Slides for committee and public

Lead team presentation

Brigatinib for treating ALK-positive advanced non-small-cell lung cancer after crizotinib – STA

1st Appraisal Committee meeting

Background, Clinical Effectiveness & Cost Effectiveness

Committee D

Lead team: David Bowen, Rob Hodgson and Rebecca Harmston

ERG: PenTAG

NICE technical team: Emily Eaton Turner, Christian Griffiths

12th July 2018

Key issues
Clinical effectiveness

- **All brigatinib studies were single-arm studies**
- **What is the most appropriate data to include when estimating PFS?**
  - Company base case = Study-101 (investigator assessed)
  - ERG = ASCEND-5 (independent review committee)
- **Duration of treatment effect:** Is a treatment benefit beyond progression experienced in this patient population?
  - How long is the treatment benefit sustained for?

Brigatinib (Alunbrig)
Takeda

Mechanism of action	Tyrosine kinase inhibitor (TKI)
Anticipated marketing authorisation	As monotherapy for the treatment of adult patients with ALK+ advanced NSCLC previously treated with crizotinib
Administration	Oral
Dose	90 mg once daily for first 7 days, then 180 mg 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 PAS has been submitted**. This provides a simple discount to list price

* Updated following the committee meeting to correct for factual inaccuracy
** Updated to approved after the committee meeting

Non-small cell lung cancer (NSCLC)
Disease background

- Lung cancer → ~36,000 people diagnosed in England in 2016
  - With NSCLC = estimated 88.5% of lung cancer cases
- NSCLC highly heterogeneous with different driver mutations (including anaplastic lymphoma kinase (ALK) gene rearrangement)
  - With 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 tyrosine-kinase inhibitor 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
- Supporting a person with NSCLC is stressful → patient's symptoms are apparent and debilitating
- Improved quality of life, 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 & professional organisation perspectives

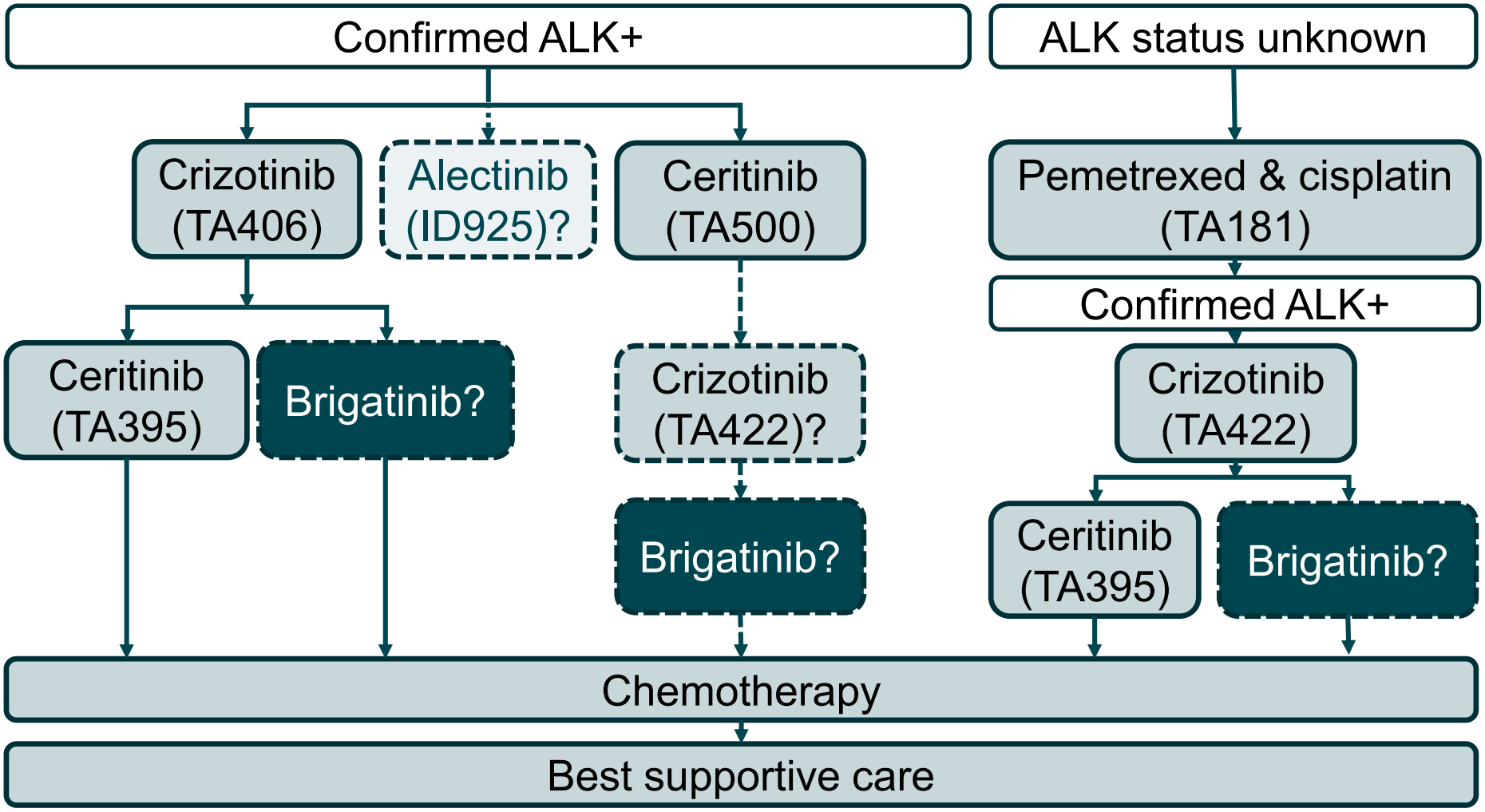
- **Submissions: Consultant Medical Oncologist (The Christie), British Thoracic Society & BTOG/NCRI/RCP/RCR/ACP**
- Unmet clinical need due to acquired resistance to available ALK inhibitors
- Poor prognosis → *'urgent need'* for more treatment options
- If approved, brigatinib would be second line ALK-TKI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

NHS England perspective

- Alectinib is the main 1st line option used in NHS England for newly diagnosed patients
- Only one treatment sequence commissioned → 1st line crizotinib > 2nd line ceritinib
  - Only applies to those who commenced on crizotinib in the past or who cannot tolerate alectinib and/or ceritinib
- Crude comparison of efficacy shows brigatinib to have higher response rates and greater effect on progression free survival than ceritinib
- Toxicity of brigatinib also appears to be less than ceritinib
  - Less gastrointestinal side-effects → main issue with ceritinib
- Treatment with brigatinib will continue after disease progression in 2 specific scenarios
- Drug wastage needs to be included in the economic model → likely more waste with ceritinib than brigatinib
- Drug administration cost per cycle is underestimated in the analysis → should be £120
- If recommended by NICE, NHSE treatment criteria will reflect the MA if confined patient population of brigatinib post-crizotinib is confirmed

Current treatment for ALK+ NSCLC

based on current NICE guidance



*Alectinib = ongoing appraisal (expected publication August 2018)

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 180 mg once daily (7 day of 90 mg once daily)	
Comparator	Brigatinib 90 mg once daily	-
Population	Adults with locally advanced or metastatic ALK+ NSCLC, previously treated with crizotinib	
1◦ outcome	Objective response rate (ORR) (investigator, RECIST)	
2◦ outcomes	Progression free survival (PFS), overall survival (OS), central nervous system response (PFS, ORR), duration of response	
	Health-related quality of life, adverse effects, ORR (independent review committee), time to response	-

Key baseline characteristics

Brigatinib trials

- In ATLA, 74% of people had received any chemotherapy as prior therapy

		ALTA: 180 mg n=110	ALTA: 90 mg 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)
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) Not reported 83 (74.1)	25 (100) Not reported 17 (68.0)

Clinical trial results - brigatinib

Months (95% CI)	ALTA: 180 mg	ALTA: 90 mg	Study 101
Median follow-up	24.3 months	19.6 months	Not reported
Median overall survival	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, DOR = duration of response, ORR = objective response rate

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

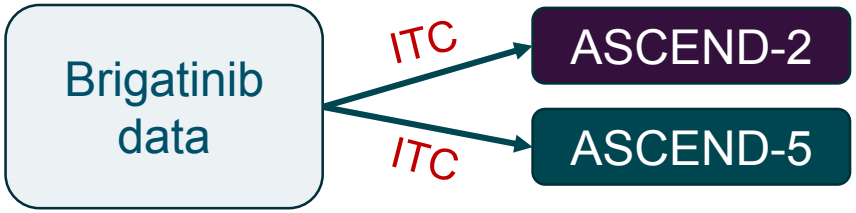
Clinical evidence for comparator: ceritinib

- No direct evidence of brigatinib vs ceritinib
- Therefore need to use indirect treatment comparisons (ITCs)
- ASCEND-2 & ASCEND-5 studies used for ceritinib effectiveness

	ASCEND-2 (n=140)	ASCEND-5 (n=231)
Design	Single-arm	RCT
Intervention	Ceritinib 750 mg 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)

RCT = randomised controlled trial, IRC = independent review committee, ORR = objective response rate, PFS = progression free survival, OS = overall survival, DCR = disease control rate, DOR = duration of response, TTR = time to response, QoL = quality of life

Indirect treatment comparison (ITC)



- Company provided different ways to do an indirect treatment comparison:
- Different data included for brigatinib:
  - Combining all **brigatinib** data (ALTA & Study 101)
    - Investigator Assessed progression free survival (INV-PFS)
  - Some **brigatinib** data (ALTA only)
    - Independent review committee progression free survival (IRC-PFS)
- Different way of doing the ITC (brigatinib vs ceritinib)
  - Naive ITC = no adjustment for differences in study populations
  - Unanchored matching-adjusted indirect comparisons (MAIC) = adjusts for imbalances in study populations
    - MAIC analyses conducted for 'full' and 'reduced' set of covariates

ERG comment: • ITC analysis is broadly appropriate.
- There is broad consistency of the results from the MAIC and naive ITC approaches

Meta-analysis of the indirect treatment comparison analyses

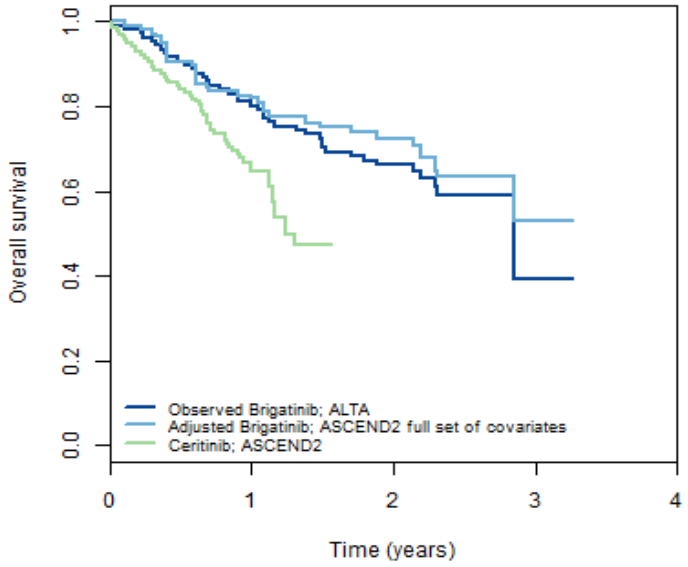
- Bayesian meta-analysis was used to provide overall estimates of clinical effectiveness from the indirect treatment comparison results
- For the MAIC and naive ITC approaches, the ITC results against ASCEND-2 were meta-analysed separately with the ITC results against ASCEND-5
- The meta-analysis was run using a fixed-effect model and a random-effects model
- Estimates of overall survival and progression free survival and objective response rate included different data from the ITC in the meta-analysis:
    - Overall survival: ITC data including the combined brigatinib data
    - Progression free survival and objective response rate: ITC data including ALTA data only

ERG comment:

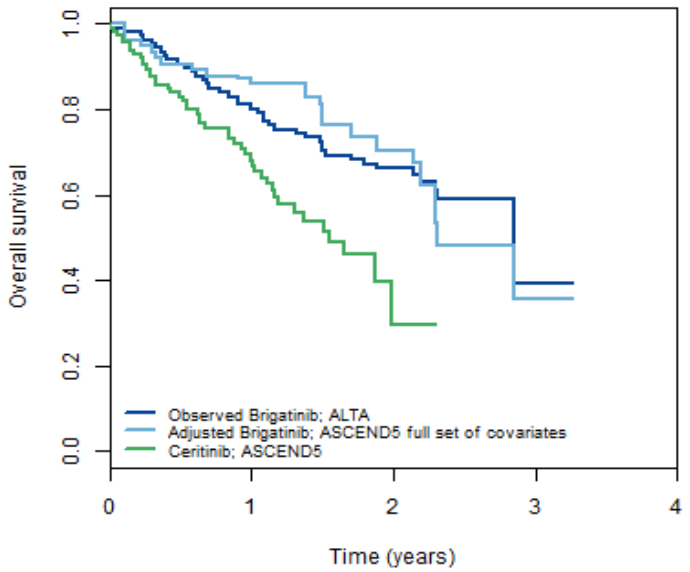
- No correction applied for correlated data because data from the brigatinib trials contribute twice to the meta-analyses → confidence intervals may be unrealistically precise
- The "prior" chosen was relatively generic. A "prior" specifically for pharmacological data was also available
- Consistent results produced using each analytical strategy to meta-analyse the ITC analyses

Overall survival ITC and meta-analysis results

ASCEND-2 vs pooled



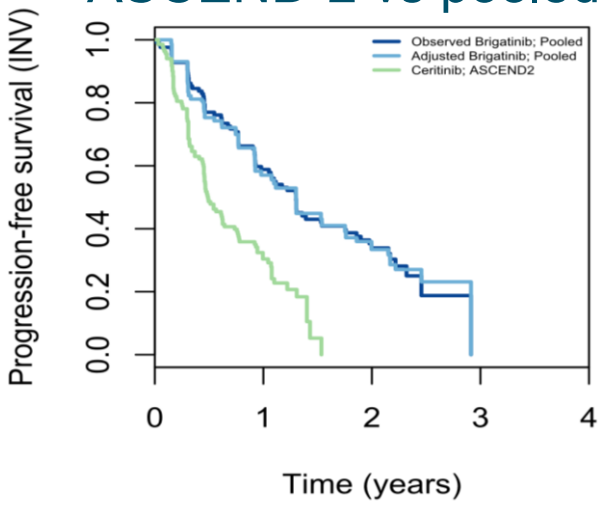
ASCEND-5 vs pooled



Ceritinib vs brigatinib, HR (95% CI)		Ceritinib				
		using ASCEND-2 (Naive)	using ASCEND-5 (Naive)	using ASCEND-2 (MAIC)	using ASCEND-5 (MAIC)	Meta-analysis ASCEND-2 & 5 (MAIC)
Brigatinib	using 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)
	Using ALTA + 101	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)

Progression free survival ITC and meta-analysis results

ASCEND-2 vs pooled



Ceritinib vs brigatinib, HR (95% CI)		Ceritinib				
		using ASCEND-2 (Naive)	using ASCEND-5 (Naive)	using ASCEND-2 (MAIC)	using ASCEND-5 (MAIC)	Meta-analysis ASCEND-2 & 5 (MAIC)
Brigatinib	using 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)
	using ALTA + 101	2.59 (1.87, 3.59)	NA	2.62 (1.77, 3.88)	NA	NA

ERG's comment on clinical trial, indirect comparison and tolerability

- Largest risk of bias for trials from lack of comparator (although ASCEND-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)
- **Results show brigatinib significantly increases OS, PFS & ORR**
- Could have meta-analysed data from ALTA & Study 101 rather than pool the data
- **Brigatinib better tolerated than ceritinib (naive comparison) for common adverse events (but had slightly more serious adverse events)**

Duration of treatment effect

- The company assumes a continued treatment benefit associated with overall survival and progression free survival for brigatinib and ceritinib
- **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

ERG comment:

- The ERG consider it plausible that the benefit of brigatinib gained over ceritinib during trial observation is carried through the model's lifetime horizon
- Observe that convergence begins at about 3-years and overall survival benefit lasts up to 14 years
  - Expert clinical opinion = treatment effect lost earlier than this
    - Loss of clinically meaningful effect triggers discontinuation
- 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

Key issues
Clinical effectiveness

- **All brigatinib studies were single-arm studies**
- **What is the most appropriate data to include when estimating PFS?**
  - Company base case = Study-101 (investigator assessed)
  - ERG = ASCEND-5 (independent review committee)
- **Duration of treatment effect:** Is a treatment benefit beyond progression experienced in this patient population?
  - How long is the treatment benefit sustained for?

Lead team presentation
Cost-effectiveness slides

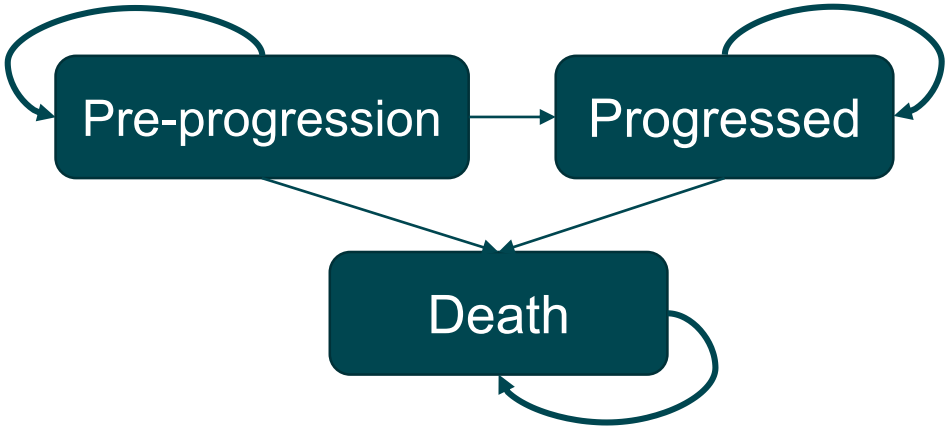
Key issues
Cost effectiveness (1)

- **Time on treatment:** Is treatment continued following disease progression?
  - For how long is treatment given following progression?
    - Company = 1.53 months for both brigatinib and ceritinib
    - ERG = 1.53 months for brigatinib and 3.1 months for ceritinib
- **Duration of treatment effect :** Is it reasonable to assume that treatment benefit continues beyond stopping treatment?
    - Company = lifetime
    - ERG = decline in treatment effect starting at 1.46 years for brigatinib and 1.07 years for ceritinib
- **Overall survival extrapolation:** which distribution is reasonable?
  - Company preferred Gompertz distribution
    - But this implies that end-of-life criteria might not apply
- **Progression free survival extrapolation:** which distribution is reasonable?
    - Company = Gompertz
    - ERG = Gamma

Key issues
Cost effectiveness (2)

- **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?

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

ERG comment:

- The model structure is consistent with those used in other ALK+ lung cancer NICE appraisals

Clinical parameters in the company base case

- Overall survival and time on treatment are key drivers of the 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

Treatment beyond progression

- ALTA protocol allowed treatment beyond progression with brigatinib if investigator believed there was clinical benefit
- Company's model assumption: additional treatment duration of 1.53 months beyond progression for brigatinib and ceritinib

ERG comment:

- Advice to the ERG from clinical experts supports treatment beyond progression
  - In clinical practice ALK inhibitors are often continued beyond radiological progression when some meaningful clinical benefit is being attained
- The ERG reject the company's method of using the additional treatment duration observed in ALTA for both brigatinib and ceritinib
- The ERG use 3.1 months for ceritinib based on ASCEND-2

Duration of treatment effect

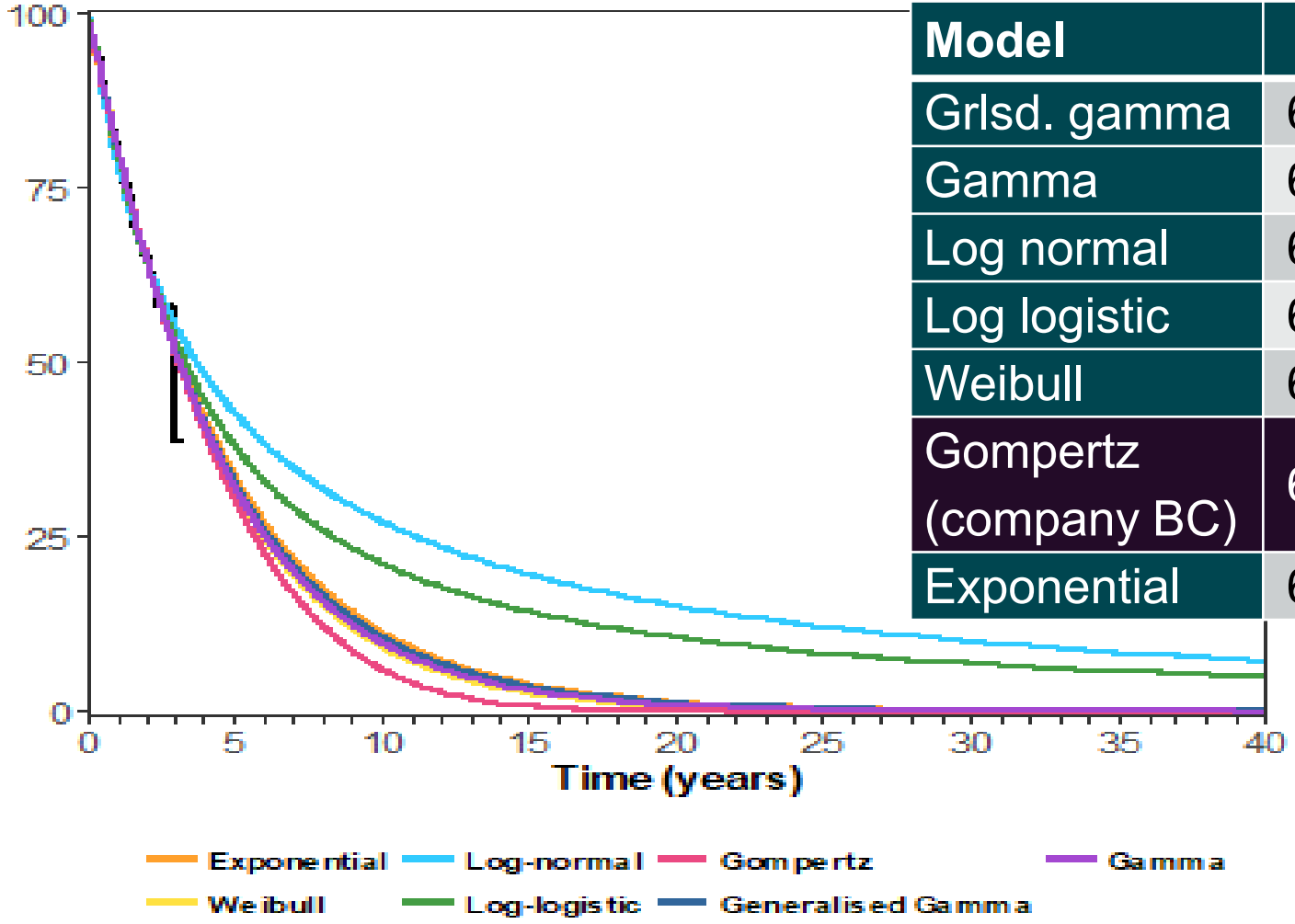
- The company assumed a continuation of response and mortality benefit for the lifetime of the model

ERG comment:

- Observed that convergence begins at about 3-years and overall survival benefit lasts up to 14 years
  - Expert clinical opinion is that treatment effect is lost earlier
    - Loss of clinically meaningful effect triggers treatment discontinuation
- The beginning of decline in effect should be at the point of convergence of overall survival for each strategy versus best supportive care
- This is 1.46 years for brigatinib and 1.07 years for ceritinib

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 (company BC)	664.34	670.15
Exponential	662.43	665.34

Overall survival extrapolations for brigatinib (2)

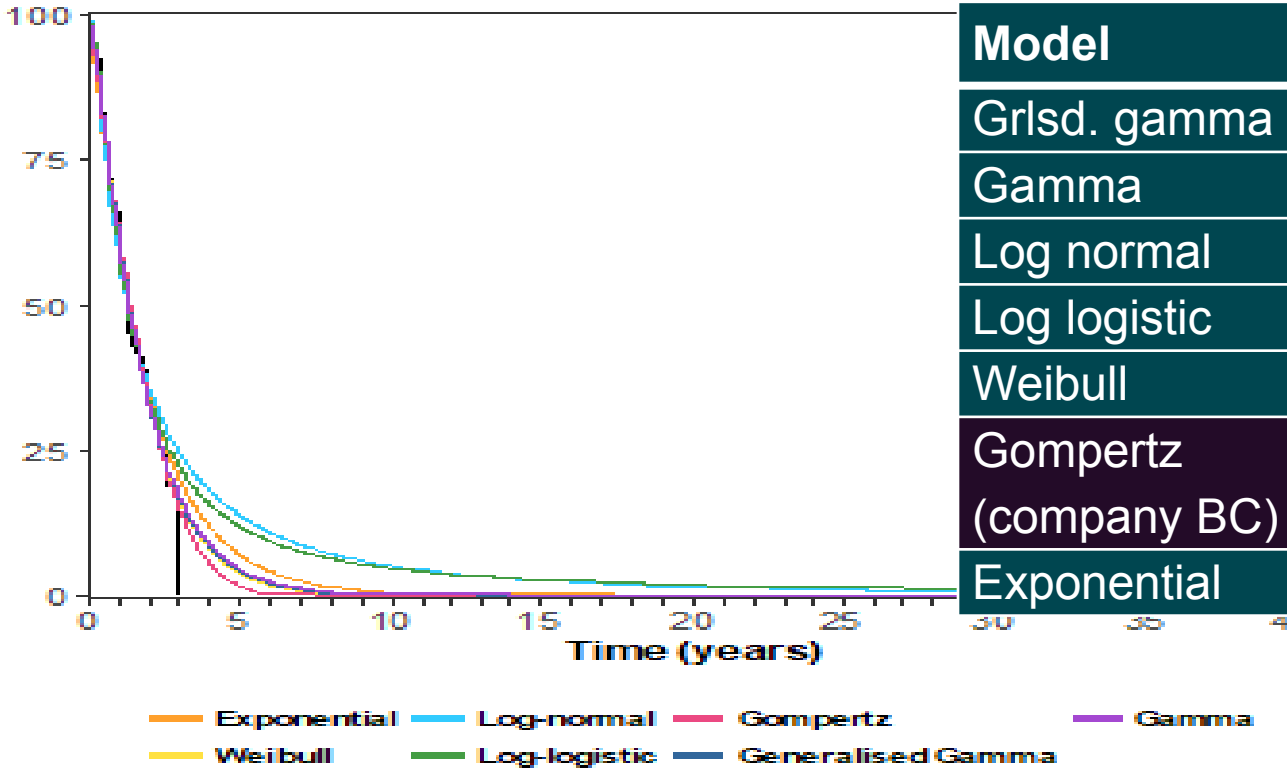
	3-years	5-years	10-years	20-years
Company clinician's opinion, avg (range)	50.00% (35 to 65%)	28.50% (17.5 to 50%)	5.83% (<5% to 7.5%)	0.00% (0 to <5%)
Extrapolated outcomes				
Generalised gamma	51.46%	32.64%	10.61%	1.19%
Gamma	51.29%	32.03%	9.68%	0.86%
Log-normal	55.14%	42.69%	27.10%	15.03%
Log-logistic	52.82%	37.89%	21.12%	10.51%
Weibull	51.20%	31.67%	9.12%	0.68%
Gompertz (company BC)	51.05%	30.24%	5.90%	0.03%
Exponential	52.01%	33.63%	11.31%	1.28%

ERG comment: • Also use Gompertz in base case

- Accuracy of the extrapolation of OS is very uncertain
- 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 the results based on a time-horizon of 14.03 years should be treated with caution

Progression free survival extrapolations for brigatinib

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 (company BC)	870.57	876.38
Exponential	870.54	873.45

ERG comment: • Choice of Gompertz distribution not justified

- Preferred choice is Gamma
- Preferred data is the random effects meta-analysis combining two MAIC analyses: ALTA vs ASC-2 (INV data) with ALTA vs ASC-5 (IRC data) [full covariate sets]

Utility values used in the model

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

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

ERG comment:

- Estimate of mean utility for progressed disease state of 0.643 is higher than 2 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

Question for committee: is utility value of 0.643 for progressed disease appropriate for people having 2nd line treatment?

Cost-effectiveness results – summary
Based on list prices

- 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**
- Summary of results based on list price:
  - Deterministic results:
  - Life years gained: brigatinib = 3.49 & 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

The company base case ICER is most sensitive to:

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

Company scenario analysis

- The company provided a range of scenarios for alternative approaches
- 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	ICER £/QALY range using other distributions
Company base case ICER = £54,311 per QALY gained	
OS – pooled data	35,649 to 54,311
OS – ALTA data	34,252 to 47,361
PFS – pooled INV data	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. Survival has been capped using ONS lifetables

Company scenario analysis results
Continuation of benefit beyond progression

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

ERG exploratory analyses (1)

- The ERG did not agree with some important model assumptions or their justification
- Preferential approaches were taken in 6 aspects of the modelling by the ERG

Aspect of modelling	Company's approach	ERG approach
(1) Time on treatment beyond progression	Brigatinib & ceritinib = 1.53 months (based on ALTA)	Ceritinib = 3.1 months* (based on ASCEND-2) Brigatinib = 1.53 months* (based on ALTA)
(2) Duration of treatment effect following stopping treatment	Assume continuation of response and mortality benefit for the lifetime of the model (14.02 years)	Benefits continue up to the predicted decline in effect vs best supportive care: Brigatinib = 1.46 years Ceritinib = 1.07 years

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

ERG exploratory analyses (2)

Aspect of modelling	Company's approach	ERG approach
(3) Data sources for modelling progression free survival – included studies in the meta-analysis	MAIC full – pooled ALTA and Study-101 vs. ASCEND-2. Includes Study-101 (investigator assessed) in preference to ASCEND-5 (independent review committee assessed). No meta-analysis	Meta-analysis of the MAIC of ALTA vs. ASCEND-2 using INV data and the MAIC of ALTA versus ASCEND-5 using the IRC data
(4) PFS extrapolation distribution	Gompertz	Gamma
(5) Drug wastage	Assume no wastage	Apply half the difference between the observed and expected dose
(6) Administration/ delivery cost	Assume no cost	Cost of £42.50 per item included

ERG exploratory analyses

Brigatinib vs ceritinib (list prices)

	ICER £/QALY	ICER change (% from company base case)
Company base case	54,311	-
(1) Time on treatment after progression	48,580	-5,731 (-10.55%)
(2) Duration of treatment effect	100,110	45,799 (84.33%)
(3) Progression free survival data source	59,671	5,360 (9.87%)
(4) Progression free survival extrapolation	58,869	4,558 (8.39%)
(5) Drug wastage	55,892	1,582 (2.91%)
(6) Administration cost	55,906	1,595 (2.94%)
ERG base case (including all revisions, 1+2+3+4+5+6)	**90,801**	**36,490 (67.19%)**

End of life considerations

- **Treatment indicated for short life expectancy:**
  - Company: Median survival on ceritinib is less than 24 months
  - ERG: Mean life expectancy on ceritinib = 24.4 months. The company's choice of distribution (Gompertz) gives the shortest life expectancy for ceritinib
- **Offer of relative extension to life:**
  - **Company & ERG:** Incremental mean life expectancy = 22.49 months, median = 16 to 19.2 months
- **Estimates are robust:**
  - ERG: doubt that estimates for OS are robust, 4 single arm trials as evidence. However, suggest that extension to life is at least 3 months
- **The modelling assumptions are plausible, objective and robust:**
  - ERG: 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 → systemically 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 central nervous system, improved tolerability & potential suppression of resistance

Key issues
Cost effectiveness (1)

- **Time on treatment:** Is treatment continued following disease progression?
  - For how long is treatment given following progression?
    - Company = 1.53 months for both brigatinib and ceritinib
    - ERG = 1.53 months for brigatinib and 3.1 months for ceritinib
- **Duration of treatment effect :** Is it reasonable to assume that treatment benefit continues beyond stopping treatment?
    - Company = lifetime
    - ERG = decline in treatment effect starting at 1.46 years for brigatinib and 1.07 years for ceritinib
- **Overall survival extrapolation:** which distribution is reasonable?
  - Company preferred Gompertz distribution
    - But this implies that end-of-life criteria might not apply
- **Progression free survival extrapolation:** which distribution is reasonable?
    - Company = Gompertz
    - ERG = Gamma

Key issues
Cost effectiveness (2)

- **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?