39
ORR IRC - Log odds ratio for brigatinib vs. ceritinib - MAIC full - ALTA - ASCEND-5	0.96	95% CI: 0.18 - 1.7	
ORR IRC - Log odds ratio for brigatinib vs. ceritinib - MAIC reduced - ALTA - ASCEND-5	0.65	95% CI: -0.01 - 1.19	
HR meta-analysis - OS ALTA - MAIC full - fixed effects	2.6	95% CI: 1.64 - 3.92	CODA values, not reported in submission. Available in the "CODA" sheet in the model.
HR meta-analysis - OS ALTA - MAIC full - random effects	2.63	95% CI: 1.43 - 4.6	
HR meta-analysis - OS ALTA - Naïve ITC - fixed effects	2.13	95% CI: 1.53 - 2.9	
HR meta-analysis - OS ALTA - Naïve ITC - random effects	2.15	95% CI: 1.29 - 3.36	
HR meta-analysis - OS ALTA - MAIC reduced - fixed effects	2.6	95% CI: 1.71 - 3.8	
HR meta-analysis - OS ALTA - MAIC reduced - random effects	2.64	95% CI: 1.46 - 4.32	
HR meta-analysis - OS pooled - MAIC full - fixed effects	2.18	95% CI: 1.51 - 3.06	
HR meta-analysis - OS pooled - MAIC full - random effects	2.21	95% CI: 1.29 - 3.54	
HR meta-analysis - OS pooled - Naïve ITC - fixed effects	2.14	95% CI: 1.56 - 2.86	
HR meta-analysis - OS pooled - Naïve ITC - random effects	2.16	95% CI: 1.32 - 3.34	
HR meta-analysis - OS pooled - MAIC reduced - fixed effects	2.18	95% CI: 1.51 - 3.06	
HR meta-analysis - OS pooled - MAIC reduced - random effects	2.21	95% CI: 1.29 - 3.54	
HR meta-analysis - PFS - ALTA - MAIC full - fixed effects	3.45	95% CI: 2.39 - 4.82	CODA values, not reported in submission. Available in the "CODA" sheet in the model.
HR meta-analysis - PFS - ALTA - MAIC full - random effects	3.67	95% CI: 2.06 - 6.26	
HR meta-analysis - PFS - ALTA - Naïve ITC - fixed effects	3.04	95% CI: 2.34 - 3.89	
HR meta-analysis - PFS - ALTA - Naïve ITC - random effects	3.1	95% CI: 1.91 - 4.78	
HR meta-analysis - PFS - ALTA - MAIC reduced - fixed effects	3.47	95% CI: 2.5 - 4.69	
HR meta-analysis - PFS - ALTA - MAIC reduced - random effects	3.55	95% CI: 2.07 - 5.7	
HR meta-analysis - ORR - ALTA - MAIC full - fixed effects	0.49	95% CI: 0.3 - 0.76	CODA values, not reported in submission. Available in the "CODA" sheet in the model.
HR meta-analysis - ORR - ALTA - MAIC full - random effects	0.49	95% CI: 0.26 - 0.85	
HR meta-analysis - ORR - ALTA - Naïve ITC - fixed effects	0.5	95% CI: 0.34 - 0.71	
HR meta-analysis - ORR - ALTA - Naïve ITC - random effects	0.51	95% CI: 0.29 - 0.82	

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in original submission
HR meta-analysis - ORR - ALTA - MAIC reduced - fixed effects	0.54	95% CI: 0.35 - 0.8	
HR meta-analysis - ORR - ALTA - MAIC reduced - random effects	0.55	95% CI: 0.3 - 0.92	
Response data: Brigatinib - ALTA patient level data - Investigator (INV) - proportion PD	0.09	Beta tree 95% CI: 0.08-0.11	ORR – HRQL – Appendix L.5.2.1
Response data: Brigatinib - ALTA patient level data - Investigator (INV) - proportion SD/Non-complete response or non-progressive disease	0.3	Beta tree 95% CI: 0.28-0.32	
Response data: Brigatinib - ALTA patient level data - Investigator (INV) - proportion PR	0.55	Beta tree 95% CI: 0.57-0.53	
Response data: Brigatinib - ALTA patient level data - Investigator (INV) - proportion CR	0.06	Beta tree 95% CI: 0.07-0.04	
Response data: Ceritinib - ASCEND-2 - Investigator (INV) - proportion PD	0.15	Beta tree 95% CI: 0.13-0.17	
Response data: Ceritinib - ASCEND-2 - Investigator (INV) - proportion SD/Non-complete response or non-progressive disease	0.43	Beta tree 95% CI: 0.41-0.44	
Response data: Ceritinib - ASCEND-2 - Investigator (INV) - proportion PR	0.39	Beta tree 95% CI: 0.42-0.37	
Response data: Ceritinib - ASCEND-2 - Investigator (INV) - proportion CR	0.03	Beta tree 95% CI: 0.05-0.02	
Mean days of duration - ANAEMIA	32.00	Normal 95% CI: 25.73-38.27	AEs – Appendix L.5.3
Mean days of duration - APPENDICITIS	4.00	Normal 95% CI: 3.22-4.78	
Mean days of duration - ASTHENIA	22.70	Normal 95% CI: 18.25-27.15	
Mean days of duration - BEHCET'S SYNDROME	22.70	Normal 95% CI: 18.25-27.15	
Mean days of duration - CARDIAC FAILURE	22.70	Normal 95% CI: 18.25-27.15	
Mean days of duration - CARDIAN ARRHYTHMIA	2.00	Normal 95% CI: 1.61-2.39	
Mean days of duration - CATARACT	77.50	Normal 95% CI: 62.31-92.69	
Mean days of duration - CELLULITIS	12.00	Normal 95% CI: 9.65-14.35	
Mean days of duration - CLOSTRIDIUM DIFFICILE COLITIS	36.00	Normal 95% CI: 28.94-43.06	
Mean days of duration - COAGULATION	7.00	Normal 95% CI: 5.63-8.37	

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in original submission
Mean days of duration - COGNITIVE DISORDER	22.70	Normal 95% CI: 18.25-27.15	
Mean days of duration - CONFUSIONAL STATE	5.00	Normal 95% CI: 4.02-5.98	
Mean days of duration - DECREASED APPETITE	18.00	Normal 95% CI: 14.47-21.53	
Mean days of duration - DERMATITIS ALLERGIC	8.00	Normal 95% CI: 6.43-9.57	
Mean days of duration - DEVICE OCCLUSION	5.00	Normal 95% CI: 4.02-5.98	
Mean days of duration - DIABETES MELLITUS	22.70	Normal 95% CI: 18.25-27.15	
Mean days of duration - DYSARTHRIA	8.00	Normal 95% CI: 6.43-9.57	
Mean days of duration - DYSPEPSIA	11.00	Normal 95% CI: 8.84-13.16	
Mean days of duration - DYSPNOEA	13.00	Normal 95% CI: 10.45-15.55	
Mean days of duration - ELECTROCARDIOGRAM QT PROLONGED	4.33	Normal 95% CI: 3.48-5.18	
Mean days of duration - FOOD POISONING	2.00	Normal 95% CI: 1.61-2.39	
Mean days of duration - GENERALISED TONIC-CLONIC SEIZURE	1.00	Normal 95% CI: 0.8-1.2	
Mean days of duration - HAEMOPTYSIS	3.00	Normal 95% CI: 2.41-3.59	
Mean days of duration - HAEMORRHAGIC ANAEMIA	1.00	Normal 95% CI: 0.8-1.2	
Mean days of duration - HEPATIC FUNCTION ABNORMAL	22.70	Normal 95% CI: 18.25-27.15	
Mean days of duration - HYDRONEPHROSIS	5.00	Normal 95% CI: 4.02-5.98	
Mean days of duration - HYPERGLYCAEMIA	2.00	Normal 95% CI: 1.61-2.39	
Mean days of duration - HYPERLIPASAEMIA	8.00	Normal 95% CI: 6.43-9.57	
Mean days of duration - HYPERTENSION	22.25	Normal 95% CI: 17.89-26.61	
Mean days of duration - HYPONATRAEMIA	22.83	Normal 95% CI: 18.36-27.31	
Mean days of duration - HYPOPHOSPHATAEMIA	22.70	Normal 95% CI: 18.25-27.15	
Mean days of duration - HYPOXIA	189.50	Normal 95% CI: 152.36-226.64	
Mean days of duration - INFUSION SITE THROMBOSIS	26.00	Normal 95% CI: 20.9-31.1	
Mean days of duration - INTERMITTENT CLAUDICATION	22.70	Normal 95% CI: 18.25-27.15	
Mean days of duration - JAUNDICE CHOLESTATIC	4.00	Normal 95% CI: 3.22-4.78	

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in original submission
Mean days of duration - LABORATORY RESULTS	16.69	Normal 95% CI: 13.42-19.96	
Mean days of duration - LIVER DISORDER	10.50	Normal 95% CI: 8.44-12.56	
Mean days of duration - MACULAR OEDEMA	36.00	Normal 95% CI: 28.94-43.06	
Mean days of duration - MALIGNANT PLEURAL EFFUSION	7.33	Normal 95% CI: 5.9-8.77	
Mean days of duration - MENINGITIS BACTERIAL	13.00	Normal 95% CI: 10.45-15.55	
Mean days of duration - MUSCULAR WEAKNESS	22.70	Normal 95% CI: 18.25-27.15	
Mean days of duration - NAUSEA	18.00	Normal 95% CI: 14.47-21.53	
Mean days of duration - NERVOUS SYSTEM DISORDER	22.70	Normal 95% CI: 18.25-27.15	
Mean days of duration - OSTEOARTHRITIS	22.70	Normal 95% CI: 18.25-27.15	
Mean days of duration - OSTEONECROSIS	42.00	Normal 95% CI: 33.77-50.23	
Mean days of duration - PAIN	24.67	Normal 95% CI: 19.83-29.5	
Mean days of duration - PANCREATIC DISORDER	9.00	Normal 95% CI: 7.24-10.76	
Mean days of duration - PARAESTHESIA	1.00	Normal 95% CI: 0.8-1.2	
Mean days of duration - PERIPHERAL ARTERY STENOSIS	37.00	Normal 95% CI: 29.75-44.25	
Mean days of duration - PERIPHERAL SENSORY NEUROPATHY	85.00	Normal 95% CI: 68.34-101.66	
Mean days of duration - PHOTOSENSITIVITY REACTION	19.00	Normal 95% CI: 15.28-22.72	
Mean days of duration - PLEURAL EFFUSION	61.00	Normal 95% CI: 49.04-72.96	
Mean days of duration - PNEUMONIA	12.83	Normal 95% CI: 10.32-15.35	
Mean days of duration - PULMONARY EMBOLISM	155.00	Normal 95% CI: 124.62-185.38	
Mean days of duration - PYREXIA	1.00	Normal 95% CI: 0.8-1.2	
Mean days of duration - RADIATION NECROSIS	7.00	Normal 95% CI: 5.63-8.37	
Mean days of duration - RESPIRATORY INFECTION	4.00	Normal 95% CI: 3.22-4.78	
Mean days of duration - SIMPLE PARTIAL SEIZURES	1.50	Normal 95% CI: 1.21-1.79	
Mean days of duration - SKIN INFECTION	54.00	Normal 95% CI: 43.42-64.58	
Mean days of duration - SUBCUTANEOUS ABSCESS	46.00	Normal 95% CI: 36.98-55.02	

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in original submission
Mean days of duration - SWELLING/RASH	11.83	Normal 95% CI: 9.51-14.15	
Mean days of duration - SYNCOPE	3.00	Normal 95% CI: 2.41-3.59	
Mean days of duration - TOOTH ABSCESS	8.00	Normal 95% CI: 6.43-9.57	
Mean days of duration - TOOTH SOCKET HAEMORRHAGE	6.00	Normal 95% CI: 4.82-7.18	
Mean days of duration - TUBERCULOUS PLEURISY	22.70	Normal 95% CI: 18.25-27.15	
Mean days of duration - UROSEPSIS	6.00	Normal 95% CI: 4.82-7.18	
Mean days of duration - WEIGHT DECREASED	22.70	Normal 95% CI: 18.25-27.15	
Brigatinib (ALTA) Rate - ANAEMIA	0.01	Beta 95% CI: 0-0.05	AEs – Appendix L.5.3
Brigatinib (ALTA) Rate - APPENDICITIS	0.01	Beta 95% CI: 0-0.05	
Brigatinib (ALTA) Rate - ASTHENIA	0.01	Beta 95% CI: 0-0.03	
Brigatinib (ALTA) Rate - BEHCET'S SYNDROME	0.01	Beta 95% CI: 0-0.03	
Brigatinib (ALTA) Rate - CARDIAC FAILURE	0.01	Beta 95% CI: 0-0.03	
Brigatinib (ALTA) Rate - CARDIAN ARRHYTHMIA	0.02	Beta 95% CI: 0.01-0.06	
Brigatinib (ALTA) Rate - CATARACT	0.01	Beta 95% CI: 0-0.05	
Brigatinib (ALTA) Rate - CELLULITIS	0.01	Beta 95% CI: 0-0.03	
Brigatinib (ALTA) Rate - CLOSTRIDIUM DIFFICILE COLITIS	0.01	Beta 95% CI: 0-0.03	
Brigatinib (ALTA) Rate - COAGULATION	0.01	Beta 95% CI: 0-0.03	
Brigatinib (ALTA) Rate - COGNITIVE DISORDER	0.01	Beta 95% CI: 0-0.05	
Brigatinib (ALTA) Rate - CONFUSIONAL STATE	0.01	Beta 95% CI: 0-0.05	
Brigatinib (ALTA) Rate - DECREASED APPETITE	0.01	Beta 95% CI: 0-0.05	
Brigatinib (ALTA) Rate - DERMATITIS ALLERGIC	0.01	Beta 95% CI: 0-0.03	
Brigatinib (ALTA) Rate - DEVICE OCCLUSION	0.01	Beta 95% CI: 0-0.03	
Brigatinib (ALTA) Rate - DIABETES MELLITUS	0.01	Beta 95% CI: 0-0.03	
Brigatinib (ALTA) Rate - DYSARTHRIA	0.01	Beta 95% CI: 0-0.03	
Brigatinib (ALTA) Rate - DYSPEPSIA	0.01	Beta 95% CI: 0-0.03	
Brigatinib (ALTA) Rate - DYSPNOEA	0.02	Beta 95% CI: 0.01-0.06	

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in original submission
Brigatinib (ALTA) Rate - ELECTROCARDIOGRAM QT PROLONGED	0.02	Beta 95% CI: 0.01-0.06	
Brigatinib (ALTA) Rate - FOOD POISONING	0.01	Beta 95% CI: 0-0.03	
Brigatinib (ALTA) Rate - GENERALISED TONIC-CLONIC SEIZURE	0.01	Beta 95% CI: 0-0.03	
Brigatinib (ALTA) Rate - HAEMOPTYSIS	0.01	Beta 95% CI: 0-0.03	
Brigatinib (ALTA) Rate - HAEMORRHAGIC ANAEMIA	0.01	Beta 95% CI: 0-0.03	
Brigatinib (ALTA) Rate - HEPATIC FUNCTION ABNORMAL	0.01	Beta 95% CI: 0-0.03	
Brigatinib (ALTA) Rate - HYDRONEPHROSIS	0.01	Beta 95% CI: 0-0.03	
Brigatinib (ALTA) Rate - HYPERGLYCAEMIA	0.01	Beta 95% CI: 0-0.03	
Brigatinib (ALTA) Rate - HYPERLIPASAEMIA	0.01	Beta 95% CI: 0-0.03	
Brigatinib (ALTA) Rate - HYPERTENSION	0.10	Beta 95% CI: 0.09-0.23	
Brigatinib (ALTA) Rate - HYPONATRAEMIA	0.04	Beta 95% CI: 0.03-0.12	
Brigatinib (ALTA) Rate - HYPOPHOSPHATAEMIA	0.01	Beta 95% CI: 0-0.03	
Brigatinib (ALTA) Rate - HYPOXIA	0.02	Beta 95% CI: 0.01-0.08	
Brigatinib (ALTA) Rate - INFUSION SITE THROMBOSIS	0.01	Beta 95% CI: 0-0.03	
Brigatinib (ALTA) Rate - INTERMITTENT CLAUDICATION	0.01	Beta 95% CI: 0-0.03	
Brigatinib (ALTA) Rate - JAUNDICE CHOLESTATIC	0.01	Beta 95% CI: 0-0.03	
Brigatinib (ALTA) Rate - LABORATORY RESULTS	0.31	Beta 95% CI: 0.41-0.59	
Brigatinib (ALTA) Rate - LIVER DISORDER	0.06	Beta 95% CI: 0.05-0.16	
Brigatinib (ALTA) Rate - MACULAR OEDEMA	0.01	Beta 95% CI: 0-0.03	
Brigatinib (ALTA) Rate - MALIGNANT PLEURAL EFFUSION	0.02	Beta 95% CI: 0.01-0.08	
Brigatinib (ALTA) Rate - MENINGITIS BACTERIAL	0.01	Beta 95% CI: 0-0.03	
Brigatinib (ALTA) Rate - MUSCULAR WEAKNESS	0.01	Beta 95% CI: 0-0.03	
Brigatinib (ALTA) Rate - NAUSEA	0.01	Beta 95% CI: 0-0.03	
Brigatinib (ALTA) Rate - NERVOUS SYSTEM DISORDER	0.01	Beta 95% CI: 0-0.03	
Brigatinib (ALTA) Rate - OSTEOARTHRITIS	0.01	Beta 95% CI: 0-0.03	

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in original submission
Brigatinib (ALTA) Rate - OSTEONECROSIS	0.01	Beta 95% CI: 0-0.03	
Brigatinib (ALTA) Rate - PAIN	0.08	Beta 95% CI: 0.07-0.2	
Brigatinib (ALTA) Rate - PANCREATIC DISORDER	0.02	Beta 95% CI: 0.01-0.08	
Brigatinib (ALTA) Rate - PARAESTHESIA	0.01	Beta 95% CI: 0-0.05	
Brigatinib (ALTA) Rate - PERIPHERAL ARTERY STENOSIS	0.01	Beta 95% CI: 0-0.03	
Brigatinib (ALTA) Rate - PERIPHERAL SENSORY NEUROPATHY	0.01	Beta 95% CI: 0-0.03	
Brigatinib (ALTA) Rate - PHOTOSENSITIVITY REACTION	0.01	Beta 95% CI: 0-0.03	
Brigatinib (ALTA) Rate - PLEURAL EFFUSION	0.01	Beta 95% CI: 0-0.03	
Brigatinib (ALTA) Rate - PNEUMONIA	0.08	Beta 95% CI: 0.07-0.2	
Brigatinib (ALTA) Rate - PULMONARY EMBOLISM	0.02	Beta 95% CI: 0.01-0.06	
Brigatinib (ALTA) Rate - PYREXIA	0.01	Beta 95% CI: 0-0.03	
Brigatinib (ALTA) Rate - RADIATION NECROSIS	0.01	Beta 95% CI: 0-0.03	
Brigatinib (ALTA) Rate - RESPIRATORY INFECTION	0.01	Beta 95% CI: 0-0.03	
Brigatinib (ALTA) Rate - SIMPLE PARTIAL SEIZURES	0.01	Beta 95% CI: 0-0.05	
Brigatinib (ALTA) Rate - SKIN INFECTION	0.01	Beta 95% CI: 0-0.03	
Brigatinib (ALTA) Rate - SUBCUTANEOUS ABSCESS	0.01	Beta 95% CI: 0-0.03	
Brigatinib (ALTA) Rate - SWELLING/RASH	0.03	Beta 95% CI: 0.02-0.1	
Brigatinib (ALTA) Rate - SYNCOPE	0.01	Beta 95% CI: 0-0.05	
Brigatinib (ALTA) Rate - TOOTH ABSCESS	0.01	Beta 95% CI: 0-0.03	
Brigatinib (ALTA) Rate - TOOTH SOCKET HAEMORRHAGE	0.01	Beta 95% CI: 0-0.03	
Brigatinib (ALTA) Rate - TUBERCULOUS PLEURISY	0.01	Beta 95% CI: 0-0.03	
Brigatinib (ALTA) Rate - UROSEPSIS	0.01	Beta 95% CI: 0-0.03	
Brigatinib (ALTA) Rate - WEIGHT DECREASED	0.01	Beta 95% CI: 0-0.03	

Submission from Roy Castle Lung Cancer Foundation, for consideration by NICE, in their review of Brigatinib for treating ALK-positive non-small cell lung cancer after Crizotinib [ID1328]

Submitting Organisation

Roy Castle Lung Cancer Foundation is a UK wide lung cancer charity. We fund lung cancer research, tobacco control initiatives and work in lung cancer patient care (information, support and advocacy activity).

The Foundation has contact with patients/carers through its UK wide network of over 50 monthly Lung Cancer Patient Support Groups, online Forums and its Lung Cancer Information Helpline.

Clearly, our patient group members and contacts are a self-selected group, who have taken the step to seek out information or have accessed specialist support services. As most lung cancer sufferers tend to be older, from lower social class groups and with the five year survival being around 10%, less physically well, we acknowledge that our patients are perhaps not representative of the vast majority of lung cancer patients, who are not so well informed. It is, however, important that the opinions expressed to us, be passed on to NICE, as it considers the place of this product in the management of non small cell lung cancer (nsclc).

General Points

1. For patients with advanced or metastatic nsclc, cure is not a treatment option. In this scenario, improving quality of life, symptom management and even small extensions in duration of life are of considerable significance to the individual and their family.

2. The relatively recent addition of targeted therapies and immunotherapy, in the treatment of nsclc, has ensured active therapy options for many with nsclc. However, overall outcomes for many of this patient population remains poor. The availability of new targets and therapy choices being of key future importance.

3. The importance of 'end of life' therapies. When considering the cost of treatment, it is not appropriate, for example, to give the same weighting to the final six months of life, as to all other six months of life. It is important for this to be part of any numeric equation, which is looking at cost and quality of life. This point is of crucial importance to patients and relatives in this situation

4. Improvement in symptoms. Patients with advanced or metastatic non small cell lung cancer are often debilitated with multiple and distressing symptoms. Symptoms such as breathlessness are very difficult to manage clinically. Therapies with anti-tumour activity often provide the best option for symptom relief.

This Product

1. Very targeted population.

   The ALK gene rearrangement is found in about 2% to 7% of patients with nsclc. These patients tend to be younger and more likely to be light/non-smokers, as compared to the general lung cancer population. With that in mind, it is our observation that, though a younger, fitter patient group (fewer co-morbidities), ALK positive patients tend to be diagnosed later, as they do not fit the 'typical' lung cancer patient profile.

   Crizotinib and Certitinib have both been approved by NICE for untreated ALK positive nsclc patients. Alectinib is currently undergoing NICE appraisal in the untreated group. Ceritinib has NICE approval for this patient group, after Crizotinib treatment

   These drugs work in part by blocking the activity of the ALK protein, ultimately inhibiting the growth of tumour cells. Patients typically develop resistance to these drugs when tumour cells develop new gene alterations, in the ALK gene, which renders the protein insensitive to the inhibitor. It appears that most patients progress under ALK inhibition within two years, the brain being a common site of relapse. Each ALK inhibitor has a different spectrum of sensitivity to ALK mutations, thus making complex the optimal sequencing of ALK inhibitors. We understand that studies have suggested that Brigatinib may be able to overcome a broader range of the resistance mechanisms that result from secondary mutations in the ALK gene, compared with other currently available ALK inhibitors.

2. Well tolerated
   Oral therapy - therefore, ease of administration.

   As above, there are several ALK inhibitors already in regular practice. As such, experience in use and side effect management is now commonplace. We understand that common side effects associated with Brigatinib include diarrhea, nausea, vomiting, tiredness, abdominal pain, cough, headache and decreased appetite. Brigatinib may also cause more serious side effects, such as high blood pressure, high blood sugar, pancreatitis, hepatotoxicity, lung toxicity and cardiac problems including bradycardia. In the anecdotal patient experience available to us, it appears to be generally well tolerated.

3. Outcome of treatment

   We do not have any additional data, beyond that publically available.

   We note, however, the results of the Phase 11 ALTA Study. All patients in the study had progressed on Crizotinib treatment and had tumours with a positive ALK test. A total of 222 patients were randomised to receive Brigantinib orally either 90mg once daily or 180mg once daily, following a 7 day lead in at 90mg daily. 154 patients (69%) had baseline brain metastasis.
   Overall Response Rate (ORR) was 48% in the 90mg arm and 53% in the 180mg arm. Results were reported after a median follow-up of 8 months., showing an ORR of 45% and 54% in the 90mg and 180mg arms respectively. Median PFS was 9.2months and 12.9months respectively.

In patients with measurable brain metastasis at baseline, intracranial ORR was 42% in the 80mg arm and 67% in the 180mg arm. For patients with an intracranial response, 78% (in the 90mg arm) and 68% (in the 180mg arm) maintained an intracranial response for at least 4 months.

Our observations come from a combination of one-to-one discussion with lung cancer patients, published research, on line patient contact and our patient information helpline.

In summary

ALK gene rearrangement is found in a very small number of lung cancer patients. Brigatinib offers a further therapy option for those patients who have relapsed after Crizotinib treatment. In particular, it shows intracranial activity and response in a broader range of ALK resistance mutations.

[redacted]

March 2018.

NICE National Institute for Health and Care Excellence

Professional organisation submission

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

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	BTOG/NCRI/RCP/RCR/ACP

3. Job title or position	Consultant Medical Oncologist
4. Are you (please tick all that apply):	☐ other (please specify): Joint BTOG/NCRI/RCP/RCR/ACP response
5a. Brief description of the organisation (including who funds it).	The British Thoracic Oncology Group (BTOG) is a not-for-profit charity aiming to improve outcomes for patients with thoracic malignancies through optimal care, professional education, and research. It is funded by unrestricted educational grants from Industry and delegate registrations. It explicitly receives no funding from the tobacco or asbestos industries. National Cancer Research Institute (NCRI) Royal College of Physicians (RCP) Royal College of Radiologists (RCR) The Association of Cancer Physicians (ACP)
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to	The main aims of treatment for metastatic ALK+ NSCLC patients are to improve progression-free survival through tumour responses, and thereby improve patient quality-of-life and ultimately survival. Many patients

stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	with relapsed ALK+ NSCLC progressing on crizotinib will progress with brain metastases. A key aim of treatment is to result in intra-cranial responses and thus improved intracranial control.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	The current NICE-approved therapies for ALK+ patients progressing on first-line crizotinib are ceritinib (TA395) or platinum-based chemotherapy. In practice chemotherapy is rarely used due to toxicities and its limited efficacy and ceritinib is generally used due to marked superior efficacy over chemotherapy (ASCEND 5 trial). A clinically significant treatment would result in both extracranial and intracranial tumour responses in patients, and result in a median progression-free survival at least as good as that observed with ceritinib and ideally superior. Given the difficult toxicities observed with ceritinib (including nausea, vomiting, and diarrhoea, which compromise ceritinib dosing and result in frequent dose reductions) even an equivalent efficacy with less toxicities (a surrogate being dose-intensity) would be welcome.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, there is an unmet need currently, but this will change. The current usual treatment for patients progressing after crizotinib is ceritinib (TA395). However, the toxicities of ceritinib (eg gastrointestinal) are very difficult for patients and usually compromise dose administered. There is therefore a significant need for an alternative agent that has at least as good efficacy (progression-free survival) as ceritinib with better tolerability. However, the numbers of patients on crizotinib will gradually fall over time. This is because the first-line treatment for ALK+ NSCLC patients is changing and currently few patients are being commenced on crizotinib. This is because ceritinib and alectinib are more efficacious. Ceritinib has been recently NICE approved (January 2018) as an alternative to crizotinib for first-line use (TA500), but its clinical uptake has been modest, given its toxicities, with clinicians preferring to use alectinib instead. Alectinib is licensed for first-line ALK+ NSCLC, was shown to be superior to crizotinib in a randomized phase 3 trial (ALEX trial, Peters et al. NEJM 2017) and seems more efficacious and less toxic than ceritinib in cross trial comparisons. Since September 2017 it has been accessed in the UK via the UK EAMS scheme until closure December 2017. Thereafter some access may have been granted on a compassionate use basis

	from the manufacturer. The NICE appraisal for first-line alectinib is ongoing (ID925). If NICE approve first-line alectinib, this will become used as standard and if not, ceritinib will be used. It is therefore unlikely that newly diagnosed ALK+ NSCLC patients will be commenced on crizotinib and thus the pool of ALK+ patients progressing on crizotinib suitable for brigatinib will fall over time. Nevertheless, since crizotinib has been standard care for ALK+ NSCLC initially since July 2012 (licensing date and UK access via compassionate use from the manufacturer prior to CDF approval, and then TA422 approval, with subsequent TA406), there will be significant numbers of patients still alive taking crizotinib for whom brigatinib would be suitable on progression, and a potentially a preferred option over ceritinib.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	In general, untreated ALK+ advanced NSCLC is currently treated with first-line ceritinib (TA500) or the preferred option has been to use alectinib. This was accessed via the UK EAMS scheme until closure in December 2017 and thereafter some access may have been granted on a compassionate use basis from the manufacturer. The NICE appraisal for first-line alectinib is ongoing (ID925). If NICE approve first-line alectinib, this will become used as standard and if not, ceritinib will be used. It is therefore unlikely that newly diagnosed ALK+ NSCLC patients will be commenced on crizotinib and thus the pool of ALK+ patients progressing on crizotinib suitable for brigatinib will fall over time. Nevertheless, until 4Q2017 the standard of care for ALK+ advanced NSCLC has been crizotinib, which has been used in the UK since July 2012 (licensing date and access via compassionate use from manufacturer prior to CDF approval and then TA422 approval, with subsequent TA406), there will be significant numbers of patients still alive taking crizotinib. For ALK+ NSCLC patients on crizotinib, either commenced when untreated (TA406) or when previously treated (TA422), the current standard on progression is ceritinib (TA395). However, the drug is poorly tolerated due to toxicities (eg gastrointestinal) and dose reductions are frequent.

• Are any clinical guidelines used in the treatment of the condition, and if so, which?	The updated ESMO clinical practice guidelines for advanced NSCLC (Novello et al. Ann Oncol (2016)) have been updated and will be published in 3Q2018. The current ASCO 2016 clinical practice guideline update (Masters et al. J Clin Oncol, 2015) The BMJ best practice guidelines: http://bestpractice.bmj.com/topics/en-gb/1082 Due to the rapidly changing trial data published for ALK+ NSCLC coupled to licensing changes, all these guidelines are currently out of date. The most up-to-date guidelines are the US NCCN guidelines on NSCLC v3.2018 https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	As of 2018 there is broad consensus in the UK that using a next-generation ALK inhibitor such as ceritinib (TA500) or alectinib (ID925) is the optimal strategy as first-line for untreated ALK+ NSCLC, rather than starting with crizotinib (TA406) and then switching to a next-generation ALK inhibitor on relapse (eg ceritinib TA395). Thus the pool of patients currently receiving crizotinib will gradually reduce.
• What impact would the technology have on the current pathway of care?	No major impact, it would be a potential alternative to ceritinib post crizotinib (TA395)
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes

• How does healthcare resource use differ between the technology and current care?	No change
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	In secondary care
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Nil
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. Whilst there is no direct head-to-head data comparing brigatinib with ceritinib (the current UK standard post crizotinib), the ALTA trial data demonstrated a marked overall progression-free survival overall, intracranial progression-free survival, and favourable toxicity profile superior to that observed in trial data with ceritinib.
• Do you expect the technology to increase length of life more than current care?	Yes. Given the clinically meaningful overall progression-free survival overall, intracranial progression-free survival, and favourable toxicity profile of brigatinib observed in ALTA, beyond that observed in trial data with ceritinib, I would expect this to ultimately translate to an improved survival.

• Do you expect the technology to increase health-related quality of life more than current care?	Yes, markedly so. Ceritinib is associated with marked toxicities eg gastrointestinal, including diarrhoea (with urge incontinence), nausea and vomiting. Other limiting toxifies of ceritinib include transaminitis, hyperglycaemia and hypophosphataemia. Marked dose reductions are required for ceritinib to be tolerable which may impact of clinical efficacy given the potential subsequent inadequate CNS control. The toxicity profile of brigatinib is much more favourable and hence quality of life at the approved dose.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	There are no practical implications in implementing brigatinib. If approved, it would serve as an alternative to ceritinib in the TA395 indication.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Patients will be evaluated regularly through CT scans and if needed MRI brain imaging. This is not beyond usual care and not beyond that currently associated with ceritinib.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
16. Do you consider the technology to be innovative in its potential to make a significant and substantial	Yes, innovative in so far as it seems markedly more efficacious (cross trial comparisons) to ceritinib with much less toxicities and hence improved dose-intensity.

impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	No
• Does the use of the technology address any particular unmet need of the patient population?	Yes, there is currently a need for an efficacious non-toxic nest-generation ALK inhibitor for patients progressing on crizotinib. Currently ceritinib is NICE approved for this indication (TA395). However, whilst effective, ceritinib is limited by marked toxicities (eg gastrointestinal) and dose reductions are frequent. This may impact on efficacy outcomes. There is therefore a need for an effective tolerable ALK inhibitor post crizotinib. Alectinib is licensed for this indication but unavailable in the UK (TA438). Hence, brigatinib would be a favoured suitable alternative to ceritinib.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The side-effects are well documented from the ALTA trial data. At the established dose (180mg daily with run-in) this trial demonstrated number of patients reporting grade 3 or more toxicities was small. 6% patients developed a CPK rise (a class effect) and 6% hypertension (a unique effect). Brigatinib dose reductions were 20% in the 180mg dose arm (cf 80% for ceritinib, ACEND 5 trial) and mean quality of life measure (q29/30, EORTC QLQ-C30) measures improved on treatment compared with baseline. In practice

	quality of life of patients generally improves post crizotinib as disease responds. The CPK and hypertension adverse events causing dose reductions do not impact of quality of life.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	These were progression-free survival, objective response rate, intracranial response rate, duration of intracranial response, dose intensity, grade 3+ toxicities, quality of life. Yes, these were measured in the ALTA trial, a large phase 2 trial that confirmed the optimal dosing schedule of brigatinib.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Overall survival will be difficult to model and will have considerable uncertainty, given the relative immaturity of the ALTA trial data and that median survival for ALK+ patients is now routinely measured in years.
• Are there any adverse effects that were not apparent in clinical trials	No, not in the reported literature or my personal experience.

but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) in this patient population since the publication of NICE technology appraisal guidance TA395?	Yes. The ASCEND 8 trial data are now published (Cho et al. J Thoracic Oncol (2017)) suggesting that a ceritinib dose of 450mg OD given with food has similar progression-free survival to the standard dose (750mg OD fasting) with considerably fewer gastrointestinal toxicities. However, the impact of this dose reduction on intracranial control cannot be evaluated since routine CNS evaluation was not incorporated into the trial. Moreover the progression-free survival curves have not been presented for viewing, with only median figures presented. The ASCEND 5 trial has been published (Shaw et al. Lancet Oncol (2017)). This was a randomized phase 3 trial comparing ceritinib (750mg fasting) vs single agent chemotherapy and for ceritinib, demonstrated a median progression-free survival of 5.4 months, objective response rate of 39%, median duration of response 6.9 months, with median relative dose intensity of 82%. The intracranial response rate was 35% with a median duration of response 6.9 months.
21. How do data on real-world experience compare with the trial data?	I am not aware of UK-based real world data on ceritinib experience.

Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	N/A
Key messages	
23. In up to 5 bullet points, please summarise the key messages of your submission. • ALK+ NSCLC patients progressing on crizotinib are currently treated with ceritinib • Ceritinib use is limited by unpleasant toxicities eg gastrointestinal that result in dose reductions and may impact on efficacy • Brigatinib offers an alternative to ceritinib • Cross trials comparisons suggest superior efficacy (especially intra-cranially) and tolerability with brigatinib • The pool of patients on crizotinib will gradually dwindle as next-generation ALK inhibitors are preferred to crizotinib	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Professional organisation submission

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

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Sally Welham**
2. Name of organisation	**British Thoracic Society**

3. Job title or position	**Deputy Chief Executive**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The British Thoracic Society (BTS) is the professional society for respiratory medicine and related health care professions. The Society exists to improve standards of care for people who have respiratory diseases and to support and develop those who provide that care. It is a registered charity and a company limited by guarantee.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**NO**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	

or prevent progression or disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	The British Thoracic Society supports the proposed appraisal. There is an urgent need more treatment options for patients with advanced lung cancer given the very poor prognosis.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	
• Are any clinical guidelines used in the treatment of the	

condition, and if so, which?	
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	
• In what clinical setting should the technology be	

used? (For example, primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	
• Does the use of the technology address any particular unmet need of the patient population?	
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	

• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
20. Are you aware of any new evidence for the comparator	

treatment(s) in this patient population since the publication of NICE technology appraisal guidance TA395?	
21. How do data on real-world experience compare with the trial data?	
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	
22b. Consider whether these issues are different from issues with current care and why.	
Key messages	

23. In up to 5 bullet points, please summarise the key messages of your submission.

-
-
-
-
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Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NHS England submission on the NICE appraisal of brigatinib after previous treatment with crizotinib in the treatment of locally advanced/metastatic ALK mutation positive non small cell lung cancer

1. There are 3 NICE-recommended monotherapy options for the 1st line treatment of ALK positive non small cell lung cancer (NSCLC): alectinib, ceritinib and crizotinib. The use of crizotinib has fallen away rapidly owing to the superiority of alectinib and ceritinib. Alectinib is the main 1st line option currently used in NHS England for newly diagnosed patients on account of its better tolerability (ceritinib has considerable gastrointestinal toxicity). NHS England does not commission the use of crizotinib post ceritinib or alectinib and nor does it commission any treatment sequence other than 1st line crizotinib followed by 2nd line ceritinib. As has been stated already, this treatment sequence now only applies to patients commenced on 1st line crizotinib in the past or in those rare patients who cannot tolerate alectinib and/or ceritinib.
2. The likely marketing authorisation for brigatinib for the indication under NICE appraisal will be for use following previous treatment with crizotinib. This therefore means that the population of eligible patients for brigatinib for this indication has diminished and will continue to do so. Nevertheless, NHS England welcomes Takeda's submission to NICE for this post-crizotinib indication as another manufacturer chose not to submit to NICE for the use of alectinib post crizotinib.
3. The current correct comparator for brigatinib in this post-crizotinib indication is ceritinib.
4. Brigatinib is clearly a very active drug in ALK pos NSCLC in patients previously treated with crizotinib. Crude comparison of different data sources in respect of the efficacy of brigatinib versus ceritinib points to brigatinib appearing to have higher response rates and a greater effect on progression free survival. Toxicity of brigatinib also appears to be less, particularly with less gastrointestinal side-effects (the main issue for patients on ceritinib).
5. NHS England also knows that treatment with brigatinib will continue after RECIST-defined disease progression in two main scenarios. The first is when there is a dimensionally small increase in an already small marker lesion: this would trigger definition of disease progression but is clinically irrelevant as the patient remains well; brigatinib would thus continue until there is clinically significant progression ie the development of symptoms. The second is when there is continued systemic response to brigatinib but disease progression in the brain which is then amenable to active treatment with radiotherapy of various types. Treatment would continue until systemic progression or loss of control of the intra-cerebral disease. NHS England considers it likely that the marketing authorisation of brigatinib will recommend use to continue until there is loss of clinical benefit.

6. The economic model needs to include drug wastage because there is likely to be more drug wastage with ceritinib than brigatinib.
7. NHS England notes that the drug administration cost per cycle assumed for brigatinib/ceritinib is not the correct one. These drugs are high cost chemotherapy drugs and thus the oral chemotherapy administration tariff should be used. This in 2017/18 is £120.
8. If NICE recommends brigatinib in this expected indication, NHS England treatment criteria for the use of brigatinib will reflect the MA if it is confirmed that use of brigatinib is to be confined to patients previously treated with crizotinib for ALK pos NSCLC. In addition, ceritinib post-brigatinib and brigatinib post-crizotinib will not be commissioned unless patients show early intolerance of ceritinib/brigatinib and there is no sign of disease progression.

[redacted]

[redacted]

July 2018

NICE National Institute for Health and Care Excellence

Clinical expert statement

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

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**The Christie and Manchester University Foundation Trusts**

3. Job title or position	**Consultant Medical Oncologist**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? **x**☐ a specialist in the treatment of people with this condition? **x**☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it **x**☐ other (they didn't submit one, I don't know if they submitted one etc.) I have not seen the RCP/NIHR/RCR statement
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The treatment aims to: • improve symptoms • improve survival • delay progression of cancer • induce response (shrinkage of cancer) or stabilisation • improve or maintain quality of life
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	RECIST criteria for response are clinically meaningful. In addition, stabilisation of disease with tolerable side effects is clinically meaningful. Clinical activity in the CNS is meaningful particularly as CNS spread of cancer is a source of significant morbidity in this type of NSCLC (about 70% of patients in the ALTA study had brain metastases).
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, the patients' cancers become resistant to all currently available ALK inhibitors (crizotinib, ceritinib)
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	Patients are treated with first line ALK inhibitor (Crizotinib or Ceritinib). If ALK status is not known at diagnosis it is possible that 1st treatment could be with platinum pemetrexed chemotherapy. 2nd line treatment depends on 1st line i.e. If crizotinib used 1st line, then ceritinib would be used 2nd and chemo 3rd, if ceritinib 1st line , then chemo would be 2nd line.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	ESMO, ASCO, NCCN. However some of these guidelines include 3rd generation ALK TKIs which have not yet been NICE appraised • ESMO recommends ceritinib and alectinib second line • ASCO recommends ceritinib second line but acknowledges that the FDA has approved other agents which it has not yet assessed • NCCN recommends ceritinib, alectinib and brigatinib second line
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Yes. Variation is possible as above, depending on whether ALK status is known at outset, although it is not common in current practice to not have ALK results available at the time of making an initial treatment decision. Also further variation exists as many patients are treated within clinical trials and/or compassionate use programmes.
• What impact would the technology have on the current pathway of care?	Brigatinib would become the 2nd line ALK TKI treatment of choice
11. Will the technology be used (or is it already used) in	Yes, out-patient oncology clinic

the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	Improved: • Tolerability • Response rates and progression free survival • Quality of life • Control of brain metastases
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist oncology clinics
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Standard oncology clinic resources (CT scans, MRI scans, blood tests)
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes

• Do you expect the technology to increase length of life more than current care?	Yes. Demonstrating improved overall survival is not possible at present given the short median duration of follow up in ALTA and the fact that it is a non-comparative phase 2 study, but as care of ALK positive NSCLC patients has improved with increasing use of next generation ALK inhibitors improvements in long term survival are being demonstrated
• Do you expect the technology to increase health-related quality of life more than current care?	Yes, Brigatinib has improved efficacy parameters (as described above) compared to the current second line treatment ceritinib or chemotherapy and has better tolerability
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	no
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for	There is less need for dose reductions with brigatinib compared to ceritinib due to improved tolerability. Both of these agents are oral and so number of visits/scans would be similar, with perhaps slightly more for ceritinib to manage toxicity and dose modifications.

example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	If ceritinib has been used as first line then chemotherapy would be the comparator where there are larger differences. With chemotherapy there are: • More visits – 3 weekly treatment rather than 4 weekly • Chemotherapy unit chair time every 3 weeks (versus OP clinic attendance) • More blood tests • More toxicity • Reduced QoL compared to oral ALK inhibitor (extrapolation from other studies)
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No, patients will be stopped on disease progression, lack of clinical benefit or toxicity. In the situation where disease progression occurs at one site which is amenable to local ablative therapy (surgery or radiotherapy) there may be local treatment to the progressing area and continuation of therapy (as per ESMO guidelines)
16. Do you consider that the use of the technology will result in any substantial health-	Yes, the improved activity in the brain may not be sensitively detected by the QOL measures used to date.

related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes: • substantially improved efficacy in the brain with duration of intracranial response not yet reached in ALTA • broader mutational coverage and therefore potential suppression of resistant clones (including the G1202R mutation)
• Is the technology a 'step-change' in the management of the condition?	Yes, for reasons discussed in previous answers
• Does the use of the technology address any particular unmet need of the patient population?	Resistance to current treatment. Improved brain activity

18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	In general brigatinib is better tolerated than current NICE approved ALK inhibitors and chemotherapy. Low rates of Grade 3 toxicity (<10%) The most common toxicity is gastrointestinal (nausea 30-40% and diarrhoea 20-40%) but these are manageable. QoL of patients on ALTA improved from baselines for the first 7 months of treatment, implying that toxicity was not a significant burden.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes and UK sites participated in the clinical trials
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	The following have been measured in ALTA: RR (54%)

	PFS (12.9 months) 1Year OS (88%) Intracranial response (67%) and intracranial disease control (92%), particularly in those with active untreated brain metastases – RR 73%, intracranial disease control 93% QoL – improved compared to baseline measures
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not to my knowledge
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Yes UK audit data of brigatinib use has been submitted to the world conference on lung cancer (WCLC) and will be presented in September

21. Are you aware of any new evidence for the comparator treatment (ceritinib) since the publication of NICE technology appraisal guidance TA395?	no
22. How do data on real-world experience compare with the trial data?	Comparable. No new safety concerns
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	no
23b. Consider whether these issues are different from issues with current care and why.	no
Topic-specific questions	

24. In clinical practice, would people continue to receive brigatinib after disease progression? If so, for how long?	Some patients may receive brigatinib (or other ALK inhibitor) beyond progression, e.g. if one site of disease is progressing and is suitable for ablative treatment (e.g. radiotherapy) when other disease remains controlled. This is the subject of an on-going UK trial HALT. Data is emerging but to date most data suggests that treatment beyond progression is for around 2 cycles. I suspect that when more data is available about oligoprogressive disease that has been treated with radiotherapy or surgery the time of treatment beyond progression will be longer.
25. Would you expect the benefit of brigatinib to continue after treatment discontinuation? If so, for how long?	I would not anticipate significant benefit beyond discontinuation, but in those who may discontinue for reasons other than PD it maybe a month or two.
26. What is the life expectancy of people with this condition receiving ceritinib?	The best long term data is for patients being followed up from the original Crizotinib studies. Many of these patients have had ceritinib and other ALK inhibitors. Median 5 year survival may now be as high as 5years.
27a. What % of patients receiving brigatinib would you expect to be alive after:	These numbers are very difficult to predict and are to a large extent arbitrary and should be regarded with caution: 3 year – 65%

• 3 years • 5 years • 10 years • 20 years?	5 year – 50% 10 year – 10% 20years- <5%
27b. What % of patients receiving brigatinib would you expect to be progression-free after: • 3 years • 5 years • 10 years • 20 years?	Comment as above with regard to the value of these estimates: 3 years- 20% 5 years – <5% 10 years – 1% 20 years- 1%
27c. What % of patients receiving ceritinib would you expect to be alive after: • 3 years • 5 years • 10 years	Slightly less than brigatinib at each time point

• 20 years?	
27d. What % of patients receiving ceritinib would you expect to be progression-free after: • 3 years • 5 years • 10 years • 20 years?	Slightly less than Brigatinib at each time point
28. In clinical practice, would there be wastage of either drug?	More wastage of ceritinib is likely due to increased toxicity and increased need for dose reduction
Key messages	

29. In up to 5 bullet points, please summarise the key messages of your statement.

- Improved efficacy compared (indirectly) to current second line ALK treatment in terms of ORR, PFS, DoR and 1Year OS
- Improved intracranial activity compared to other currently available treatments, which is of prime importance in a disease where brain metastases are very common and a significant cause of morbidity, mortality and impaired QoL
- Improved tolerability compared to other currently available treatments
- Broader spectrum of mutational coverage and therefore potential suppression of resistant clones
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NICE National Institute for Health and Care Excellence

Patient expert statement

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

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]
2. Are you (please tick all that apply):	☐ A patient with the condition? ☐ a carer of a patient with the condition? x☐ a patient organisation employee or volunteer?

	☐ other (please specify):
3. Name of your nominating organisation	National Lung Cancer Forum for Nurses
4. Did your nominating organisation submit a submission?	☐ yes, they did ☐ no, they didn't **x**☐ I don't know
5. Do you wish to agree with your nominating organisation's submission?	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it **x**☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your	☐ I have personal experience of the condition

statement? (please tick all that apply)	☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: x☐ I am drawing on others' experiences. Please specify how this information was gathered: I am a lung cancer nurse working with patients and carers affected by lung cancer
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Patients advise it is can be a very debilitating disease and they worry about the poor outcomes. They are aware of new treatments and hope they will be eligible for them in the near future Carers advise they find supporting a patient with lung cancer stressful as the symptoms are very debilitating and appear more than other cancers.
Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	Aware of new treatments but worry the timescale for implementation is too long therefore they will deteriorate but having the chance to be eligible.
10. Is there an unmet need for patients with this condition?	Patients with lung cancer need more support due to the severity of symptoms also psychological aspects. Many patients feel guilty and blame themselves and society enforces this attitude. Although new treatments are being developed in order lung cancer patients are living longer there is still lack of support with regards to the psychological distress of the disease.

Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	Patients and carers are optimistic with regards to new treatments and technologies but worry the process is not quick enough for them to benefit
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	
Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Elderly and mentally disabled including those patients with pre existing addiction
Equality	
14. Are there any potential equality issues that should be	**The technology needs to be basic and understood at a level the average lay person can understand and in plain english**

taken into account when considering this condition and the technology?	
Other issues	
15. Are there any other issues that you would like the committee to consider?	
Key messages	
16. In up to 5 bullet points, please summarise the key messages of your statement: • • • • •	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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

A Single Technology Appraisal

Produced by	Peninsula Technology Assessment Group (PenTAG) University of Exeter Medical School, South Cloisters, St Luke's Campus, Heavitree Road, Exeter EX1 2LU
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Contributions of authors

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.
Helen Coelho	Critiqued the clinical effectiveness evidence; wrote the assessment of bias within and across included trials; and the safety analysis sections.
Justin Matthews	Critiqued the indirect treatment comparisons, wrote parts of Chapter 4 and performed additional clinical effectiveness analyses.
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.
Sophie Robinson	Wrote the sections of the report relating to the literature searches.
Adam Dangoor	Provided independent expert clinical advice to the ERG technical team in respect to clinical practice
Nicole Dorey	Provided independent expert clinical advice to the ERG technical team in respect to clinical practice
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)

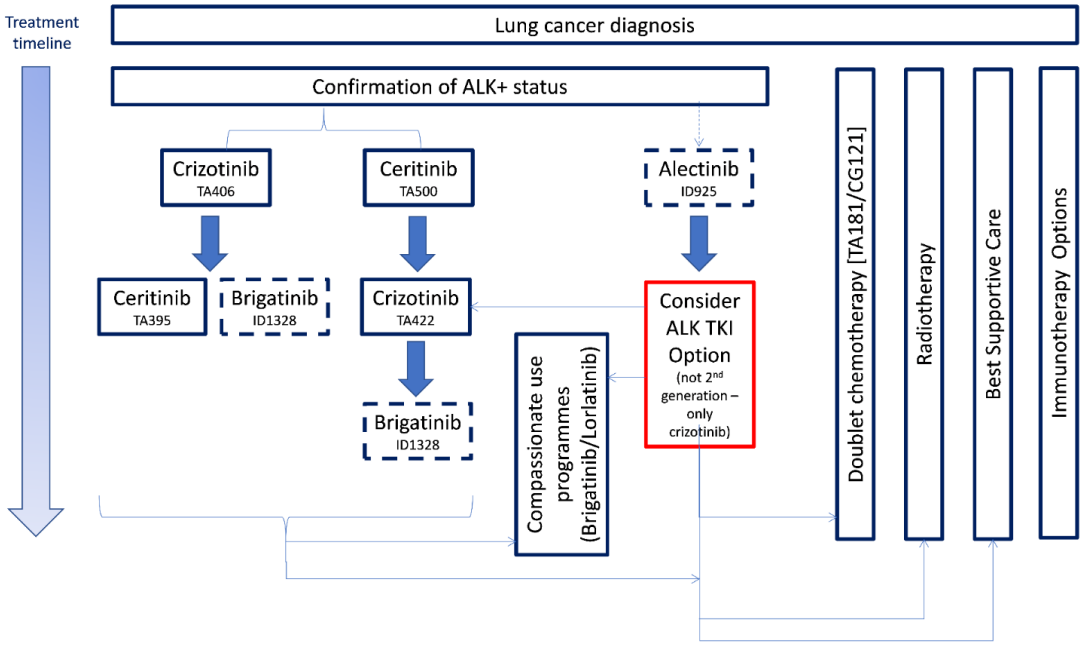
ERG opinion:

- 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		

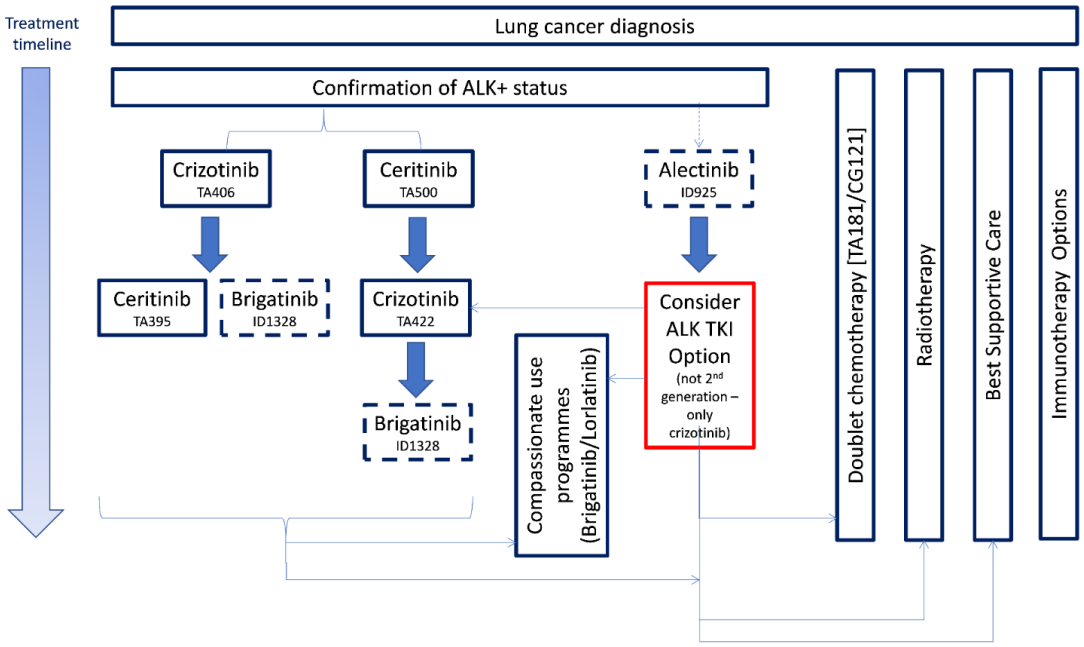
Source: CS, p33, Table 10 (Takeda Ltd)

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)

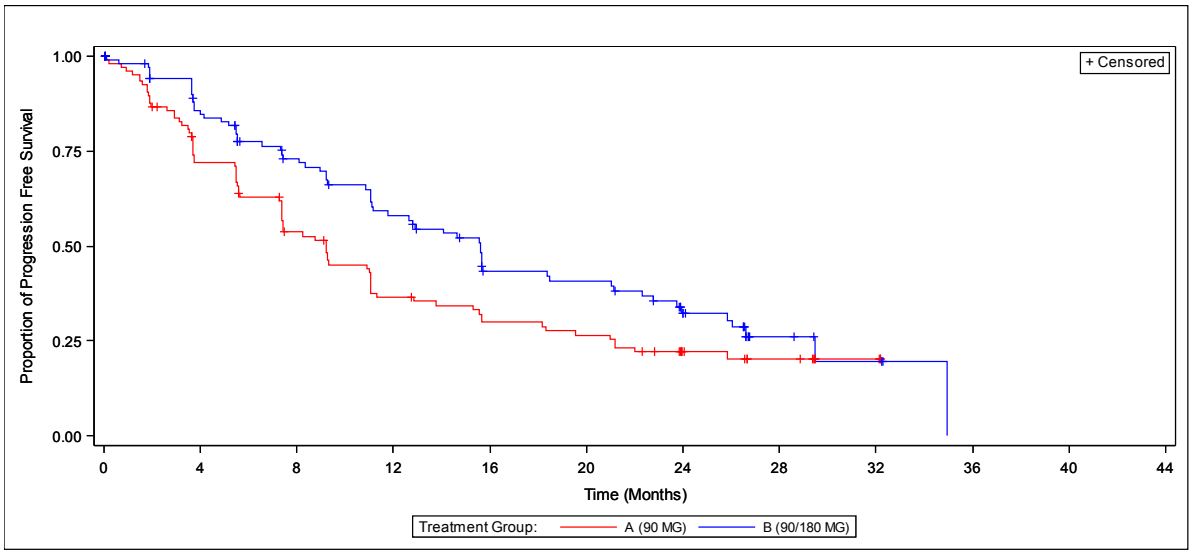
Study 101 provides only investigator-reported (INV) outcomes in this table, whereas INV and independent review committee assessed (IRC) outcomes are both available for ALTA, with the exception of overall survival (OS) for which only INV data are available.

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.

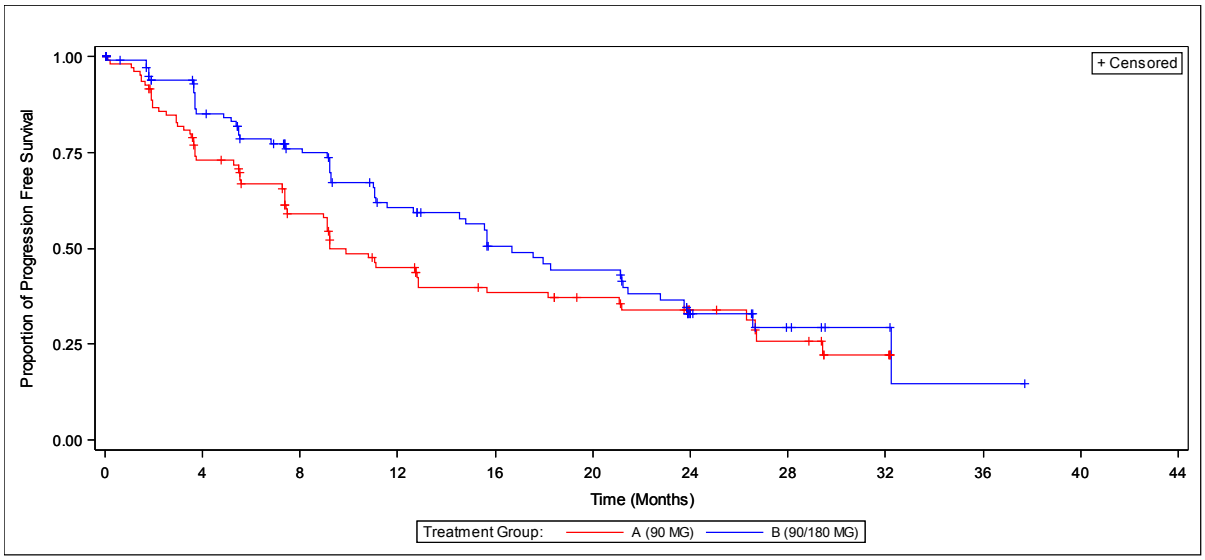
Figure 3. Kaplan-Meier plot of Investigator-assessed progression-free survival by treatment arm in ITT population (September 2017)



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.

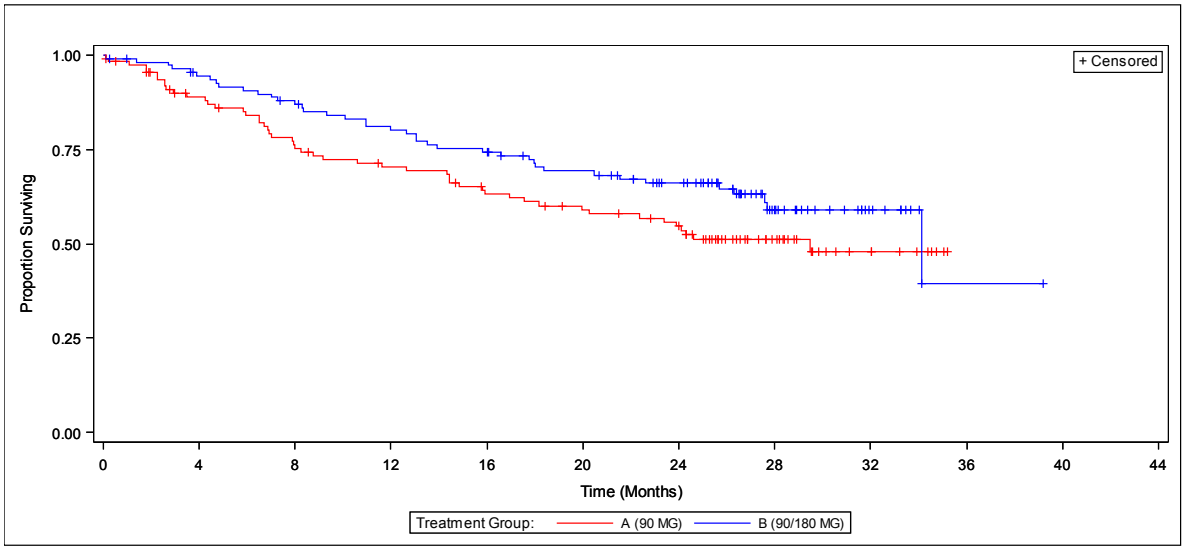
Figure 4. Kaplan-Meier plot of IRC-assessed progression-free survival by treatment arm in ITT population (September 2017)



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.

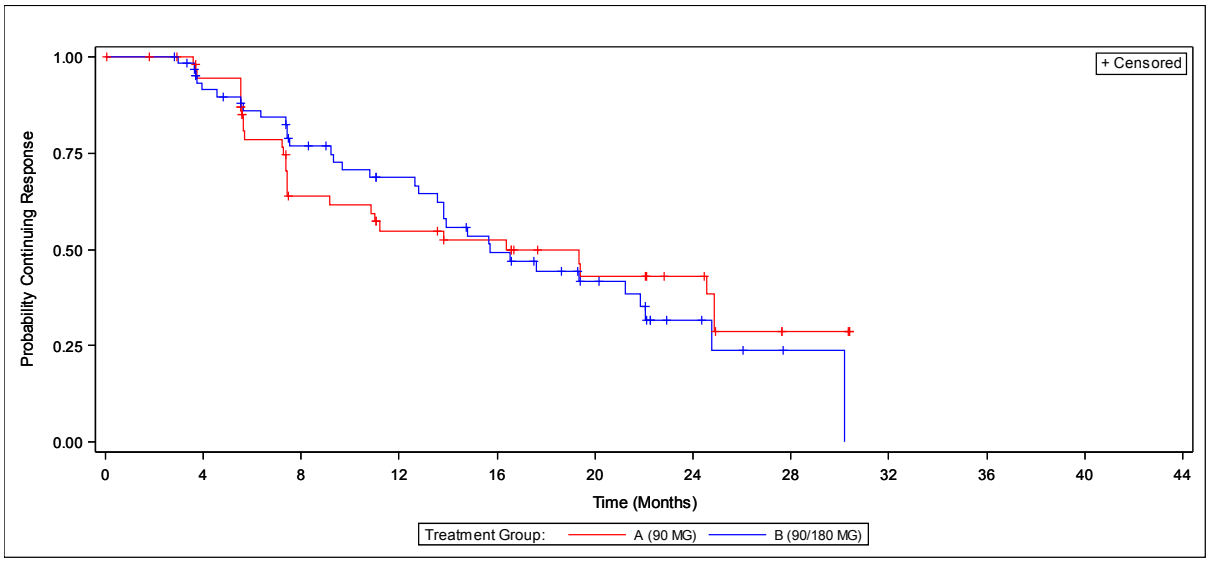
Figure 5. Kaplan-Meier plot of overall survival by treatment arm in ITT population



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.

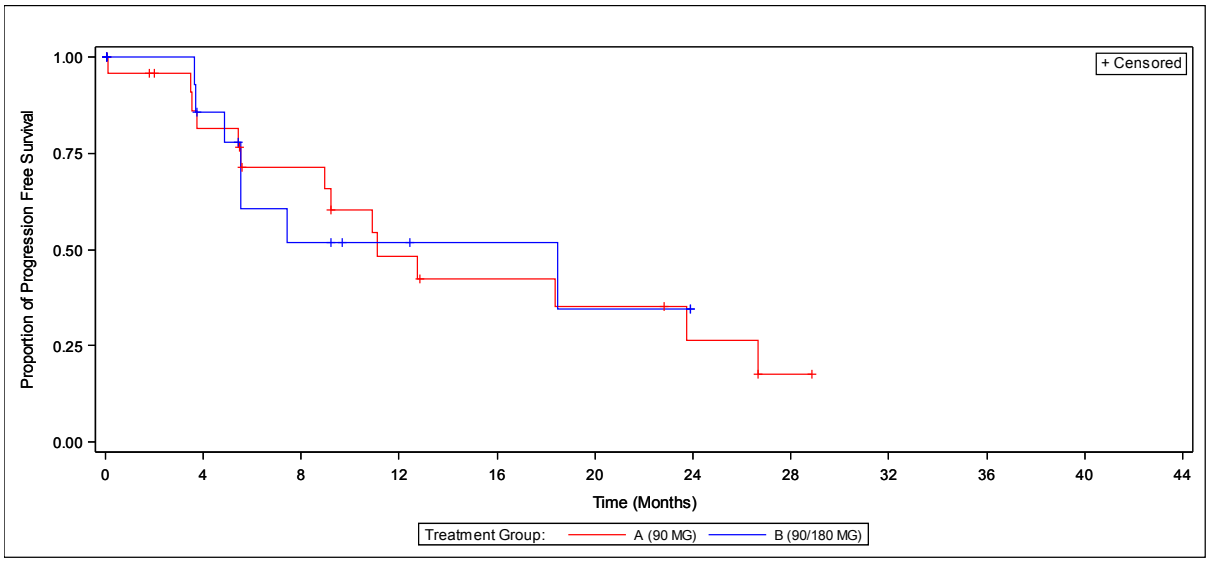
Figure 6. Kaplan-Meier plot of IRC-assessed systemic duration of response, by treatment arm, in the population with IRC-confirmed response, for ALTA



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.

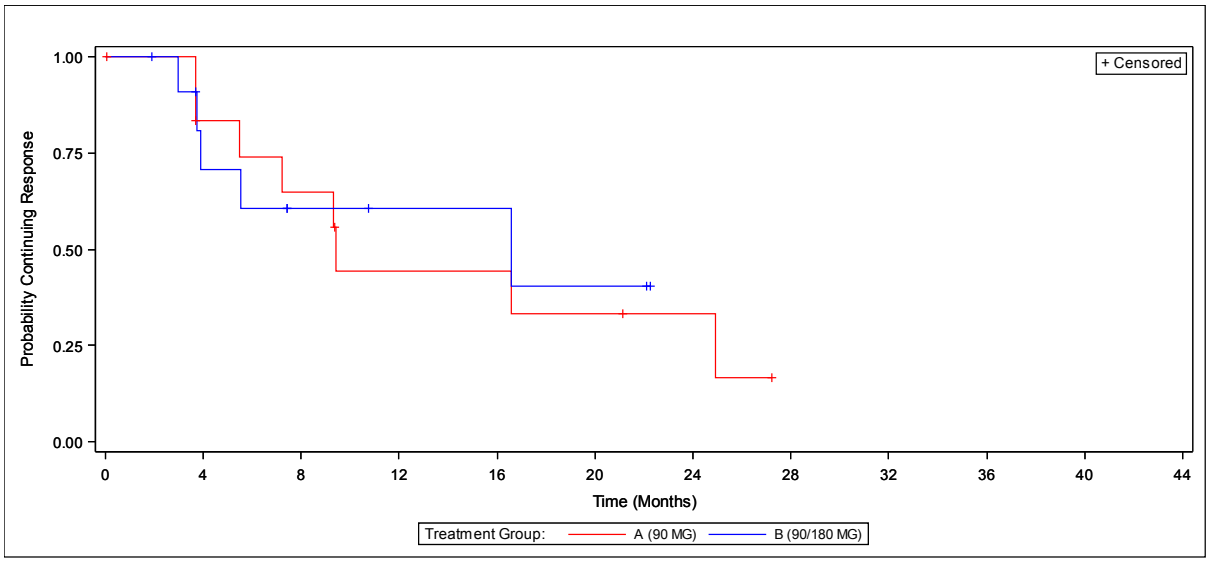
Figure 7. Kaplan-Meier plot of IRC-assessed CNS progression free survival in patients with measurable brain metastases at baseline



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.

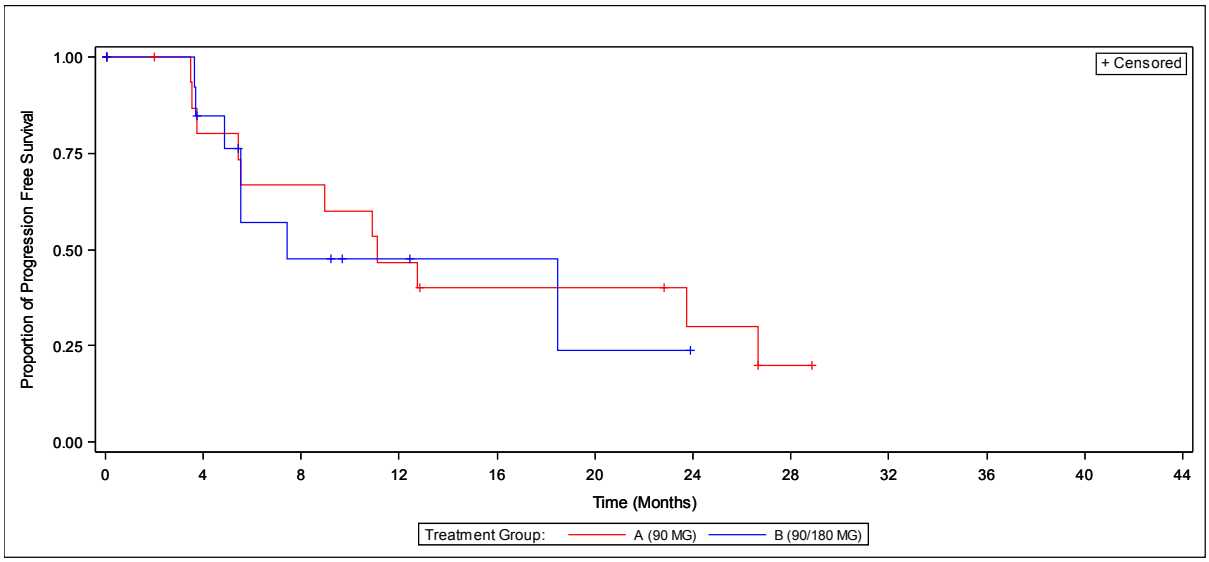
Figure 8. Kaplan-Meier plot of IRC-assessed CNS duration of response in patients with measurable baseline metastases and a confirmed CNS response



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.

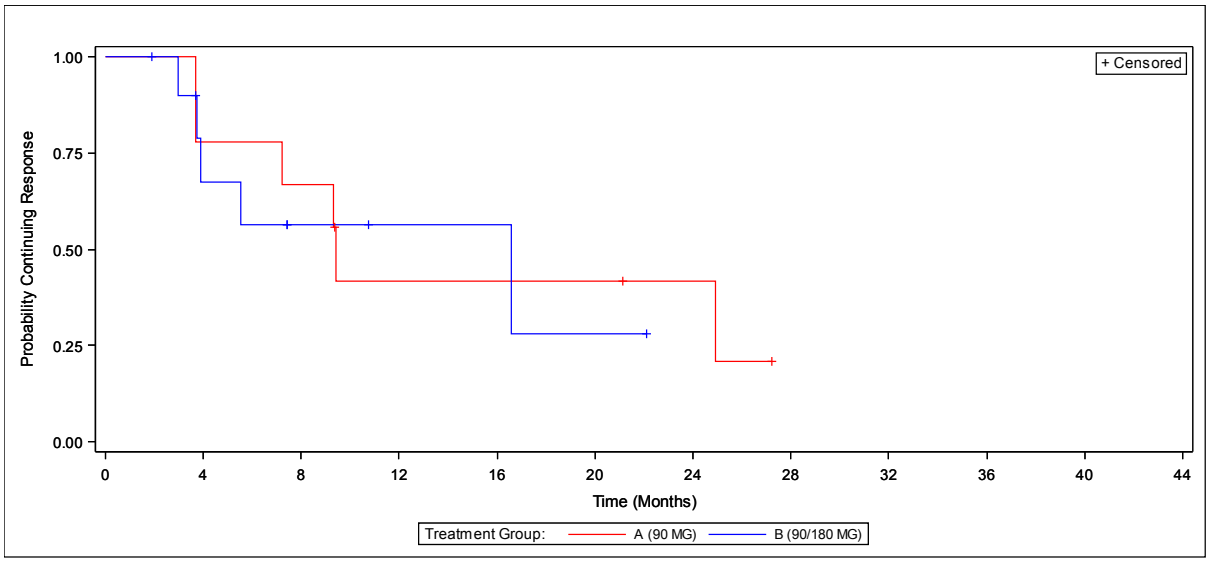
Figure 9. Kaplan-Meier plot of IRC-assessed CNS progression free survival in patients with measurable brain metastases at baseline



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

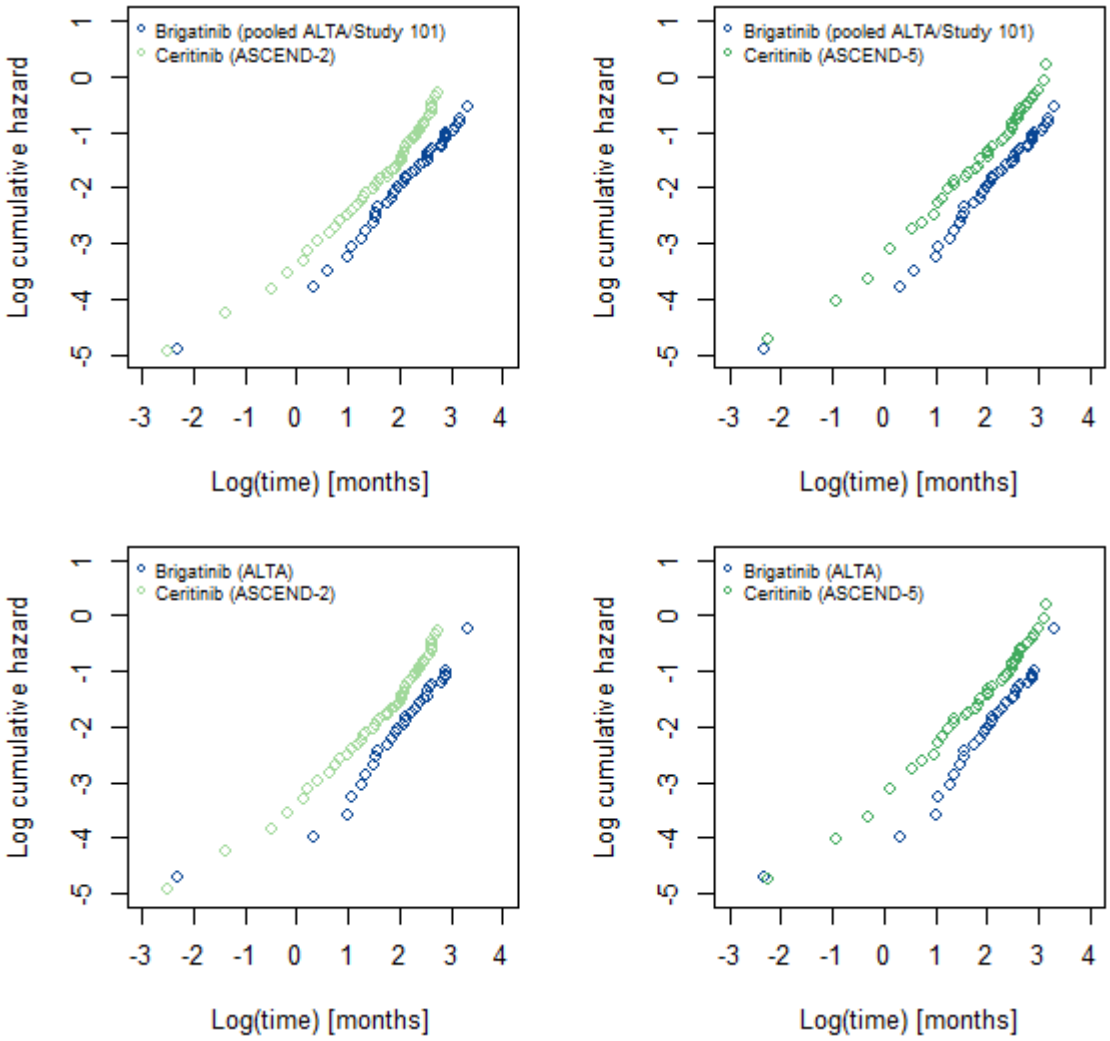
The CS includes the results of analysis conducted using reconstructed ceritinib datasets that were "recreated from published data" (e.g. CS Appendix, p66, Table 15). The table below and log cumulative hazard plots suggest an advantage for brigatinib over ceritinib in unadjusted analysis in terms of median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

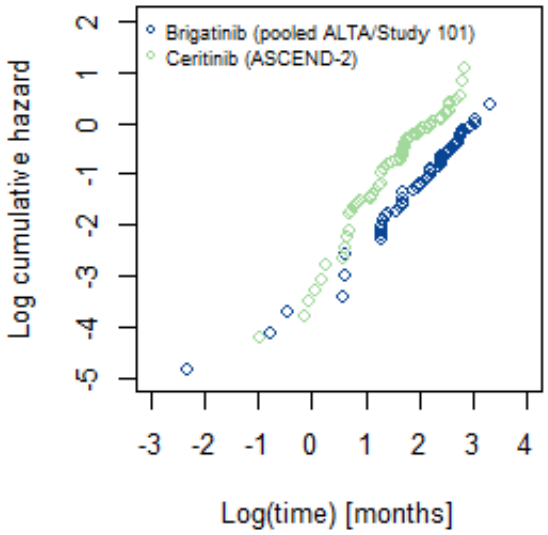
Table 20. Summary of observed median progression-free survival (PFS)

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.

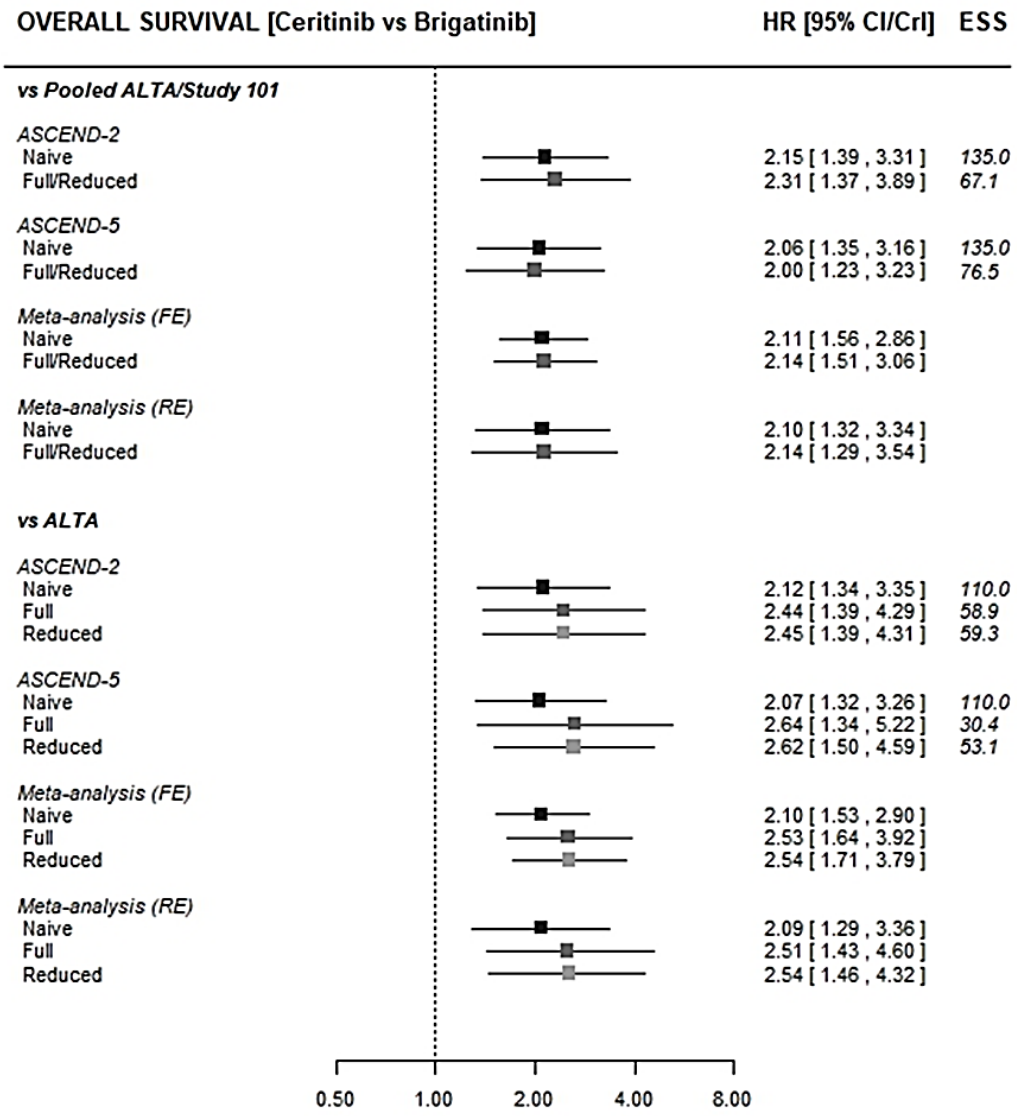
The CS itself acknowledges that there are limitations with regard to the extent of overlap between the patient populations for brigatinib and ceritinib. Assessing the weight distributions from the MAIC analysis, the CS concludes that "the medians are heavily skewed towards zero (0.03) and a large proportion 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

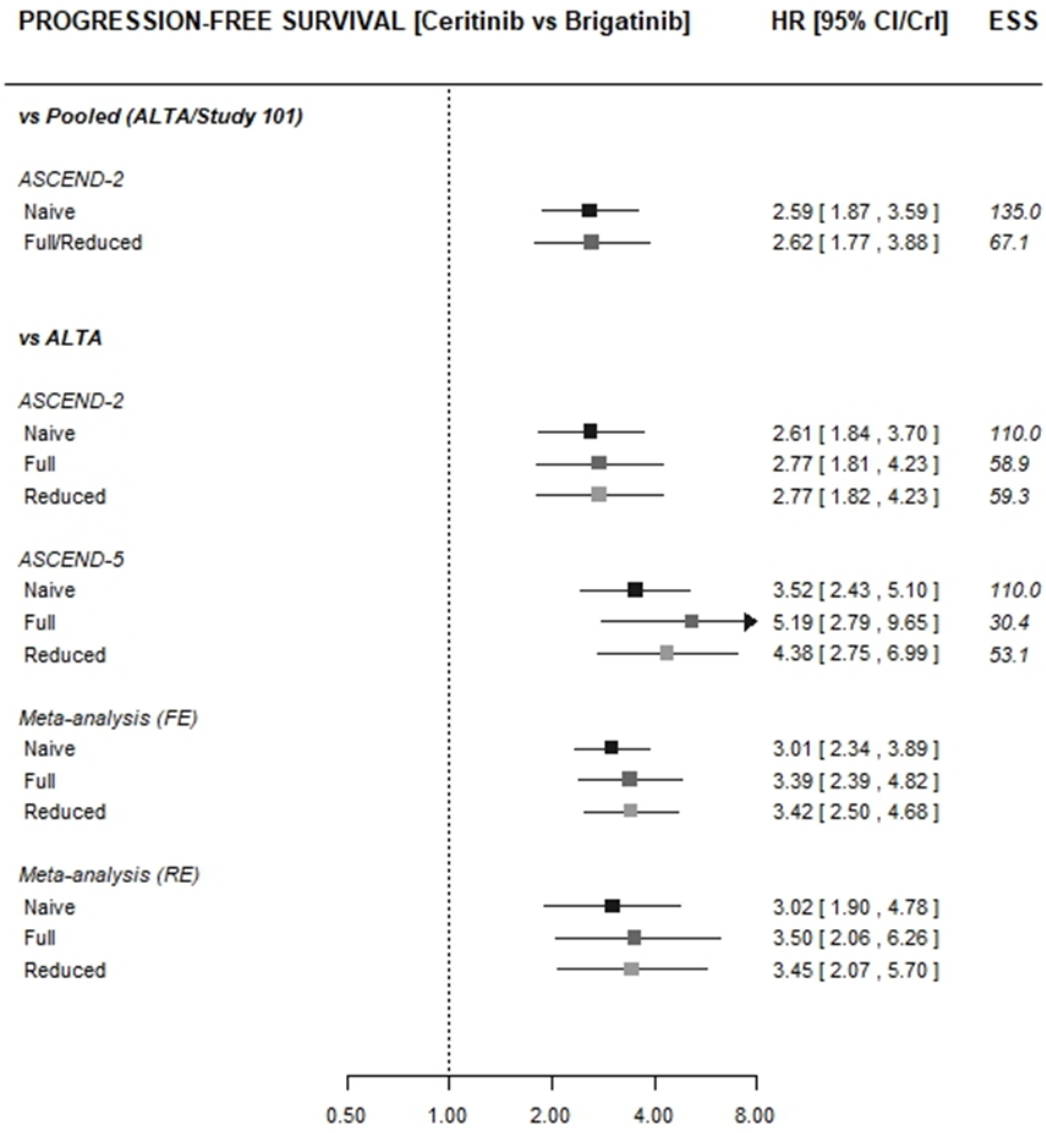


Abbreviations: CI, confidence interval; CrI, credible interval; ESS, effective sample size; FE, fixed-effect; HR, hazard ratio; RE, random-effects. Notes: Naïve estimates denote comparison without adjusting for prognostic factors. Full MAIC estimates denote analysis adjusting for all prognostic factors 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

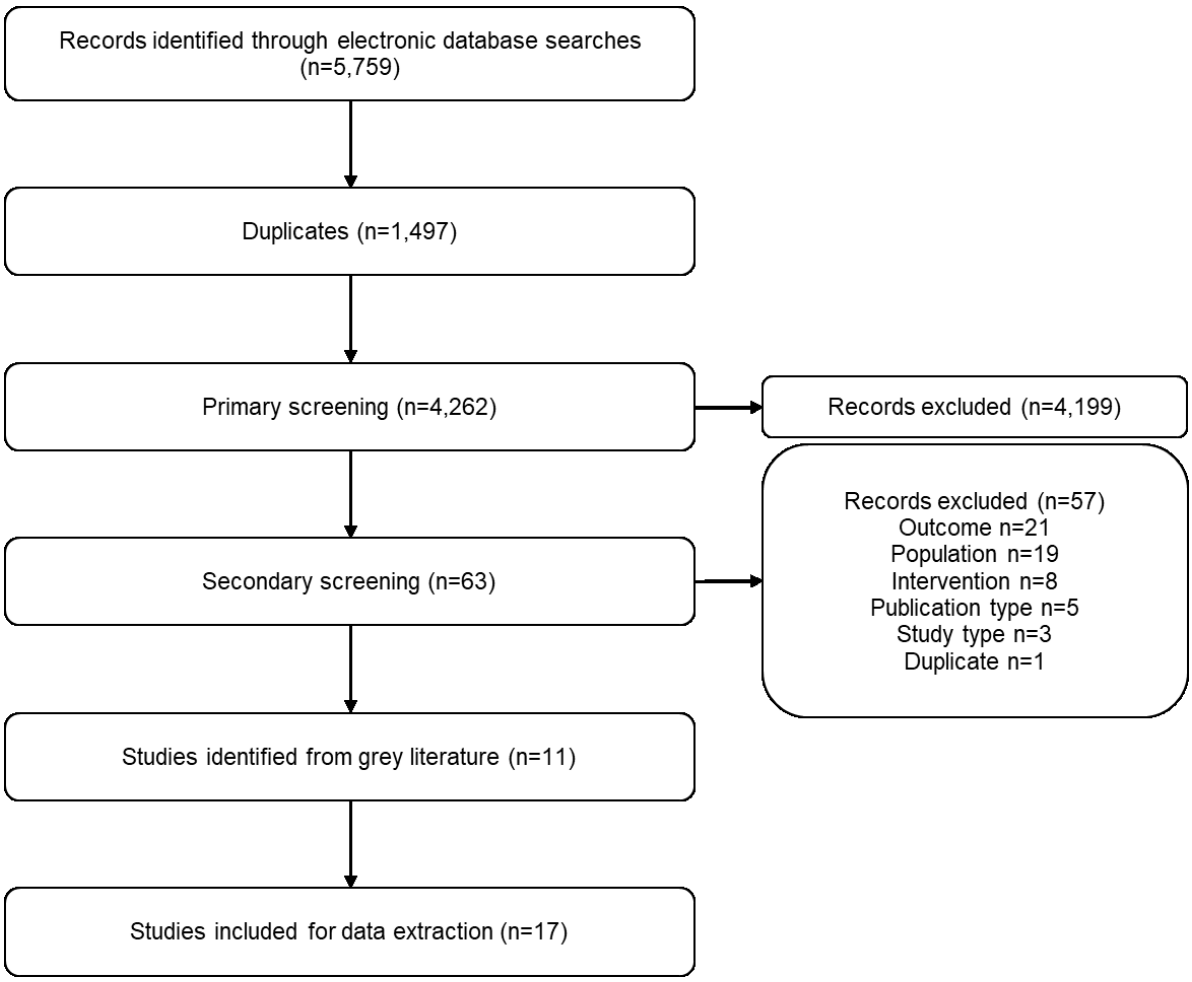
Abbreviations: ALK, anaplastic lymphoma kinase; NSCLC, non-small-cell lung cancer; QALY, quality adjusted life year; SCLC, small-cell lung cancer.

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.

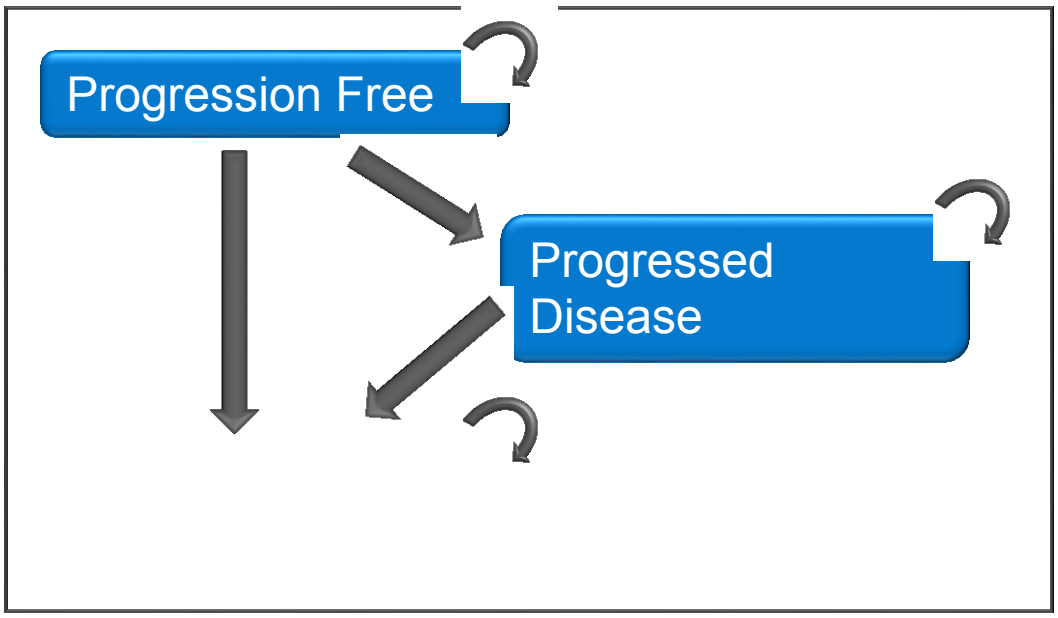
Table 29 NICE reference case checklist

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:*

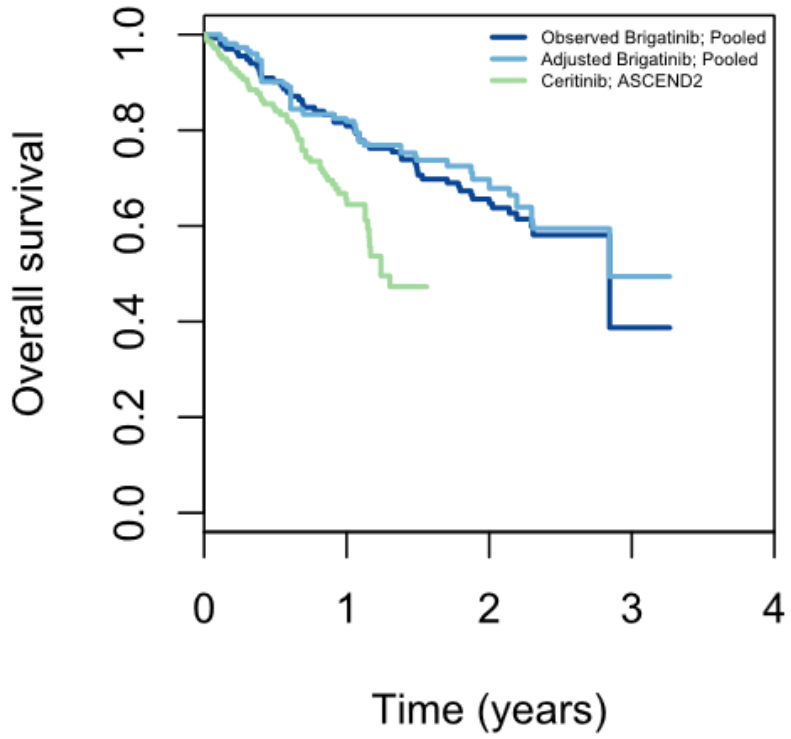
- MAIC has a small impact on the relative OS treatment effect (1% decrease in the ICER).

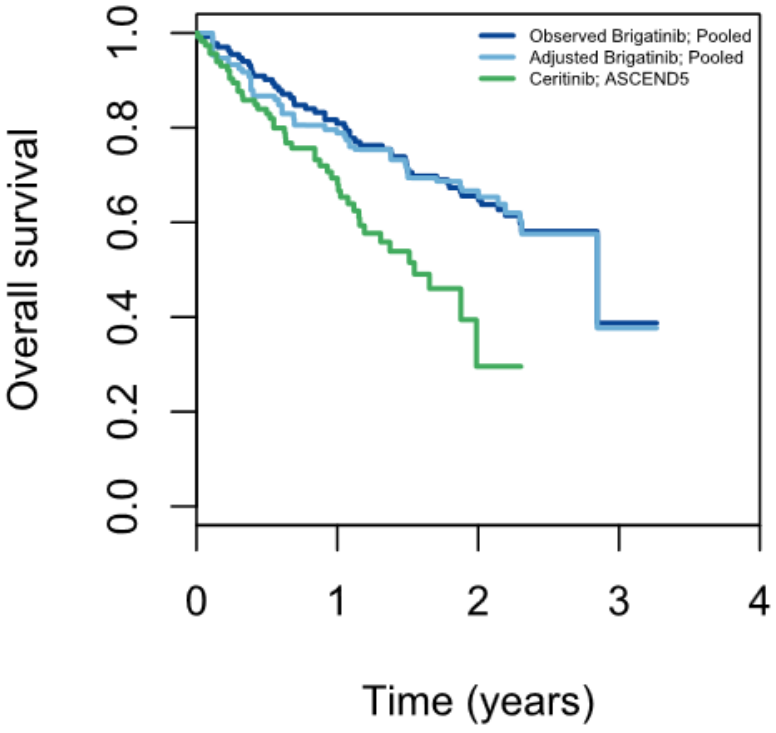
Figure 17 as the difference in the area under the light blue and dark blue plots). See section 4.4.2 for detail of the concerns with the MIAC method, and CS p109 Table 38 for full details of ITC scenario analyses.

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

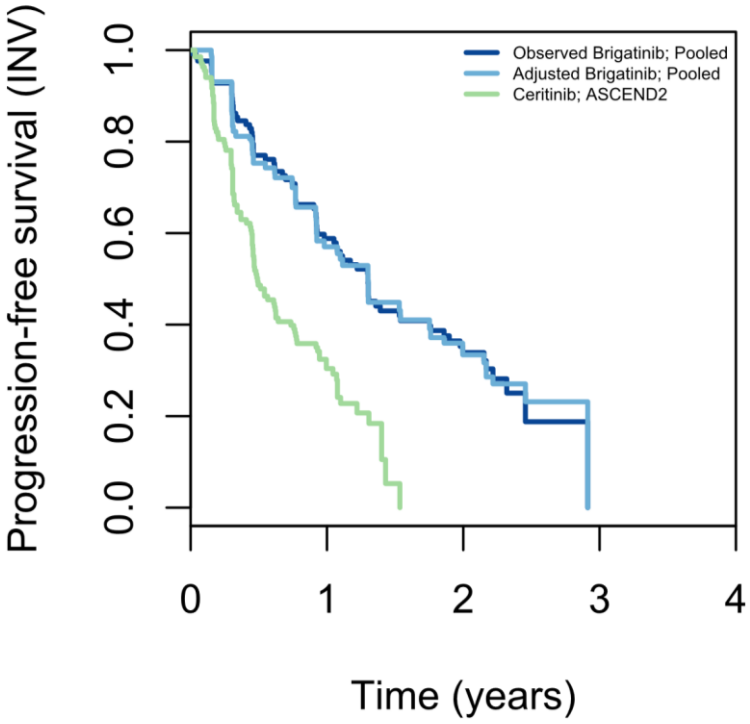
As stated above the ITC used to produce the hazard ratio determining the comparator PFS from the baseline (brigatinib) strategy did not use all the available trial information: whilst Study 101 (n=25) was included, ASCEND-5 was not (n=115). This was an unreasonable approach, because ASCEND-5 is a larger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

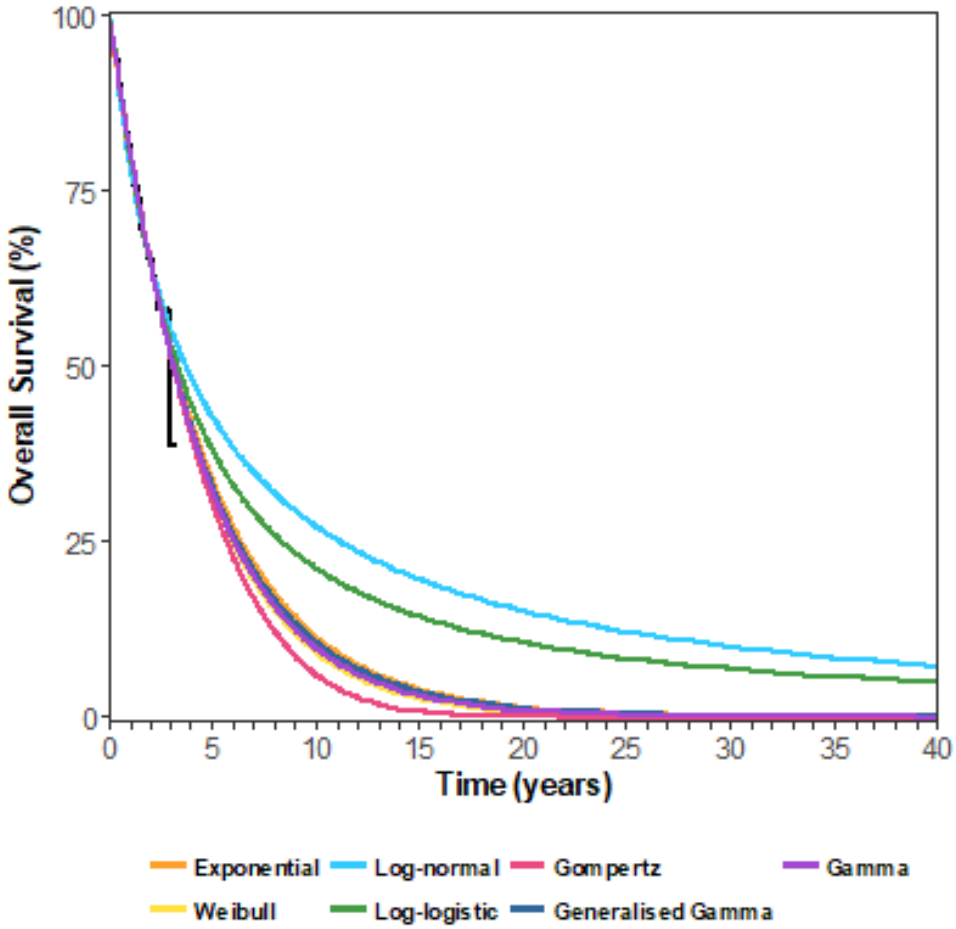
Source: CS Addendum, Table 2 (Update of original Table 33), (Takeda Ltd)

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

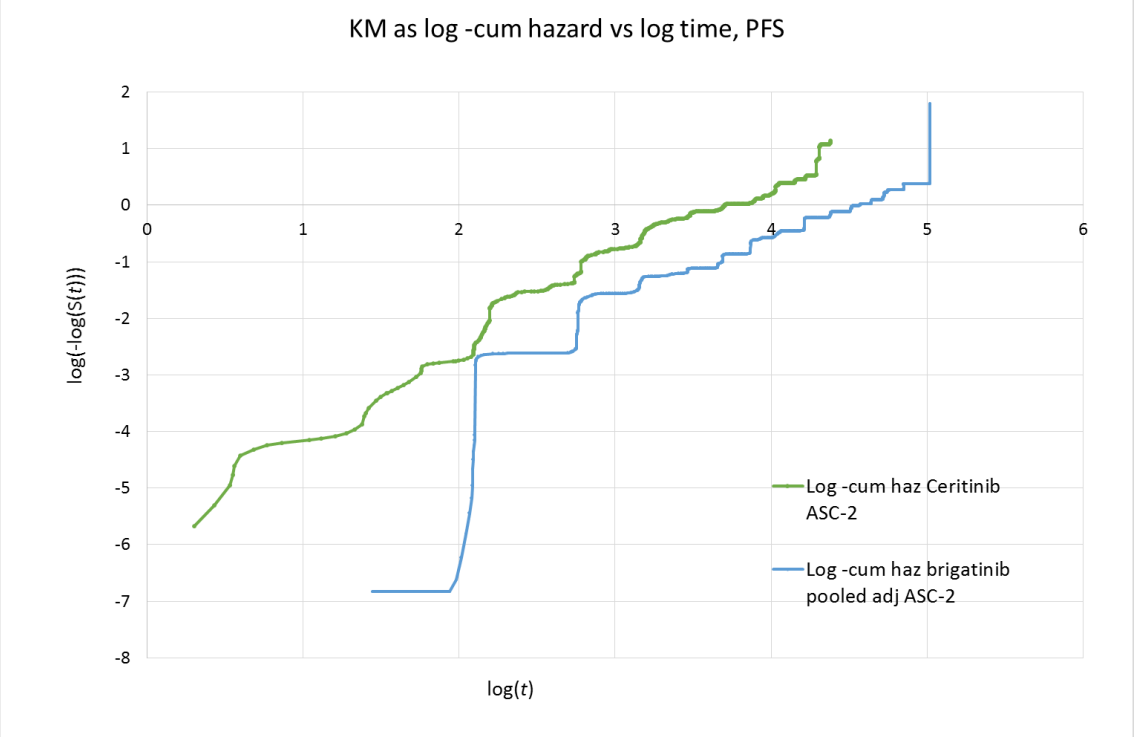


Table 34 PH test of OS HR ceritinib versus ASCEND-2 adjusted brigatinib

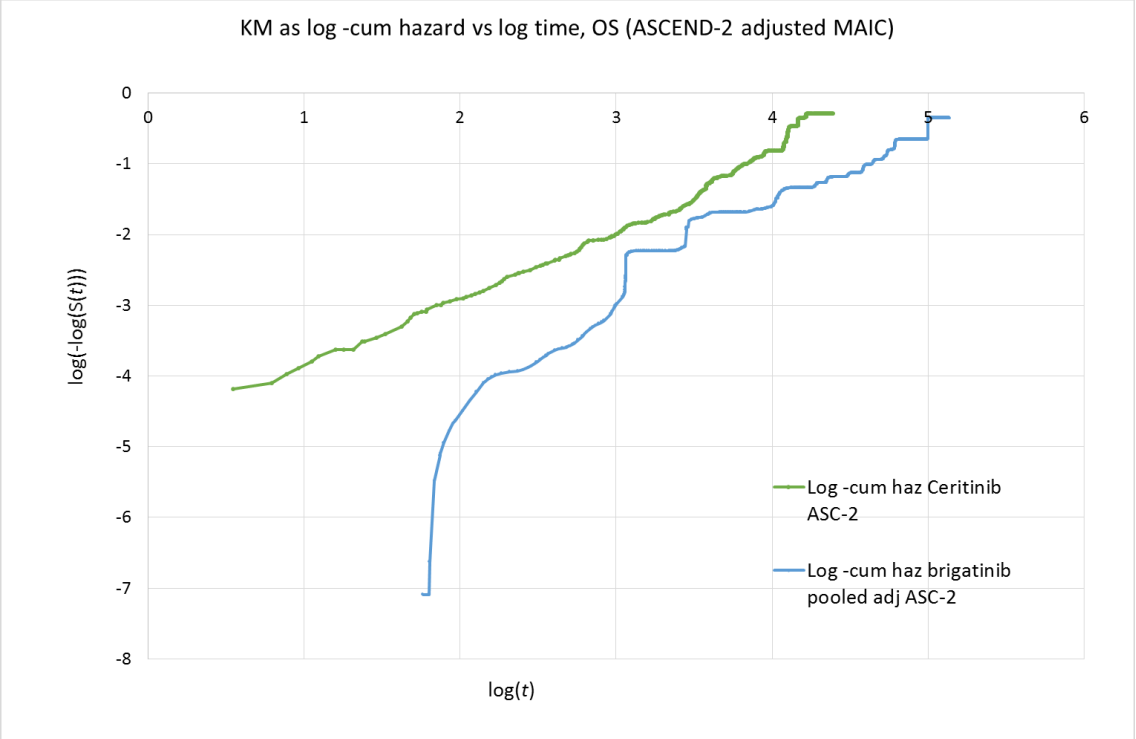
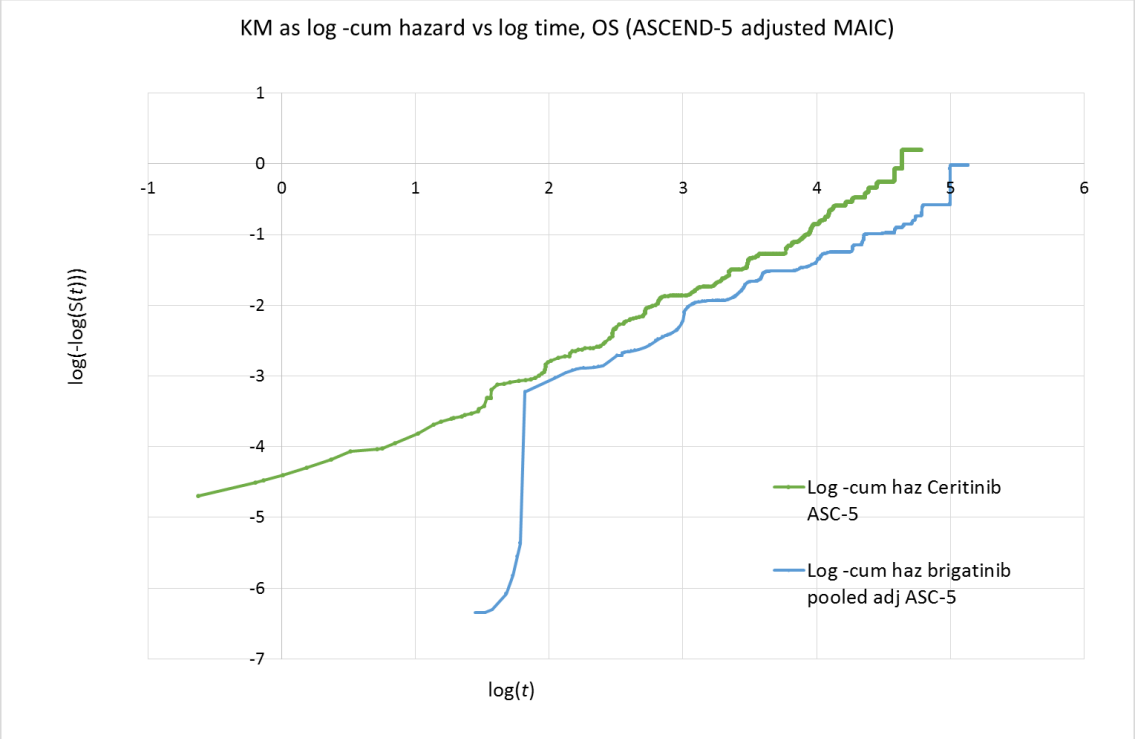


Table 35 PH test of OS HR ceritinib versus ASCEND-5 adjusted brigatinib



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)

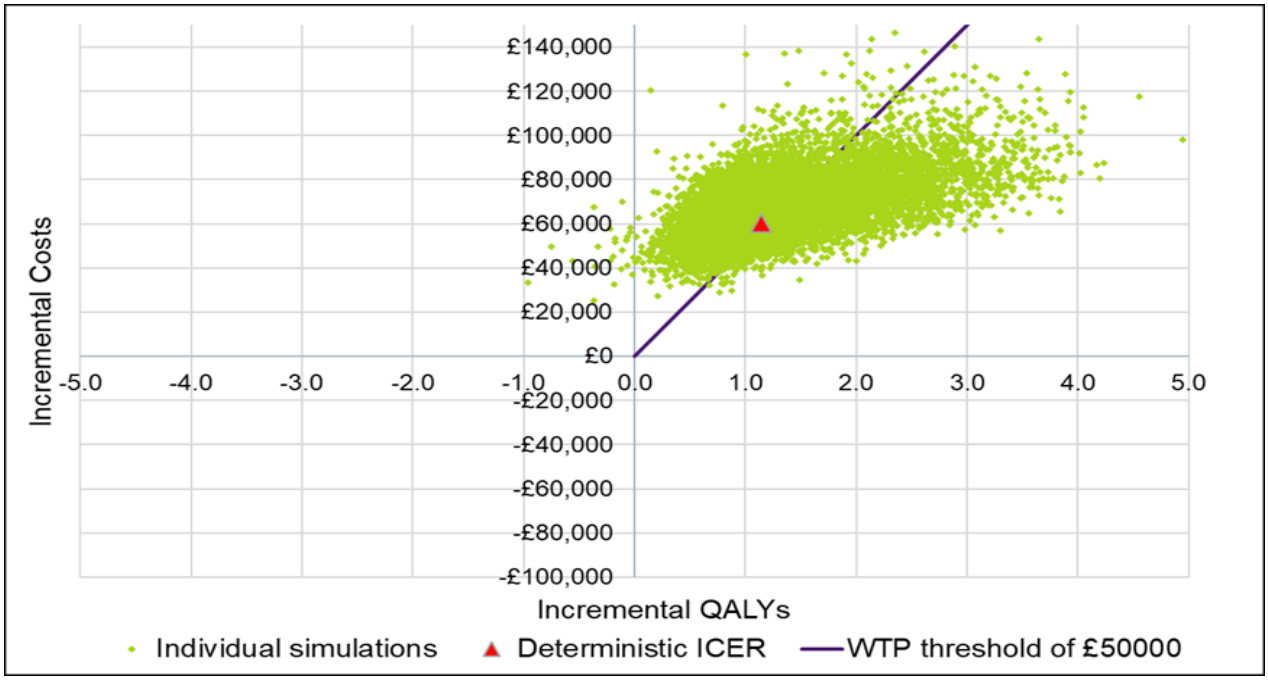
Table 45 Summary of estimated resource-use for brigatinib versus ceritinib

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

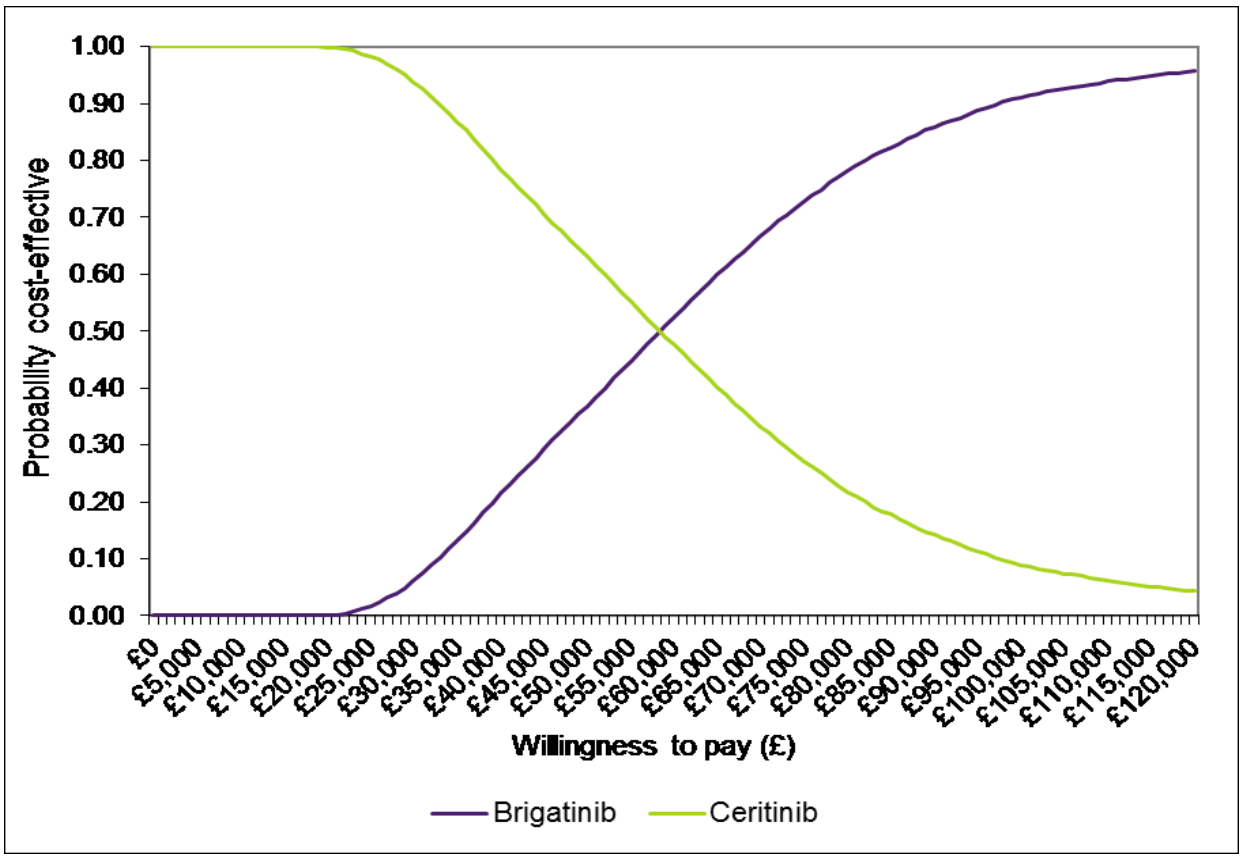
Contrast	Incremental costs (£), *mean± SD*	Incremental QALYs, *mean± SD*	ICER (£/QALY)
Brigatinib versus ceritinib	67,540± 14,270	1.30± 0.69	51,882

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).

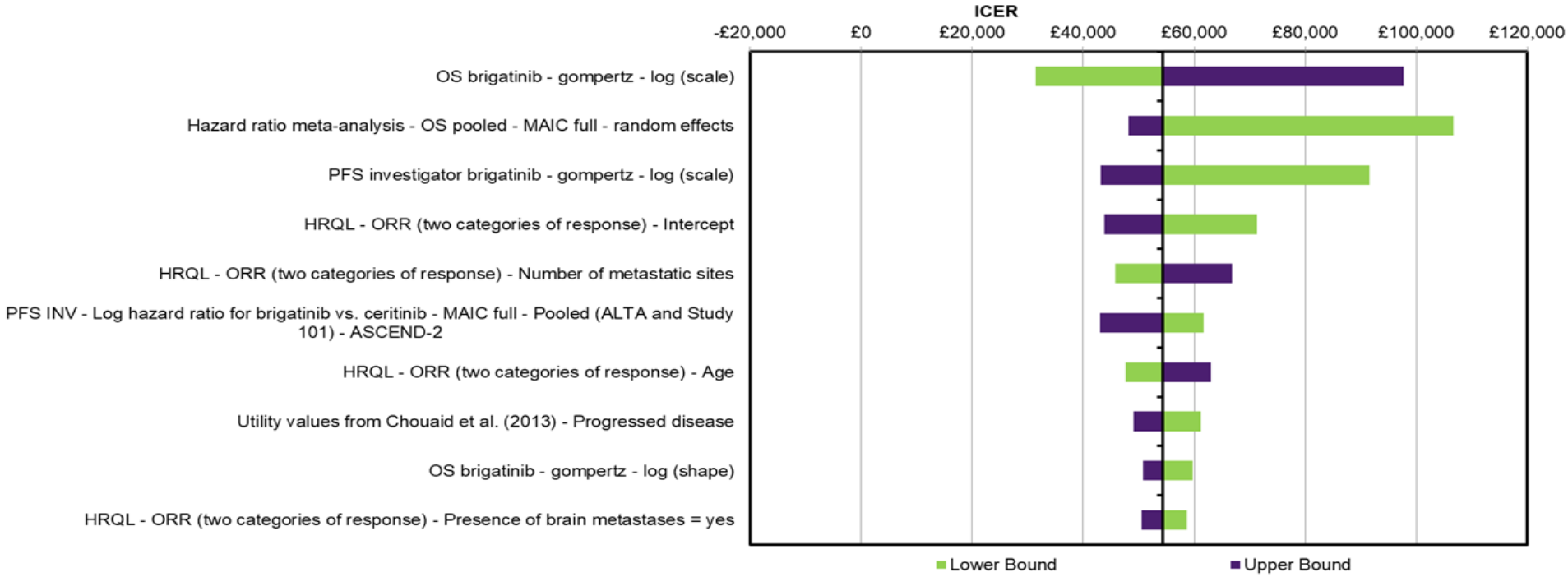
Table 47 Deterministic sensitivity analysis: variables and ranges explored

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)

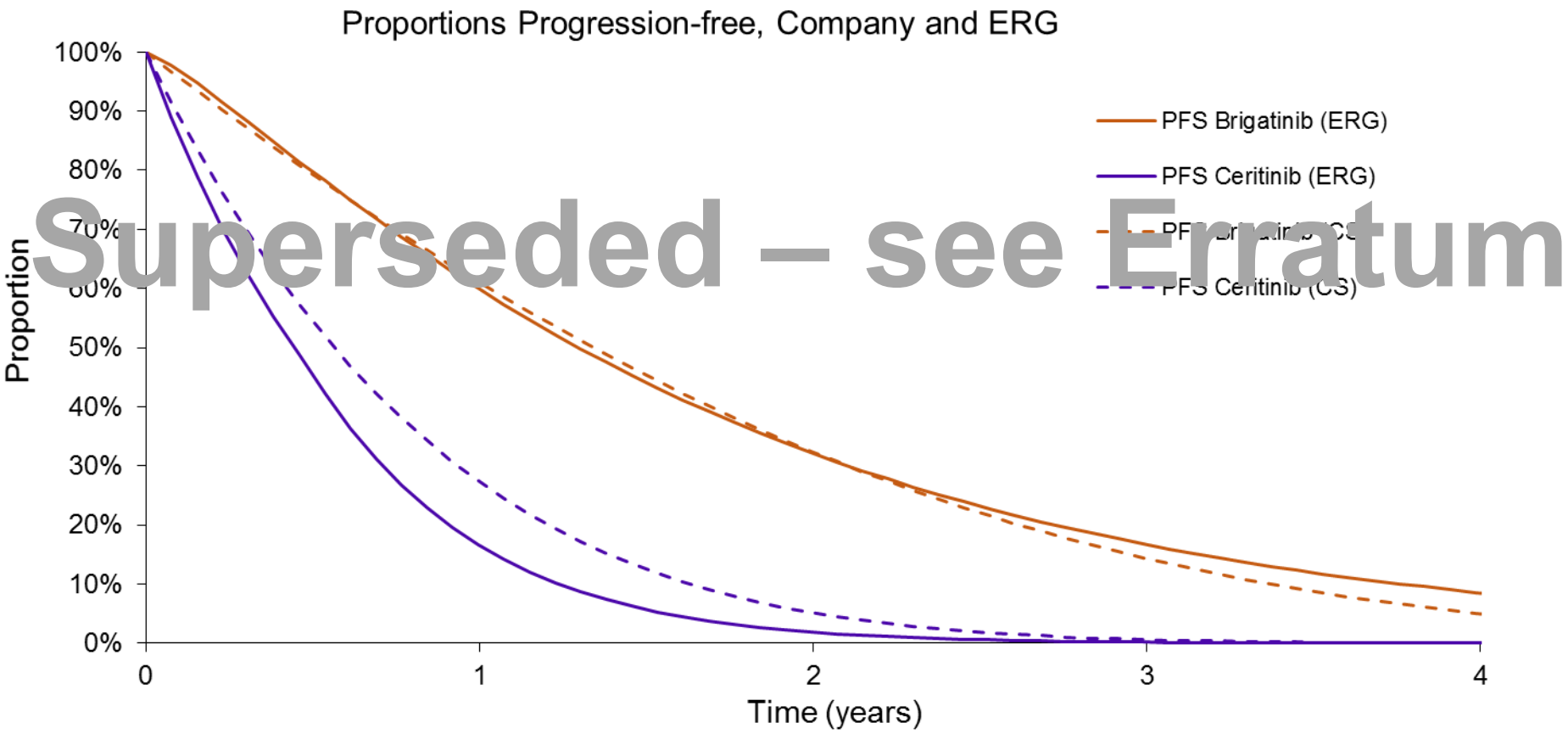
Company and ERG long-term PFS estimates are presented in Table 51. Two reasons lead to the differences observed (above): the inclusion of ASCEND-5 revised the ITC HR for PFS, so changing the relative position of the ceritinib strategy; and the gamma distribution changes the shape of the curves.

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)

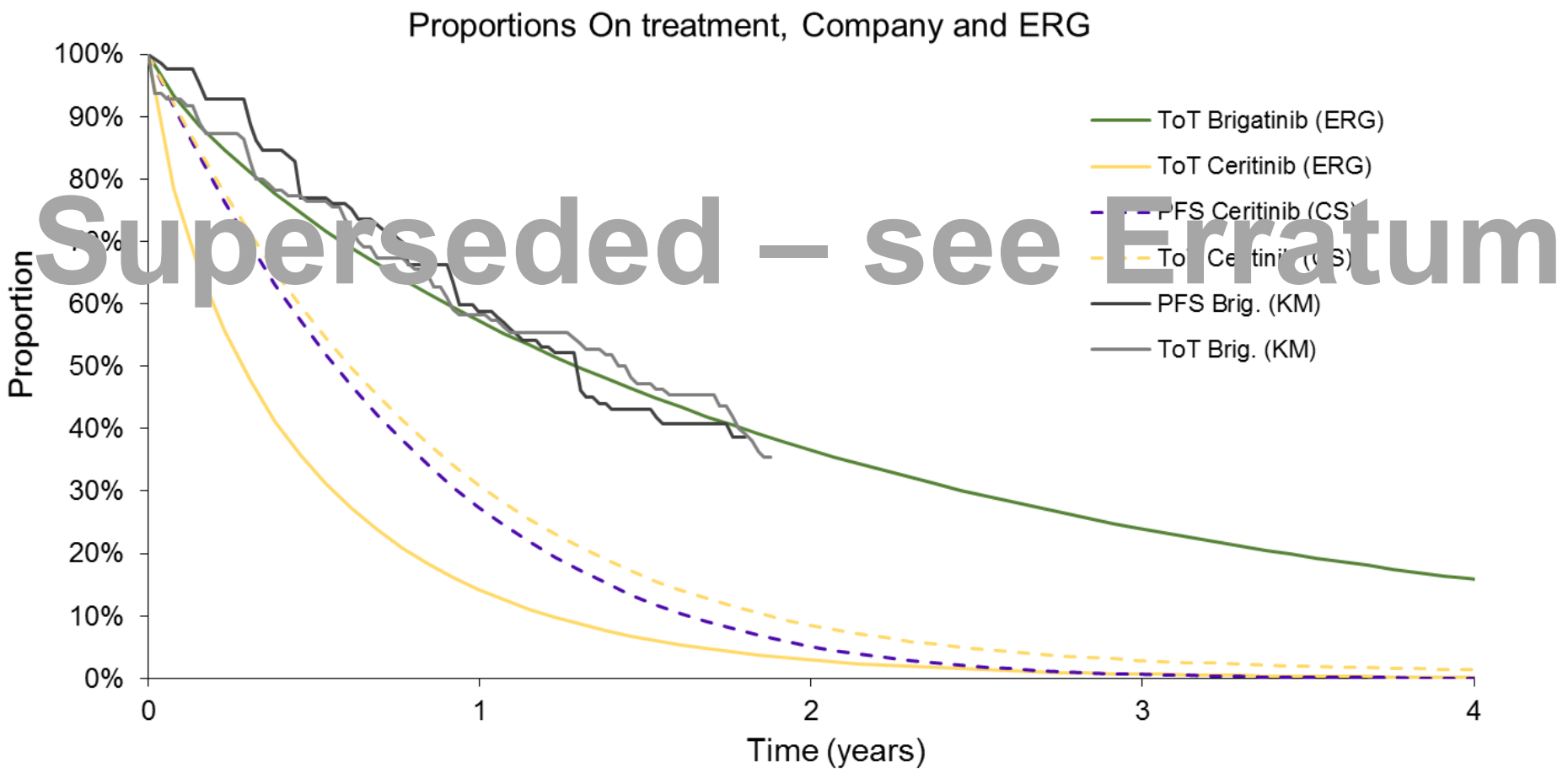
Below are the graphed company and ERG estimates for the proportion of patients remaining on treatment (Figure 23); and the proportion of patients remaining on treatment alongside the proportion progression-free (Figure 24, brigatinib; Figure 25, ceritinib).

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



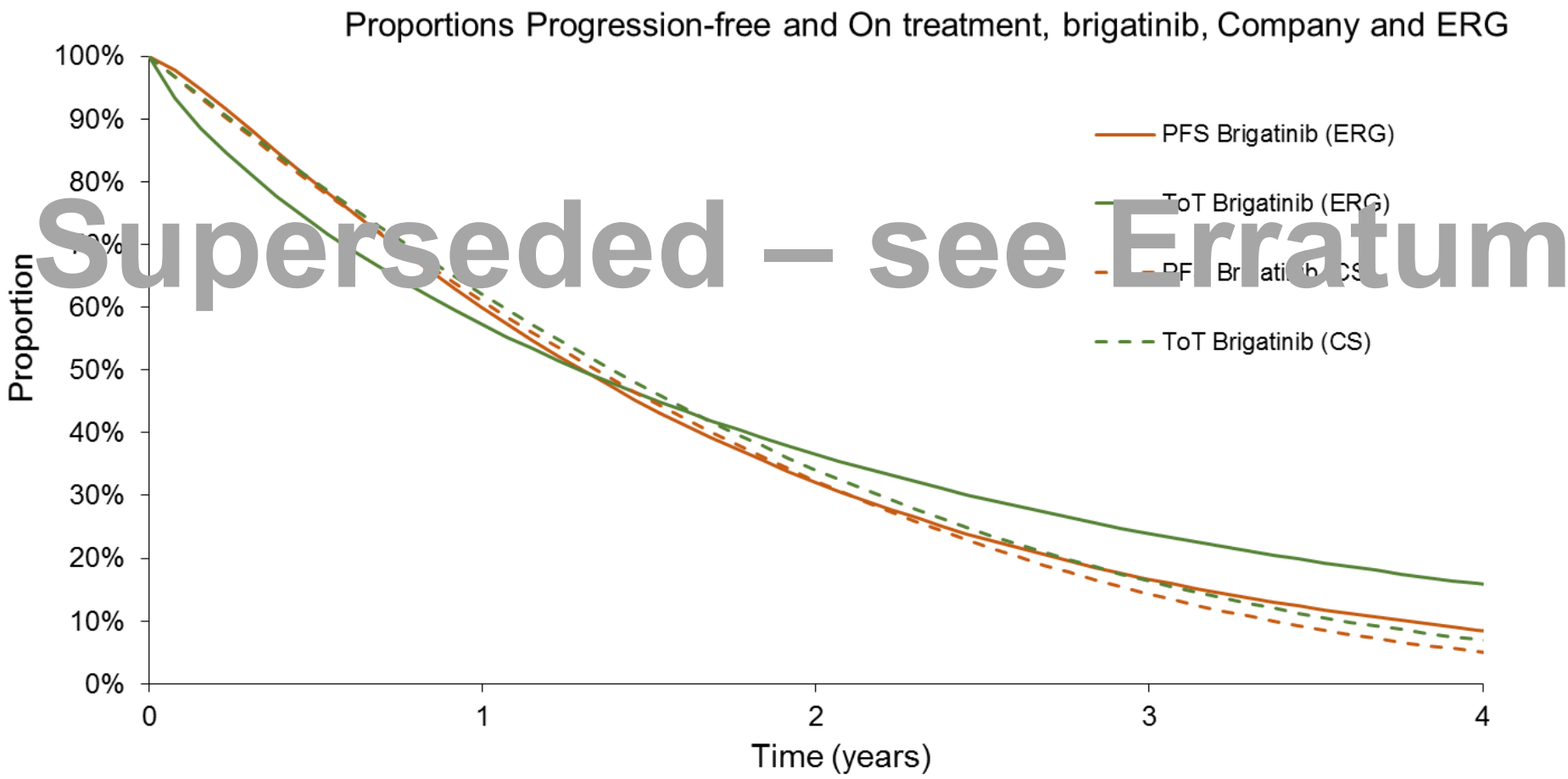
The combined effect of ERG base case changes 1 and 2 is to reduce the long term estimate of PFS on ceritinib; with a slight change to the brigatinib estimate.

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



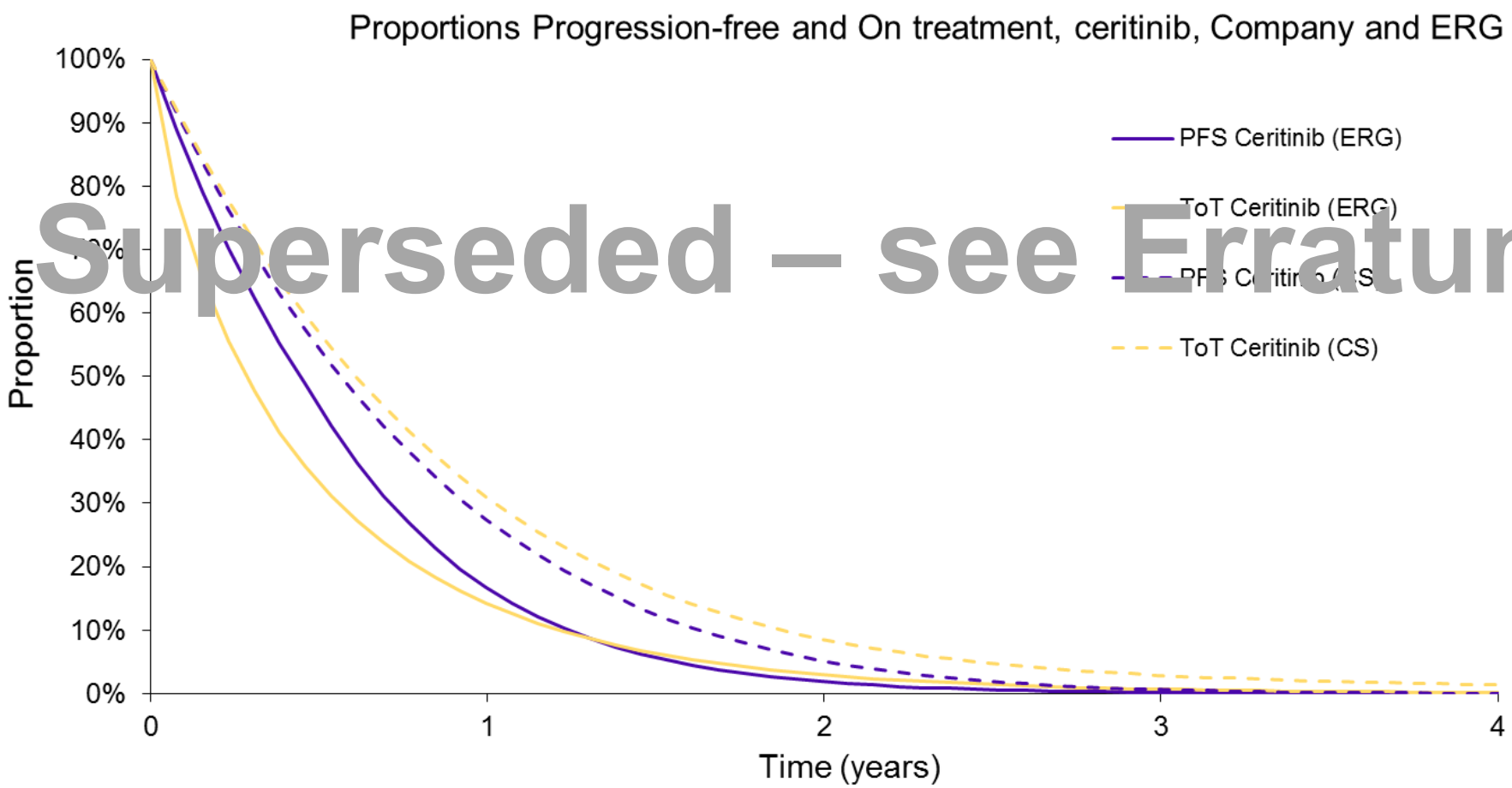
The overall effect of ERG base case changes 1, 2 and 3 is to reduce the long term estimate of time on ceritinib treatment.

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.

Acknowledgements

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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
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No.	Reference	Exclusion reason
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No.	Reference	Exclusion reason
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No.	Reference	Exclusion reason
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103.	Gettinger SN, Bazhenova L, Salgia R, Langer CJ, Gold KA, Rosell R, et al. Brigatinib (AP26113) efficacy and safety in ALK+ NSCLC: Phase 1/2 trial results. Journal of Thoracic Oncology. 2015;2):S238-S9.	Outcomes for eligible subgroup not reported
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No.	Reference	Exclusion reason
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136.	Kaneda H, Takeda M, Tanaka K, Yoshida T, Iwasa T, Okamoto K, et al. Clinical benefit of continued therapy with crizotinib beyond initial disease progression in advanced ALK positive NSCLC. Annals of Oncology. 2014;25:v70.	Abstract with insufficient information
137.	Kasan P, Berzinec P, Plank L, Andrasina I, Godal R, Mazal J, et al. Crizotinib in advanced ALK-positive NSCLC-a retrospective multicenter study in the Slovak Republic. Journal of Thoracic Oncology. 2015;2):S529.	Abstract with insufficient information
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141.	Khozin S, Blumenthal GM, Zhang L, Tang S, Brower M, Fox E, et al. FDA approval: ceritinib for the treatment of metastatic anaplastic lymphoma kinase-positive non-small cell lung cancer. Clinical Cancer Research. 2015;21(11):2436-9.	Ineligible publication
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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No.	Reference	Exclusion reason
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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
152.	Kwak EL, Bang YJ, Camidge DR, Shaw AT, Solomon B, Maki RG, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. New England Journal of Medicine. 2010;363(18):1693-703.	Phase I
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No.	Reference	Exclusion reason
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182.	Nishio M, Hirsh V, Kim DW, Wilner KD, Polli A, Reisman A, et al. Efficacy, safety, and patient-reported outcomes (PROS) with crizotinib versus chemotherapy in Asian patients in a phase iii study of previously treated advanced ALK-positive nonsmall cell lung cancer (NSCLC). Journal of Thoracic Oncology. 2013;8:S198-S9.	Pooled data not from systematic review/meta-analysis
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No.	Reference	Exclusion reason
188.	Ou SH, Tang Y, Polli A, Wilner KD, Schnell P. Factors associated with sinus bradycardia during crizotinib treatment: a retrospective analysis of two large-scale multinational trials (PROFILE 1005 and 1007). Cancer Medicine. 2016;5(4):617-22.	Pooled data not from systematic review/meta-analysis
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192.	Pailler E, Oulhen M, Borget I, Remon J, Ross K, Auger N, et al. Circulating Tumor Cells with Aberrant ALK Copy Number Predict Progression-Free Survival during Crizotinib Treatment in ALK-Rearranged Non-Small Cell Lung Cancer Patients. Cancer Research. 2017;77(9):2222-30.	Wrong outcomes
193.	Park K, Felip E, Orlov S, Yu CJ, Tsai CM, Nishio M, et al. Pros with ceritinib in ALKi-naive ALK+ NSCLC patients with and without brain metastases. Journal of Thoracic Oncology. 2015;2):S379-S80.	Phase I
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197.	Paz-Ares LG, Altug S, Vaury AT, Jaime JC, Russo F, Visseren-Grul C. Treatment rationale and study design for a phase III, double-blind, placebo-controlled study of maintenance pemetrexed plus best supportive care versus best supportive care immediately following induction treatment with pemetrexed plus cisplatin for advanced nonsquamous non-small cell lung cancer2010; 10:[85 p.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/474/CN-00729474/frame.html.	Wrong population
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No.	Reference	Exclusion reason
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206.	Rossi A, Sacco PC, Santabarbara G, Sgambato A, Casaluce F, Palazzolo G, et al. Developments in pharmacotherapy for treating metastatic non-small cell lung cancer. Expert Opinion on Pharmacotherapy. 2017;18(2):151-63.	Wrong study design
207.	Saramago P, Ines M, Saraiva F. Cost-effectiveness analysis of crizotinib for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer in Portugal. Value in Health. 2017;20 (9):A434.	Wrong outcomes
208.	Schmid S, Gautschi O, Rothschild S, Mark M, Froesch P, Klingbiel D, et al. Clinical Outcome of ALK-Positive Non-Small Cell Lung Cancer (NSCLC) Patients with De Novo EGFR or KRAS Co-Mutations Receiving Tyrosine Kinase Inhibitors (TKIs). Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer. 2017;12(4):681-8.	Outcomes for eligible subgroup not reported
209.	Schnell P, Bartlett CH, Solomon BJ, Tassell V, Shaw AT, de Pas T, et al. Complex renal cysts associated with crizotinib treatment. Cancer Medicine. 2015;4(6):887-96.	Wrong study design
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213.	Shaw AT, Janne PA, Besse B, Solomon BJ, Blackhall FH, Camidge DR, et al. Crizotinib vs chemotherapy in ALK+ advanced non-small cell lung cancer (NSCLC): Final survival results from PROFILE 1007. Journal of Clinical Oncology Conference. 2016;34(no pagination).	Wrong population
214.	Shaw AT, Kim DW, Nakagawa K, Seto T, Crino L, Ahn MJ, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. New England Journal of Medicine. 2013;368(25):2385-94.	Abstract with insufficient information
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217.	Shaw AT, Solomon BJ, Mok T, Kim DW, Wilner KD, Selaru P, et al. Effect of treatment duration on incidence of adverse events (AES) in a phase iii study of crizotinib versus chemotherapy in advanced alk-positive non-small cell lung cancer (NSCLC). Journal of Thoracic Oncology. 2013;8:S911-S2.	Pooled data not from systematic review/meta-analysis
218.	Shaw AT, Spigel DR, Tan DS, Kim DW, Mehra R, Orlov S, et al. MINI01.01: Whole Body and Intracranial Efficacy of Ceritinib in ALK-inhibitor Naive Patients with ALK+ NSCLC and Brain Metastases: Results of ASCEND 1 and 3: Topic: Medical Oncology. Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer. 2016;11(11S):S256.	Phase I
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221.	Singapore Cancer Network Lung Cancer W. Singapore Cancer Network (SCAN) Guidelines for the Use of Systemic Therapy in Advanced Non-Small Cell Lung Cancer. Annals of the Academy of Medicine, Singapore. 2015;44(10):449-62.	Wrong study design
222.	Solomon BJ, Gettinger SN, Riely GJ, Gadgeel SM, Nokihara H, Han JY, et al. Subgroup analysis of crizotinib versus either pemetrexed (PEM) or docetaxel (DOC) in the phase III study (PROFILE 1007) of advanced ALK-positive non-small cell lung cancer (NSCLC). Journal of Clinical Oncology Conference. 2013;31(15 SUPPL. 1).	Wrong population

No.	Reference	Exclusion reason
223.	Stegmann DA. ALK-positive non-small cell lung cancer: Further treatment after disease progression and quality of life with crizotinib Weiterbehandlung nach Krankheitprogress und Lebensqualitat unter Crizotinib. Arzneimitteltherapie. 2015;33(6):216-8.	Ineligible publication
224.	Taipale K, Winfree KB, Boye M, Basson M, Sleilaty G, Eaton J, et al. A cost-effectiveness analysis of first-line induction and maintenance treatment sequences in patients with advanced nonsquamous non-small-cell lung cancer in France. ClinicoEconomics and Outcomes Research. 2017;9:505-18.	Wrong outcomes
225.	Takeda M, Nakagawa K. Crizotinib for ALK rearrangement-positive non-small cell lung cancer patients with central nervous system metastasis. Translational Cancer Research. 2016;5:S554-S6.	Ineligible publication
226.	Takiguchi Y, Hida T, Nokihara H, Kondo M, Kim YH, Azuma K, et al. Updated efficacy and safety of the j-alex study comparing alectinib (ALC) with crizotinib (CRZ) in ALK-inhibitor naive ALK fusion positive non-small cell lung cancer (ALK+ NSCLC). Journal of Clinical Oncology Conference. 2017;35(15 Supplement 1).	Abstract with insufficient information
227.	Tamura T, Kiura K, Seto T, Nakagawa K, Maemondo M, Inoue A, et al. Three-Year Follow-Up of an Alectinib Phase I/II Study in ALK-Positive Non-Small-Cell Lung Cancer: AF-001JP. Journal of Clinical Oncology. 2017;35(14):1515-21.	Wrong population
228.	Tamura T, Seto T, Nakagawa K, Maemondo M, Inoue A, Hida T, et al. Updated data of a phase 1/2 study (AF-001JP) of alectinib, a cnspenetrant, highly selective ALK inhibitor in ALK-rearranged advanced NSCLC. International Journal of Radiation Oncology Biology Physics. 2014;1):S6.	Wrong population
229.	Tan D, Liu G, Kim DW, Thomas M, Felip E, Signorovitch J, et al. Continuation of ceritinib beyond disease progression is associated with prolonged post-progression survival (PPS) in ALK+ NSCLC. Journal of Thoracic Oncology. 2016;1):S134-S5.	Outcomes for eligible subgroup not reported
230.	Tan D, Liu G, Kim DW, Thomas M, Felip E, Signorovitch J, et al. 178P: Continuation of ceritinib beyond disease progression is associated with prolonged post-progression survival (PPS) in ALK+ NSCLC. Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer. 2016;11(4 Suppl):S134-5.	Wrong outcomes
231.	Tan D-W, Araujo A, Zhang J, Signorovitch JE, Zhou ZY, Cai X, et al. Comparative efficacy of ceritinib and crizotinib in previously treated crizotinib-naive anaplastic lymphoma kinase-positive (ALK+) advanced or metastatic non-small cell lung cancer (NSCLC): An adjusted indirect comparison2015; 33(15 suppl. 1). Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/379/CN-01098379/frame.html.	Wrong outcomes
232.	Tan DS, Araujo A, Zhang J, Signorovitch J, Zhou ZY, Cai X, et al. Comparative Efficacy of Ceritinib and Crizotinib as Initial ALK-Targeted Therapies in Previously Treated Advanced NSCLC: An Adjusted Comparison with External Controls. Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer. 2016;11(9):1550-7.	Outcomes for eligible subgroup not reported
233.	Tan W, Yamazaki S, Johnson TR, Wang R, O'Gorman MT, Kirkovsky L, et al. Effects of Renal Function on Crizotinib Pharmacokinetics: Dose Recommendations for Patients with ALK-Positive Non-Small Cell Lung Cancer. Clinical Drug Investigation. 2017;37(4):363-73.	Wrong outcomes
234.	Tassinari D, Scarpi E, Sartori S, Tamburini E, Santelmo C, Tombesi P, et al. Second-line treatments in non-small cell lung cancer: a systematic review of literature and metaanalysis of randomized clinical trials (Structured abstract)2009; 135(6):[1596-609 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/cldare/articles/DARE-12009106610/frame.html.	Wrong population
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
236.	Tiseo M, Popat S, Gettinger SN, Peters S, Haney J, Kerstein D, et al. Design of ALTA-1L (ALK in lung cancer trial of brigatinib in first-line), a randomized phase 3 trial of brigatinib (BRG) versus crizotinib (CRZ) in tyrosine kinase inhibitor (TKI)-naive patients (pts) with advanced anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC). Journal of Clinical Oncology Conference. 2017;35(15 Supplement 1).	Abstract with insufficient information
237.	Tonelli M, Scaldaferri M, Barila D, Bianco A, Ferroni M, Valinotti G, et al. Analysys of therapeutic response and tolerability in patients treated with crizotinib in alk positive nsclc. European Journal of Hospital Pharmacy. 2016;23:A59.	Outcomes for eligible subgroup not reported
238.	Viala M, Brosseau S, Planchard D, Besse B, Soria JC. [Second generation ALK inhibitors in non-small cell lung cancer: systemic review]. Bulletin du Cancer. 2015;102(4):381-9.	Wrong study design
239.	Wakelee H, Altorki N, Vallieres E, Zhou C, Zuo Y, Howland M, et al. IMpower010: Phase III study of atezolizumab vs bsc after adjuvant chemotherapy in patients with completely resected NSCLC. Journal of Thoracic Oncology. 2017;12 (1 Supplement 1):S1305.	Wrong population
240.	Wang M, Wang G, Ma H, Shan B. Crizotinib versus chemotherapy on ALK-positive NSCLC :a systematic review of efficacy and safety. Current Cancer Drug Targets. 2017:23.	Relevant SLR hand searched

No.	Reference	Exclusion reason
241.	Wang TJC, Saad S, Qureshi YH, Jani A, Nanda T, Yaeh AM, et al. Does lung cancer mutation status and targeted therapy predict for outcomes and local control in the setting of brain metastases treated with radiation? Neuro-Oncology. 2015;17(7):1022-8.	<10 eligible patients
242.	Wang W, Song Z, Yu X, Lou G, Gu C, Shi X, et al. Efficacy of crizotinib for 28 cases of advanced ALK-positive non-small cell lung cancer. [Chinese]. Zhonghua zhong liu za zhi [Chinese journal of oncology]. 2015;37(10):784-7.	Wrong population
243.	Wang Y, Gao G, He Y, Li X, Zhao C, Wu C, et al. Utility of cytology specimens for ALK fusion detected by QRTPCR in patients of advanced non-small cell lung cancer. Journal of Thoracic Oncology. 2015;2):S692.	Abstract with insufficient information
244.	Wang Y, Gao G, Li X, Zhao C, He Y, Su C, et al. EML4-ALK fusion detected by RT-PCR confers similar response to crizotinib as detected by FISH in patients with advanced non-small-cell lung cancer. Journal of Thoracic Oncology. 2015;10(11):1546-52.	Wrong population
245.	Wen PY, Barlesi F, Bertino EM, Kim DW, Van Den Bent MJ, Wakelee H, et al. Ceritinib in ALK1 NSCLC metastatic to brain and/or leptomeninges: The ASCEND-7 study. Neuro-Oncology. 2015;17:v52.	Abstract with insufficient information
246.	Wendling P. Crizotinib effective in advanced NSCLC with altered ALK gene. Oncology Report. 2010(JULY-AUGUST):38.	No abstract of paper could be located
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-submissio n (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 submissio n(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/carbo platin = £21,480 Incremental = £58,404	ICER per QALY gained marked CiC Updated ICER per QALY = £47,291
Scottish Medicines Consortiu m (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

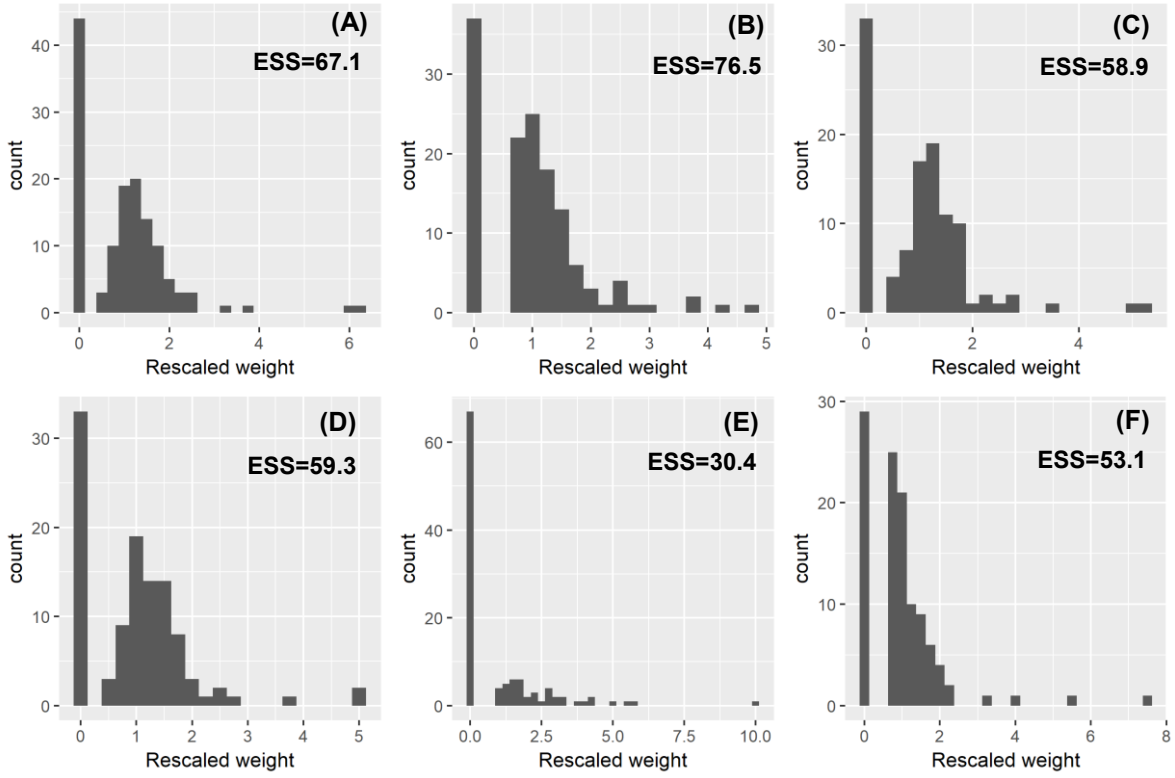
Study	Year	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Zhou et al.(75)	(2015 b)	AUC partitioned survival model with three health states: stable disease, progressive disease and death Canadian perspective Efficacy 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).

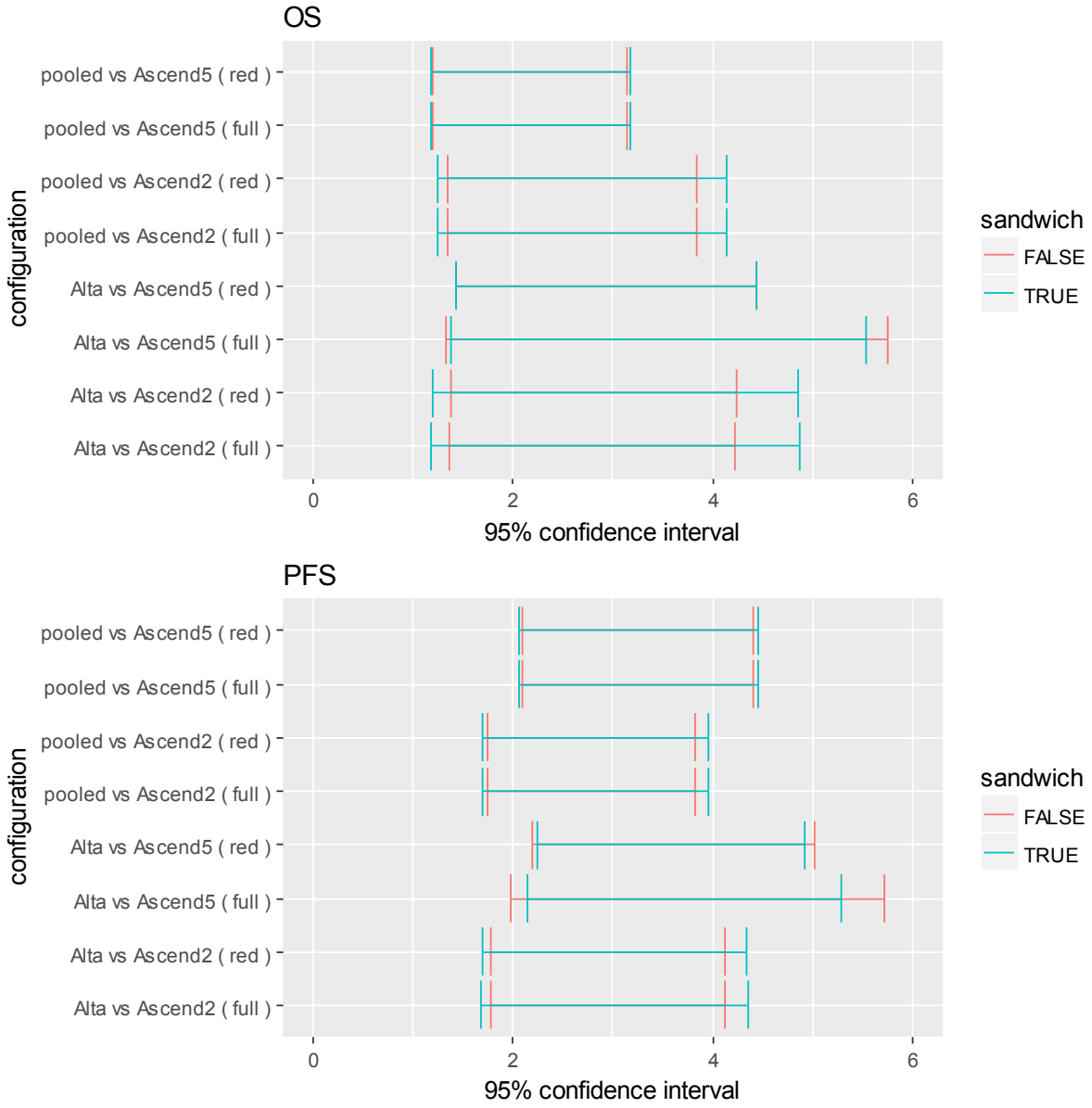
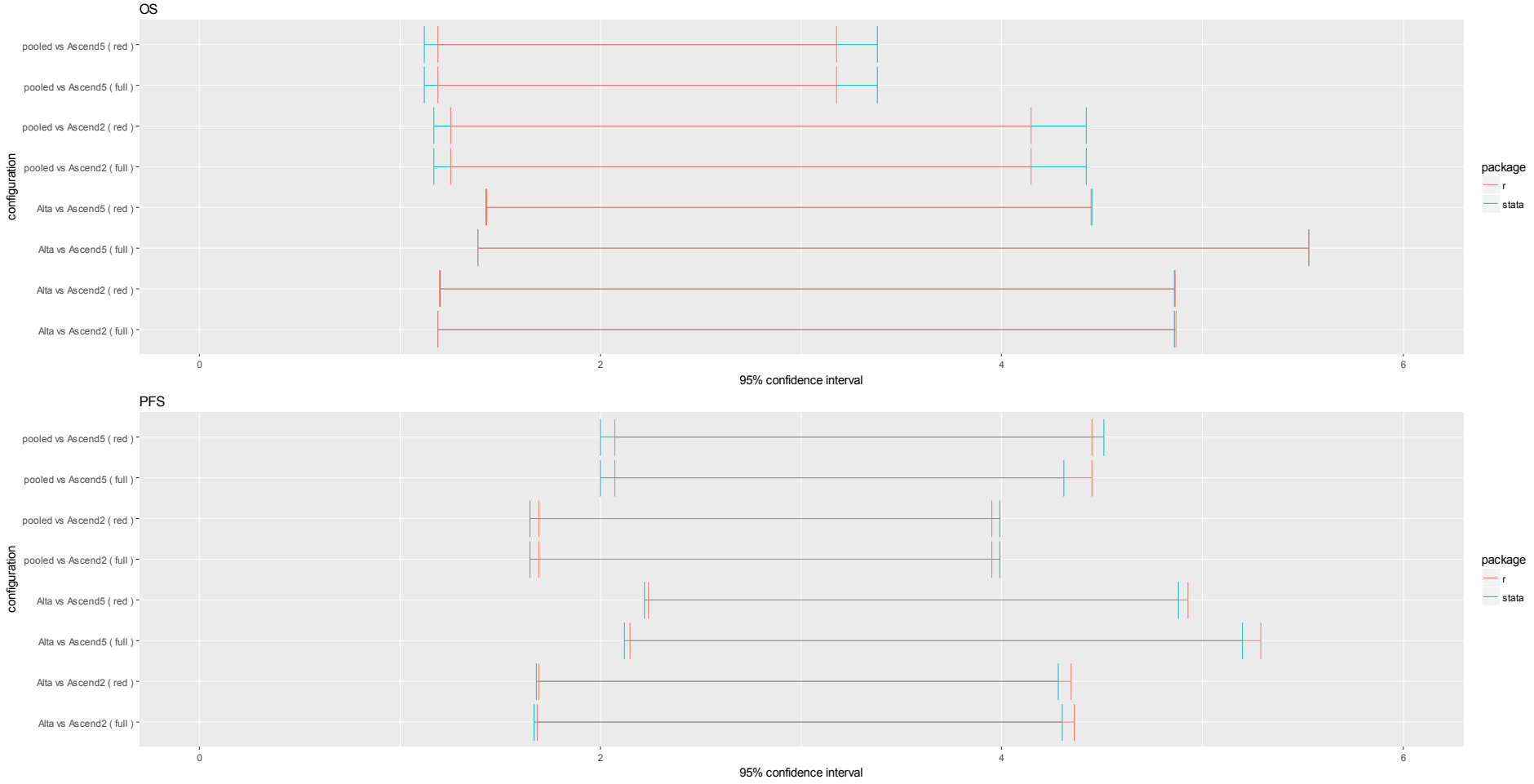


Figure 28. Comparison of confidence intervals under estimation with coxph() in R 3.5 versus stcox() in Stata 14.



National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

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

You are asked to check the ERG report from Peninsula Technology Assessment Group (PenTAG) to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on 26 June 2018** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Comparison of AE rates

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg 16 second paragraph- the ERG report compares AE rates between brigatinib and ceritinib without making clear that the comparison statements are based on a naïve comparison of event rates and therefore no inferences should be drawn.	Add language to make clear that these are naïve comparisons of event rates.	To ensure that it is clearly understood that event rates discussed are based on a naïve comparison.	Thank you for raising this issue. We are happy to make this correction.

Issue 2 Typographical error- PFS HR from naïve ITC

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG reports the PFS HR as 3.02 (1.90-4.78) for the random effects naïve ITC. The correct CI is (1.91-4.78) as per the September data cut addendum.	Amend the reported CI to 1.91-4.78.	To ensure the reported data is correct.	Thank you for raising this issue. We are happy to make this correction.

Issue 3 Time on treatment

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg 18 first paragraph – the text	Amend to 1.53 months as per NICE Company	To correctly state the exact time on	Thank you for raising this

states that estimates for time on treatment assumed 1.5 months post-progression. The exact figure used in the company submission is 1.53 months	Submission.	treatment post-progression as per the company submission.	issue. We are happy to make this correction.

Issue 4 Mean Utility Value Before AE adjustment

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg 18 third paragraph – the text states that the mean value before AE adjustment for pre-progression was 0.774. The correct figure from the company submission is 0.744.	Amend to 0.744 as per Table 47, page 115 of the NICE Company Submission.	To correctly state the correct mean value for pre-progression before AE adjustments.	Thank you for raising this issue. We are happy to make this correction.

Issue 5 Comparison of AE rates

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg 25, paragraph 2, report states 'these are adults with ALK+ NSCLC with a good performance status (0 or 1)' with regards to treatment numbers in England with reference to the budget impact analysis submitted. The reference to performance status does not align with the expected label and therefore the eligible	Delete reference to performance status.	Alignment with the expected label	Thank you for raising this issue. An edit has been made so that a that good performance status does not appear as a requirement for consideration of the drug. PS is however a relevant characteristic of the population so is retained as an element of it's description.

patient population.			

Issue 6 Marketing Authorisation Date

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg 25 paragraph 3- the MA date stated has changed since the submission was made.	Please update to December 2018 which is the current expected date of MA	To update to the latest estimate of MA.	Thank you for raising this issue. This is not a factual error given the information submitted, but an update has been made.

Issue 7 ASCEND Median PFS

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg 26, paragraph one gives a median PFS of 5.7 months and 5.4 months for ASCEND-2 and ASCEND-5, respectively	Median PFS for ceritinib in ASCEND-2 is 5.7 months per investigator assessment (INV) and 7.2 by IRC. Median PFS for ceritinib in ASCEND-5 is 6.7months by INV and 5.4 months per IRC.	For clarity, median PFS should be referenced as either INV or IRC, for clarity.	Thank you for raising this issue. Both INV and IRC outcomes have now been provided.

Issue 8 Reference to Lorlatinib / Brigatinib

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg 27 paragraph 1- compassionate use programmes are mentioned with reference to brigatinib and lorlatinib- which are	This section should be updated to make clear that brigatinib and lorlatinib are currently unlicensed products	To ensure that the current license status of brigatinib and lorlatinib is clear.	Thank you for raising this issue. Amendments have been made to make this clear.

both currently unlicensed products.			

Issue 9 SMPC and EPAR

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg 28, section 3.2, paragraph 1: states that the SmPC and EPAR were provided in Appendix C. The SmPC is a draft version and the EPAR was not provided as it is not yet available.	The SmPC is as yet a 'draft' and should be stated as such. The EPAR is not available yet and was therefore not provided in the appendix.	For factual accuracy and to confirm the regulatory status of brigatinib and therefore what regulatory documents are available.	Thank you for raising this issue. We are happy to make this correction.

Issue 10 Comparison of AE rates

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg60 paragraph 1- as per issue 1.	As per issue 1.	As per issue 1.	Thank you for raising this issue. We are happy to make this correction.

Issue 11 Textual description of ASCEND 2/5

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg67 first paragraph The text describes ASCEND-2 as an RCT and ASCEND-5 as a single arm study when the reverse is actually true.	Change so that ASCEND-2 is described as a single arm study and ASCEND-5 as an RCT.	To ensure that the ASCEND-2 and 5 trials are correctly described.	Thank you for raising this issue. We are happy to make this correction.

Issue 12 Clarification on number of brigatinib patients included in ITC

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg68 paragraph 2- the ERG report states that the total number of brigatinib patients available for the appraisal is 247. This is misleading as this includes Arm A from ALTA which does not reflect the proposed label dosage for brigatinib.	Amend to state that the total number of patients available for efficacy outcomes was 135 (arm B of ALTA and study 101 sub-group).	To correctly state the relevant patient numbers.	Thank you for raising this issue. We are happy to make this correction.

Issue 13 Typographical Error

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg104 final paragraph. There appears to be a typographical error as there is an out of place comment on ERG opinion which is repeated again later in this section. This error is repeated in the middle of pg105	Delete text to correct	Correction for clarity	Thank you for raising this issue. We are happy to make this correction.

Issue 14 Typographical Error

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg105 final paragraph- MAIC is spelt incorrectly as MIAC	Correct to MAIC	Typographical error for correction	Thank you for raising this issue. We are happy to make this correction.

Issue 15 Figure Labelling Error

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg 142- The chart is labelled as Table 51	Correct title of figure	To correctly apply the right title to the chart	Thank you for raising this issue. We are happy to make this correction.

Issue 16 ERG estimate of Ceritinib time on treatment

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg143/145 Fig 23/25. The ERG report does not state that the method of estimation used to determine ceritinib time on treatment (ToT) preferred by the ERG leads to a ToT curve that is below the PFS curve and does not therefore reflect the observed median difference between ToT and PFS in ASCEND-2 of 3.2 months.	The ERG report should make clear that the approach taken may not accurately reflect the time on treatment for ceritinib and that therefore there is significant uncertainty with the validity of this approach.	To correctly present the potential disadvantages of the approach taken in appropriately determining ceritinib ToT. As this parameter is very influential in the ICER estimate, the ERG report needs to be clear in the disadvantages of their preferred approach.	Thank you for raising this important issue. The ERG will re-estimate ceritinib ToT. This will be incorporated as part of an addendum report.

Issue 17 ERG Scenario incorrectly described

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg 14 Table 52. The table describes ERG scenario alternative A as excluding PAS arrangements and then refers to changes 1,3,4 and 5. The excluded change (2) is further described as gamma distribution for PFS extrapolation. It is unclear why this is described as excluding PAS arrangements as the excluded scenario (2) is not related to PAS arrangements	ERG to review and confirm what this alternative should be described as.	To correctly describe this alternative in the table so that it is clearly reported.	Thank you for raising this issue. This description has been edited for clarity.

Issue 18 NICE EoL Criteria

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg152, final paragraph- the ERG report states that NICE EoL criteria refer to the mean rather than median OS estimates. The NICE Methods Guide does not actually state mean or median with respect to survival: ”the treatment is indicated for patients with a short life expectancy, normally less than 24 months…” A reference to mean is only made with the 3 months life extension criterion https://www.nice.org.uk/process/pmg9/chapter/the-appraisal-of-the-evidence-and-structured-decision-making	This section should be amended to correctly state the NICE EoL criteria as set out in the NICE Methods Guide.	To correctly report the NICE EoL criteria- as this factor is highly relevant to the decision, the ERG report needs to clearly present the relevant points of the EoL criteria and note that using median life expectancy for ceritinib meets the NICE EoL criteria.	Thank you for raising this issue. This reference has been deleted and edits made.

Issue 19 Ceritinib life expectancy

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg152 Table 55. The table states that ceritinib life expectancy from the ERG analyses is 24.34 months. The section on ERG opinion in this section then states	Correct text to match the figure stated in table.	Ensure that correct data is reported in both text and table	Thank you for raising this issue. We are happy to make this correction.

24.4 months.			

Issue 20 Table of mapped utility values

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pg116 Table 37. This table is taken from the company submission using the February 2017 data cut and was subsequently updated with the September data cut presented in the addendum submitted at clarification. The rest of the ERG report takes data from the updated data cut addendum, therefore there is a discrepancy with including this data with respect to the mapped utility values	Update Table 37 in the report with Table 9 from the September data cut addendum.	To ensure the September data cut is used consistently throughout the ERG report.	Thank you for raising this issue. We are happy to make this correction.

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

A Single Technology Appraisal

Erratum, following Company fact check

Produced by	Peninsula Technology Assessment Group (PenTAG) University of Exeter Medical School, South Cloisters, St Luke's Campus, Heavitree Road, Exeter EX1 2LU
Date of changes	28 June 2018

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 (1.91-4.78) 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.

Issue 2

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, in a naïve comparison, 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.

Issue 1

1.1 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.

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 1.53 months continuation on treatment post-progression.

Issue 3

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 0.744 for pre-progression, and 0.594 for post-progression.

Issue 4

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).

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 (currently unlicensed, with market authorisation expected from the EMA in December 2018). The company estimate that the likely eligible prevalent population for brigatinib treatment in England numbers 46. These are adults with ALK+ NSCLC, often 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.

Issue 6

Issue 5

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 2). It offers a median progression-free survival of 7.2 months (IRC) and 5.7 months (INV) in ASCEND-2; and 5.4 months (IRC) and 6.7 months (INV) in ASCEND-5. Ceritinib is also approved for use as a first-line treatment, although this is outside the scope of this appraisal.

Issue 7

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)

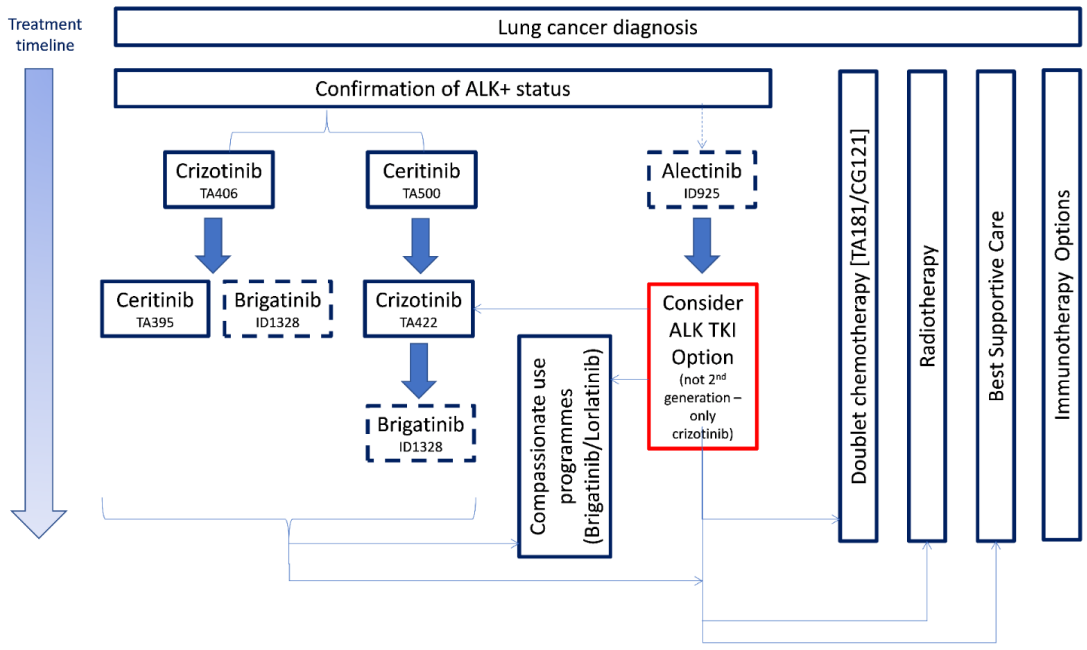
ERG opinion:

- 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 (currently unlicensed), alectinib, and lorlatinib (currently unlicensed), were sometimes available through compassionate use programmes and other initiatives, although they did not yet form part of standard routine care.

Issue 8

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, p16) 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) A draft summary of product characteristics (SmPC) was provided in Appendix C. Note that brigatinib does not currently have EU marketing authorisation, and a European public assessment report (EPAR) is not yet available. 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). Market authorisation is now expected from the EMA in December 2018. 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)

Issue 8&9

Issue 6

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)

Issue 10

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, based on naïve comparison, 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 1, 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 1. Patient deaths in the brigatinib studies are covered in section **Error! Reference source not found.**.

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 1: 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%)

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 brain metastases); 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 metastases) 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 indeed a single arm study but ASCEND-5 is an RCT of ceritinib versus chemotherapy. However, chemotherapy is not an eligible technology.

Issue 11

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 135 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).

Issue 12

3.2.1.1 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 2. 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]				

3.2.2 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 **Error! Reference source not found.** 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 **Error! Reference source not found.** 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 rejects the approach taken in the company model base case.

Issue 13

3.2.2.1 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).

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Figure 2). 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 **Error! Reference source not found.**). 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 2 as the difference in the area under the light blue and dark blue plots). See section **Error! Reference source not found.** for detail of the concerns with the MAIC method, and CS p109 Table 38 for full details of ITC scenario analyses.

ERG opinion:

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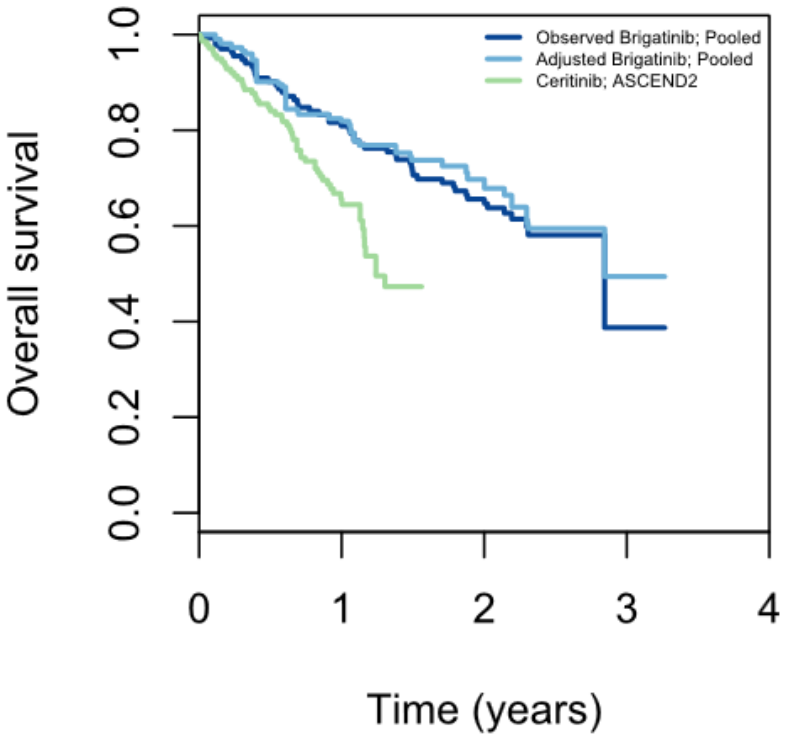
- MAIC has a small impact on the relative OS treatment effect (1% decrease in the ICER).

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



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.

3.2.3 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 3).

Issue 20

Table 3 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

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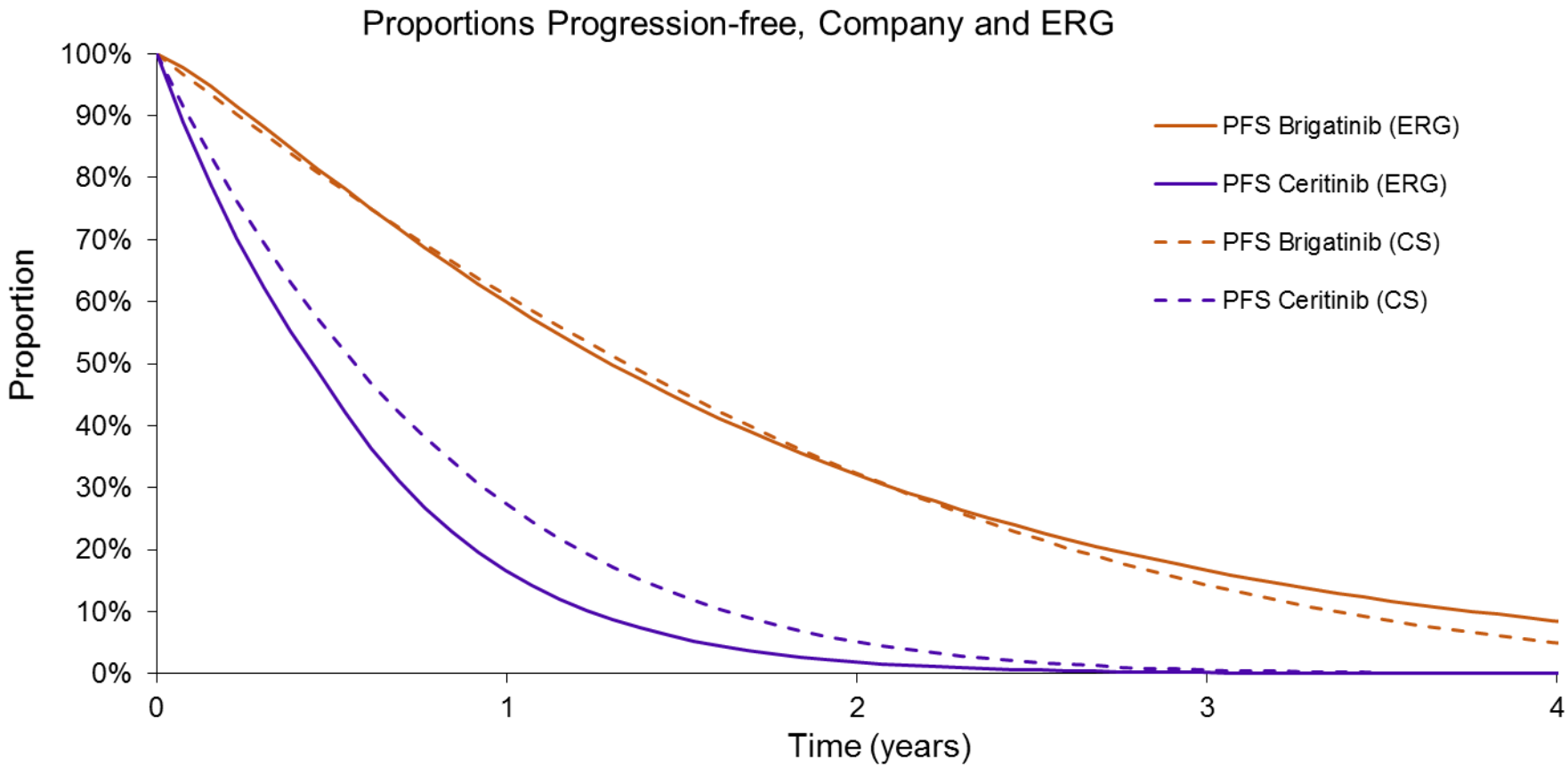
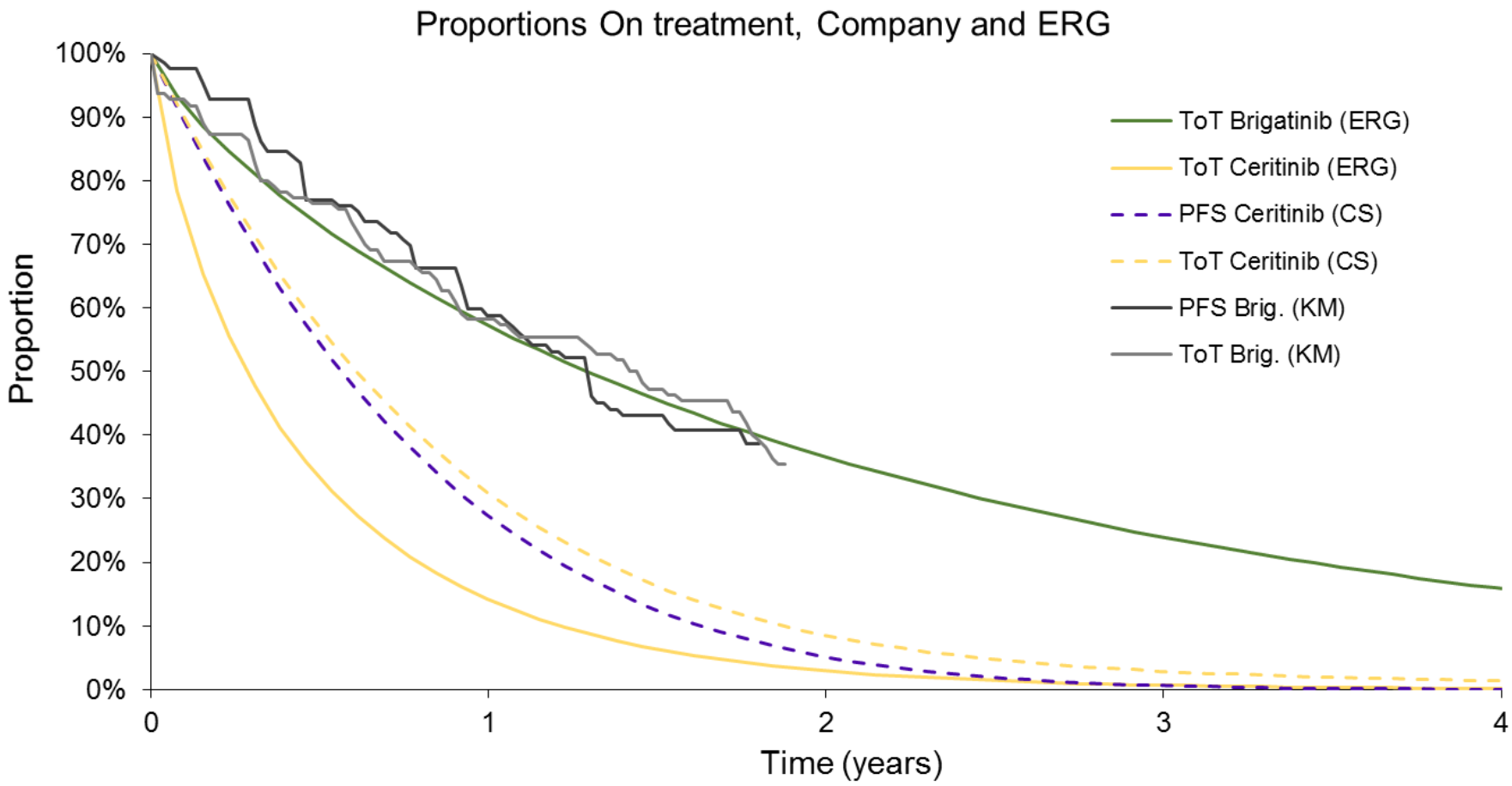
Figure 3 Long-term PFS estimates for strategies, company and ERG



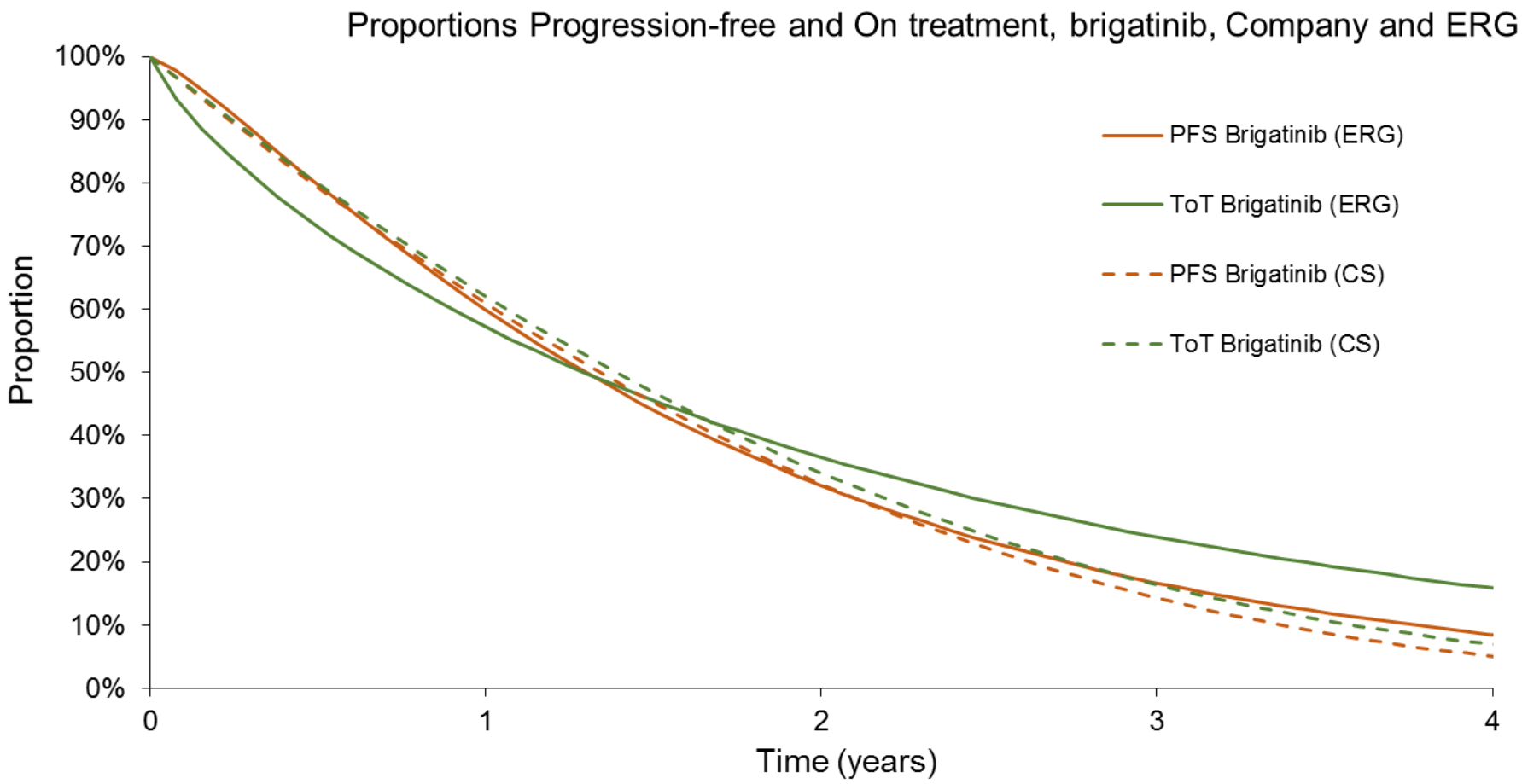
The combined effect of ERG base case changes 1 and 2 is to reduce the long-term estimate of PFS on ceritinib; with a slight change to the brigatinib estimate.

Figure 4 TOT as a proportion of patients on treatments, Company and ERG estimates



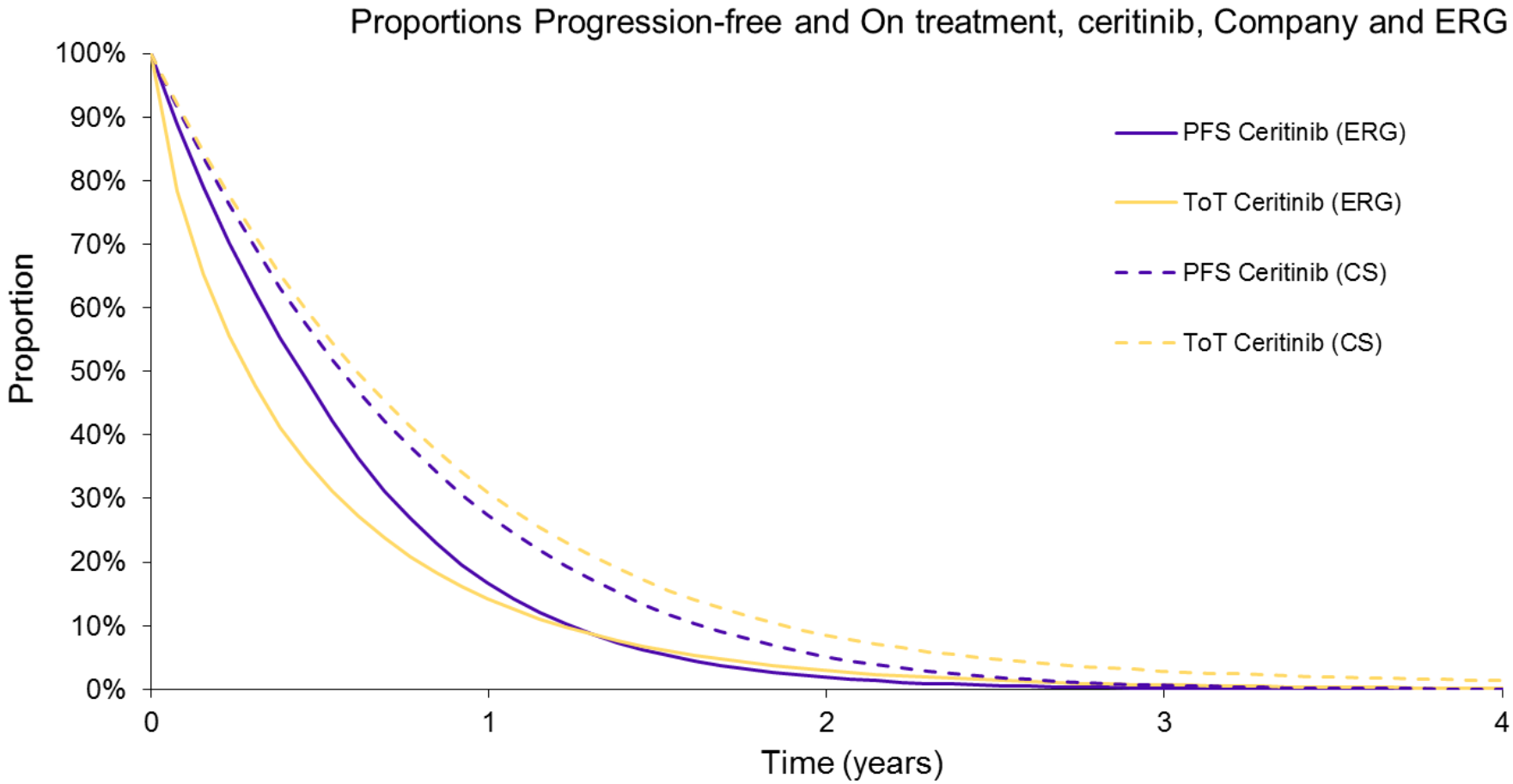
The overall effect of ERG base case changes 1, 2 and 3 is to reduce the long-term estimate of time on ceritinib treatment.

Figure 5 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 6 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).

3.3 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 4 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. **Error! Reference source not found.** presents the summary results of the 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's 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. (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%

Issue 17

Table 4 Summary derivation of ERG base case

*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.

4 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 5 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 5 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, when using the mean average survival the first EoL criterion is not strictly satisfied, since the modelled mean life expectancy on the comparator treatment is slightly greater than 24 months (24.34 months, or 2.03 undiscounted life-years). Also, the company have chosen the statistical distribution, the Gompertz which gives the shortest life expectancy for the

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Issue 19

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

A Single Technology Appraisal

Addendum – Revised ERG base case

Additional analysis

10 July 2018

1 Summary

In this addendum presents the results of new analysis from the ERG which details a base case using preferred methods, parameter estimates, and assumptions. These results supersede those presented in the main ERG report for ID1328. They do not include patient access scheme (PAS) arrangements. Results including PAS are provided separately in Addendum Appendix 1 (confidential).

Based on drug list prices, the company base case using September 2017 data cut estimated the ICER of brigatinib versus ceritinib as £54,311 per QALY gained.

The ERG base case estimated the cost-effectiveness of brigatinib versus ceritinib as £90,801 per QALY gained. Brigatinib provided an additional 0.40 life-years and 0.34 QALYs compared to ceritinib, at an incremental cost of £30,746.

Deterministic and probabilistic results are presented below. All costs and life years have been discounted at a rate of 3.5% per annum.

2 Development of the ERG base case

Preferential approaches were taken in six aspects of the modelling. These were implemented in turn and are justified as follows:

1. **Time on treatment.** The ERG would prefer to use the observed ToT data rather than use estimates based on PFS. However, ToT data is not available for ceritinib and the application of the PFS ITC hazard ratio to brigatinib underestimates the time on ceritinib. Expert clinical advice received by the ERG supports a relaxed link between treatment discontinuation and progression, since in clinical practice ALK inhibitors are often continued beyond radiological progression when some meaningful clinical benefit is still being attained. Therefore the cost of treating beyond progression is included; but rather than using the period observed in ALTA for both strategies (ToT-PFS = 1.53 months), we use the estimate specific to ceritinib from ASCEND-2 (3.1 months) for this strategy. Data was not available from ASCEND-5.

2. **Duration of effect.** The company base case assumes a continuation of response and mortality benefit for the lifetime of the model, such that the whole difference in AUC between the fitted curves is attributed to the brigatinib strategy. Here we observe that convergence begins at about 3-years, and OS benefit lasts up to 14 years. However, expert clinical opinion is that treatment effect is lost earlier; the loss of clinically meaningful effect triggers discontinuation (for those who tolerate treatment). –Therefore the ERG use the point of convergence of OS for each strategy versus BSC to mark the beginning of decline in effect. These periods are 1.46 years for brigatinib, and 1.07 years for ceritinib, and they are used in the revised base ERG base case. Scenario analyses consider these stop times plus 1, 2, 3 and 5 years.

3. **Data sources.** The data sources used for the modelling of PFS should include the ASCEND-5 trial in preference to Study 101. Because neither IRC nor INV- assessed outcomes were available for all four included trials (Study 101 has only INV data, and ASCEND-5 has only IRC data), the choice of trials to include in the PFS analysis is necessarily a trade-off of size, quality, and preference for IRC reported outcomes. The ERG's preferred approach is a meta-analysis of the 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 in the main report), and results for ASCEND-5 are reported by IRC so are less likely to be influenced by local bias.

4. **PFS extrapolation.** Rather than the Gompertz distribution, the gamma distribution 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. No implausible scenario whereby there become more patients progression-free than alive is created.

5. **Drug wastage.** 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.(1) The committee settled on the pragmatic assumption that the NHS will pay for some unused tablets; that RDI 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 the estimate reported in the CS.

6. **Administration / Delivery cost.** The company assume there is no administration cost 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: and 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 and apply it to both strategies.

3 ERG base case results (without commercial arrangements)

3.1 Summary results

Table 1 Summary results including derivation and impact of individual differences

				ICER, £ per QALY	Impact, £ per QALY (%)	Cumulative ICER, £ per QALY (impact £, %)
Company Base Case				£54,311		
ERG Base Case (+1-7)				£90,801	£36,490 (67.19%)	
Impact of revisions on company base case:						
No.	*Category*	*ERG*	*Company*			
1	Time on treatment	Trial-based treatment beyond progression: until 1.53 months post progression for brigatinib, and 3.1 months post progression for ceritinib	Assumes all brigatinib patients discontinue treatment at 1.53 months post-progression— based on extrapolation PFS K-M curves using Gompertz curve	£48,580	-£5,731 (-10.55%)	£48,580 (-£5,731, -10.6%)
2	Duration of effect	Benefits are allowed up to the predicted decline in effect versus BSC. 1.46 years for brigatinib, and 1.07 years for ceritinib	Benefits are allowed for the whole 14.02 year (lifetime) horizon	£100,110	£45,799 (84.33%)	£79,360 (£25,049, 46.1%)
3	PFS data source	Random effects meta-analysis combining the following two MAIC analyses: INV dataset ALTA vs. ASC-2 (full covariate set) IRC dataset ALTA vs. ASC-5 (full covariate set)	MAIC analyses using pooled brigatinib data and data from ASC-2 -- INV data only. Scenario effectively drops study 101 in favour of ASCEND-5	£59,671	£5,360 (9.87%)	£88,010 (£33,699, 62%)
4	PFS extrapolation	Gamma distribution used to extrapolate PFS (case for Gompertz rejected)	Gompertz distribution to extrapolate PFS	£58,869	£4,558 (8.39%)	£87,567 (£33,356, 61.2%)
5	Drug wastage	Assumes only half of wastage is financially recoverable by the NHS. Brigatinib MDI= 95.45%; Ceritinib MDI= 91.80%	Assumes all wastage is financially recovered by the NHS. Brigatinib MDI= 88.90%; Ceritinib MDI= 83.59%	£55,892	£1,582 (2.91%)	£88,794 (£34,483, 64.4%)
6	Administration cost	£42.50 per home delivered oral chemo item	£0	£55,906	£1,595 (2.94%)	£91,457 (£37,146, 68.4%)

Abbreviations: BSC, Best Supportive Care; PFS, Progression-free survival; MAIC, Matching-adjusted indirect comparison; INV, Investigator; IRC, Independent review committee; ToT, Time on treatment; K-M, Kaplan-Meier; MDI, Mean dose intensity

Table 2 ERG base case result for brigatinib versus ceritinib (deterministic)

Technology	Total discounted costs (£)	Total discounted QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Brigatinib	£83,171	0.97			
Ceritinib	£52,425	0.63	£30,746	0.34	£90,801

Abbreviations: QALY, Quality Adjusted Life Year; ICER, Incremental Cost Effectiveness Ratio

3.2 Detailed deterministic results

Table 3 Base case result of primary analysis (deterministic)

Technology	Total Costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Brigatinib	£83,171	1.28	0.97				
Ceritinib	£52,425	0.88	0.63	£30,746	0.40	0.34	£90,801

Abbreviations: LY, Life Year; Incr., Incremental

Table 4 Summary of costs by health state

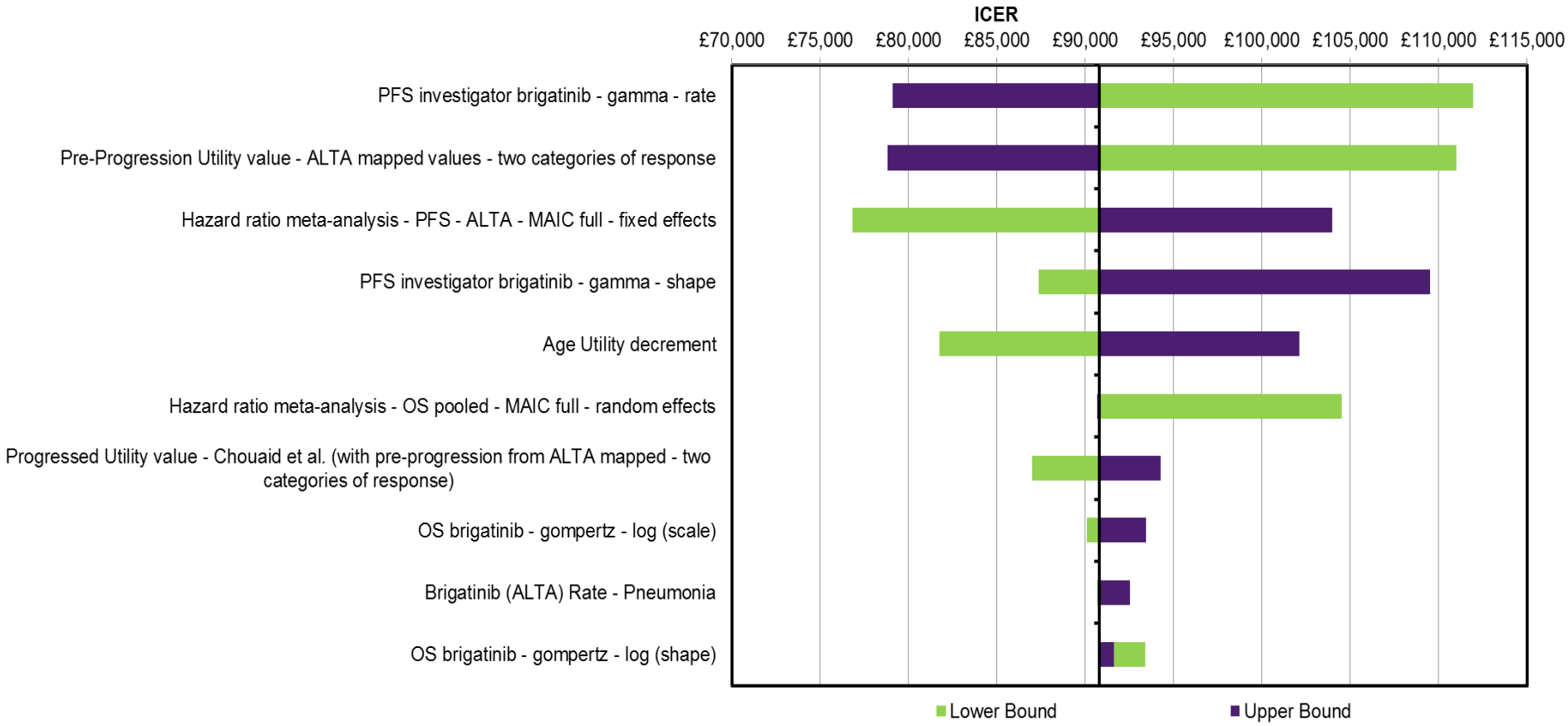
Health State	Cost (£) brigatinib	Cost (£) ceritinib	Increment (£)	Increment as % of total increment
Progression-free state	£71,887	£32,960	£38,927	126.6%
Progressed disease state	£9,673	£17,828	-£8,155	-26.5%
End of Life	£1,611	£1,638	-£26	-0.1%
Total	£83,171	£52,425	£30,746	100.0%

Table 5 Summary of estimated resource-use for brigatinib versus ceritinib

Resource use	Cost (£) brigatinib	Cost (£) ceritinib	Increment (£)	Increment as % of total increment
Progression-free state	£4,711	£2,435	£2,276	7.4%
Progressed disease state	£1,650	£2,507	-£858	-2.8%
Treatment	£72,445	£43,184	£29,261	95.2%
Concomitant medications	£868	£566	£302	1.0%
Terminal care	£1,611	£1,638	-£26	-0.1%
Adverse events	£1,886	£2,095	-£209	-0.7%
Total	£83,171	£52,425	£30,746	100.0%

3.3 Univariate deterministic sensitivity analysis

Figure 1 Tornado diagram: deterministic sensitivity analyses results

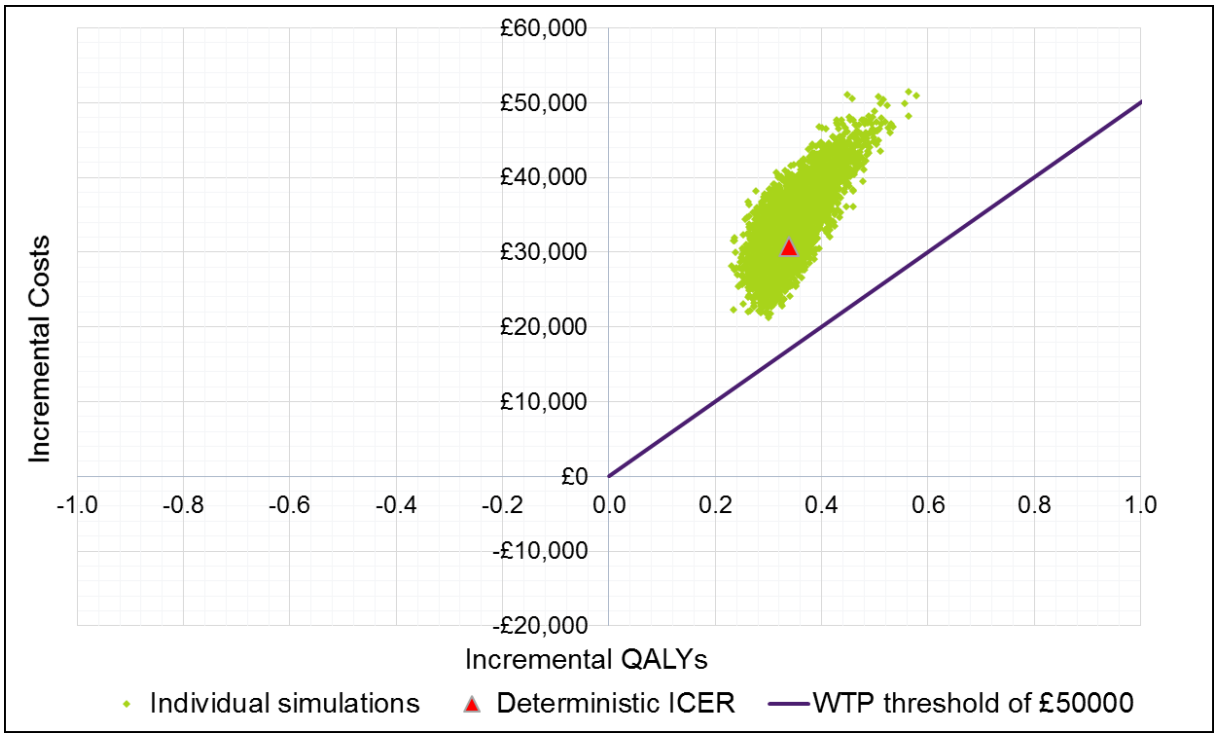


Abbreviations: ICER, incremental cost-effectiveness ratio; OS, overall survival; HR, hazard ratio; PFS, progression-free survival

Source: Extracted from CS revised model (Takeda Ltd)

3.4 Probabilistic analysis (PSA and CEAC)

Figure 2 Probabilistic sensitivity analysis: incremental cost effectiveness plane for brigatinib versus ceritinib



Source: Extracted from CS revised model (Takeda Ltd)

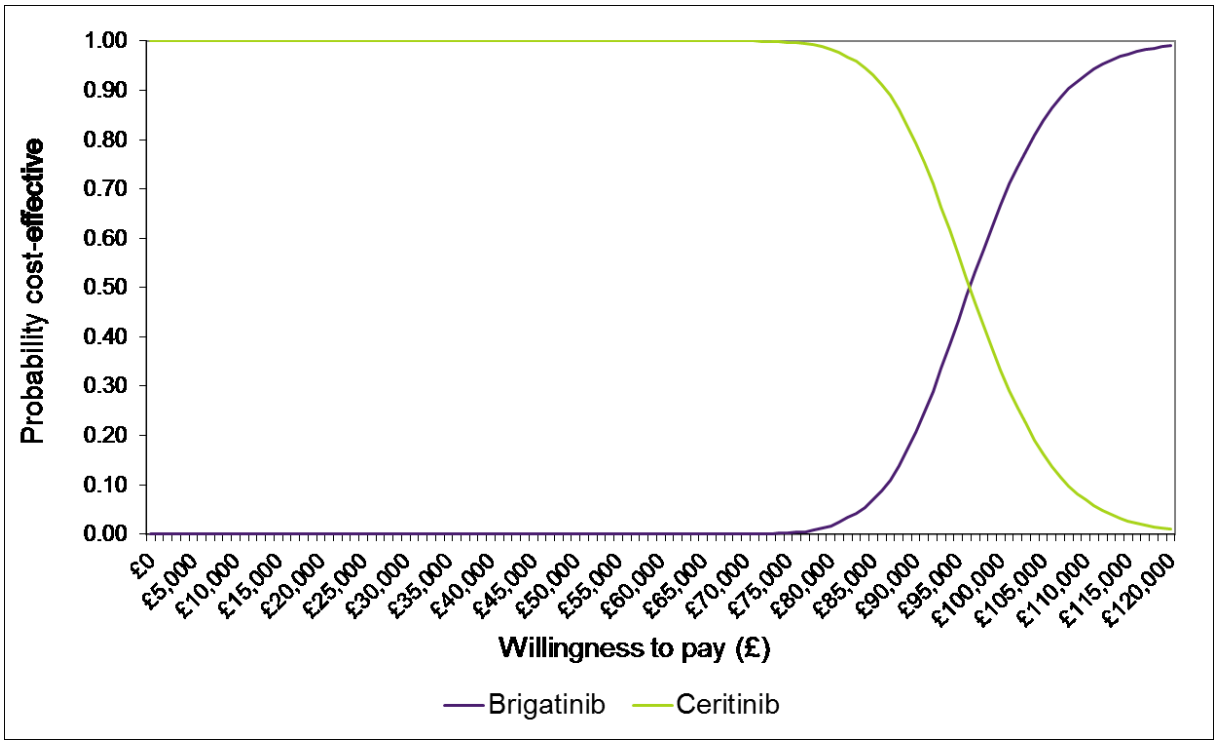
Table 6 Probabilistic base case results

Technology	Incremental costs (£), *mean± SD*	Incremental QALYs, *mean± SD*	ICER (£/QALY)
Brigatinib versus ceritinib	£32,939 ± £4,112	0.34 ± 0.04	£96,635

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.

Figure 3 Cost effectiveness acceptability curve: brigatinib vs. ceritinib



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

Source: Extracted from CS revised model (Takeda Ltd)

The probability that brigatinib is the most cost-effective option at the £50,000 per QALY threshold is 0.0%.

3.5 Scenario Analyses

Presented below are alternative scenarios to the ERG base case (Table 7). They are selected because they explore alternatives to the most important assumptions.

Table 7 Results of scenario analyses

Scenario	ICER	Difference from ERG base case ICER
Brigatinib OS data – pooled		
Gompertz (Company/ERG base case)	£90,801	0.00%
Gamma	£90,386	-0.46%
Weibull	£90,454	-0.38%
Exponential	£91,089	0.32%
Brigatinib PFS INV data – pooled		
Gompertz (Company base case)	£91,298	0.55%
Gamma (ERG base case)	£90,801	0.00%
Weibull	£90,922	0.13%
Exponential	£92,216	1.56%
Brigatinib PFS IRC data – ALTA only		
Gompertz	£92,957	2.37%
Gamma	£93,263	2.71%
Weibull	£93,560	3.04%
Exponential	£92,731	2.13%
Relative efficacy OS		
Meta-analysis (RE) pooled data - MAIC full (Company/ERG base case)	£90,801	0.00%
Meta-analysis (RE) pooled data - Naïve ITC	£91,087	0.31%
Meta-analysis (RE) ALTA only - Naïve ITC	£91,177	0.41%
Meta-analysis (RE) ALTA only - MAIC	£90,033	-0.85%
Relative efficacy PFS		
Meta-analysis (RE) ALTA only - MAIC full (ERG base case)	£90,801	0.00%
Meta-analysis (RE) ALTA only - Naïve ITC	£86,186	-5.08%
MAIC full – Pooled - ASCEND-2 (Company base case)	£80,549	-11.29%
MAIC full - ALTA - ASCEND-5	£106,489	17.28%
ToT scenarios		
Treatment until 1.53 months post progression for brigatinib, and 3.1 months post progression for ceritinib (ERG base case)	£90,801	0.00%
Treatment until 1.53 months post progression for brigatinib and ceritinib (Company base case)	£114,044	25.60%
Extrapolated ToT curve (gamma) fitted to ALTA data for brigatinib, with PFS HR applied for ceritinib	£117,668	29.59%
Extrapolated ToT (gamma) curve fitted to ALTA and capped by PFS for brigatinib, with the PFS HR applied for ceritinib	£112,167	23.53%
Treatment until progression for brigatinib and ceritinib	£112,794	24.22%
Long-term treatment effect (post initiation)		
No treatment benefit discontinuation (Company)	£62,214	-31.48%
Treatment benefit discontinuation (ERG base case)	£90,801	0.00%

Treatment benefit discontinues 1-year after decline in effect	£102,397	12.77%
Treatment benefit discontinues 2-years after decline in effect	£95,220	4.87%
Treatment benefit discontinues 3-years after decline in effect	£86,115	-5.16%
Treatment benefit discontinues 5-years after decline in effect	£73,243	-19.34%
Treatment benefit discontinues 10-years after decline in effect	£63,119	-30.49%
Cost inputs		
Include cost of used drug only	£89,627	-1.29%
No administration / home delivery costs	£88,161	-2.91%
HRQL inputs		
PF and PD utilities from Chouaid et al. (2013)	£96,599	6.39%
PF and PD utilities from Nafees et al. (2008)	£103,998	14.53%
Nafees et al. (2008) for progression decrement	£89,789	-1.11%
Time horizon		
5-year time horizon	£90,719	-0.09%
10-year time horizon	£90,718	-0.09%

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: Extracted from CS revised model (Takeda Ltd)

REFERENCES

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