For Committee, public and projector

NICE National Institute for Health and Care Excellence

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

Chair's presentation

3rd appraisal committee meeting

Committee D
Lead team: David Bowen, Rob Hodgson and Rebecca Harmston
ERG/AG: PenTAG
NICE technical team: Heather Stegenga, Christian Griffiths
Company: Takeda
6 December 2018

Key issues for consideration

- Does the committee consider the company approach or the ERG approach to be most appropriate approach to modelling treatment benefit after stopping treatment?
- Does the committee prefer using PFS + 1.53 months to estimate time on treatment for brigatinib (used by company) or from the ALTA Kaplan-Meier time on treatment data (used by ERG)?
- What is the most plausible ICER?

[redacted]

History of the appraisal

July 2018

- Discuss company and ERG approaches
- Do not recommend brigatinib post-crizotinib because most plausible cost-effectiveness estimates were too high

November 2018

- ACD responses discussed, consider updated modelling approaches from both ERG and company
- Committee unable to make recommendation because of concerns with 'clinical benefit after treatment stops' (see slide 6)

Today

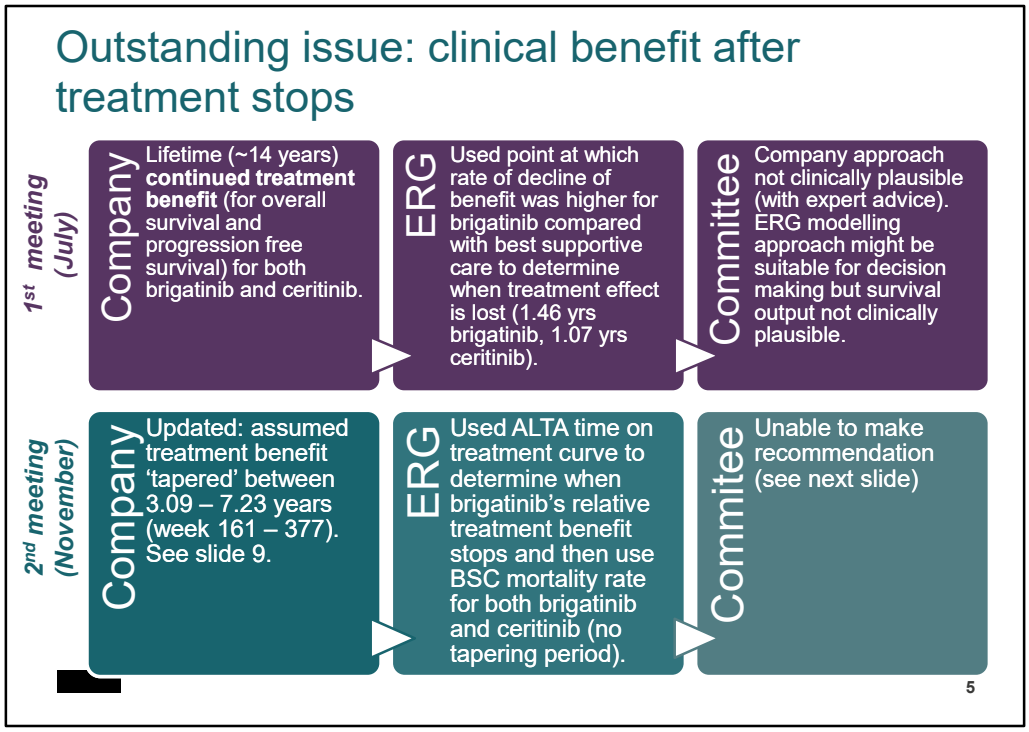
- Further discussion including consideration of ERG additional exploratory analyses of treatment benefit issue

[redacted]

Brigatinib (Alunbrig), Takeda

Mechanism of action	Tyrosine kinase inhibitor (TKI)
Anticipated marketing authorisation	As monotherapy for adults with ALK+ advanced NSCLC previously treated with crizotinib
Administration, dose	Oral, 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,180 mg/d) £4,900 per starter pack (7x90 mg tables + 21x180 mg) Cost of average treatment course (based on list prices) = £93,680
Patient access scheme	Takeda and NHS England have agreed a patient access scheme across all dosage forms. This provides a simple discount to list price

[redacted]



Optional slide to slide 5.

What happened at the 2nd meeting (8 Nov)

- ERG critique of company's approach related to
  1. The time when treatment benefit (mortality rate) changes. Rationale for 'tapering' starting at the longest follow-up, 148 weeks, unclear
  2. Change in mortality rate from this point (i.e. generous tapering).

  Therefore, ERG considered the ICER underestimated
- Clinical input received by email – focus of questions on length of treatment benefit after treatment stops (highlight lack of data but estimate 1-4.5 years)
- NICE requested further work by the ERG because:
  - there were **errors** in ERG model
  - **factual disagreements** over median overall survival between company and ERG
  - there are different approaches between the company and ERG about the long-term treatment benefit.

[redacted]

Summary of other changes to company base accepted by committee at 2nd meeting

- Clinical input to the model – removed study 101 and used ASCEND-5 for progression-free and overall survival
- Utility values – created 2 different values for progressed on- and off-treatment
- Drug wastage – assume that half of costs incurred through unfinished packs could be saved by NHS and half would be wasted
- Administrative costs – no changes to base case as relevant costs already sufficiently covered in the £217 applied per administration
- Minor corrections – to several events (PFS and adverse events) and list price amendment to 90-mg dose of brigatinib (from £4,900 per 28-tablet pack to £3,675 per 28-tablet pack)

[redacted]

Committee also noted that probabilistic ICERs preferred because of high levels of uncertainty of model inputs and structure.

7

What has happened after the 2nd meeting

- Discussions with company and ERG to resolve factual errors
  - Note: median overall survival at the last data cut in ALTA was 34.1 months (not as suggested by ERG in 2nd meeting)
  - Company provided clarification about their approach
- ERG provided:
  - Erratum: fixing modelling and ICER errors in their analyses for 2nd meeting
  - Addendum: includes explanation of different approach for treatment discontinuation and alternative scenarios
- Company provided:
  - Clarification document about their approach
  - Commentary and factual accuracy check on ERG addendum

[redacted]

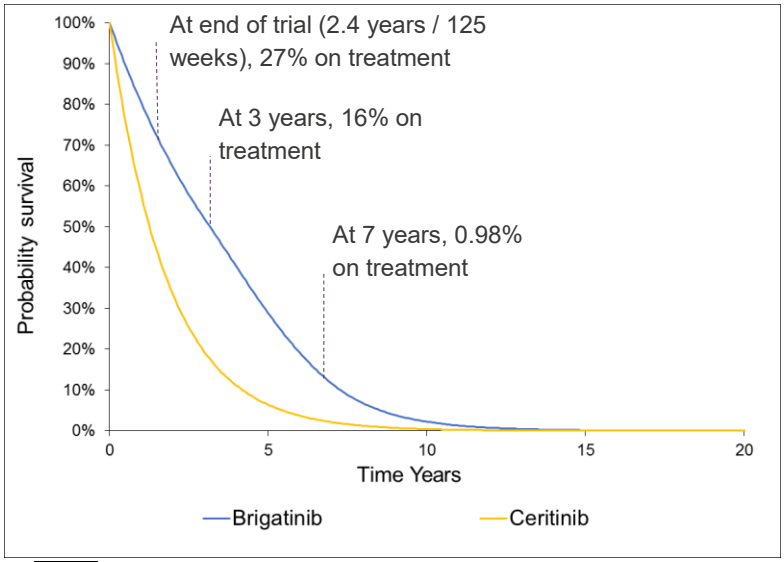
Company's revised approach discussed in November on clinical benefit after treatment stops

- 161 weeks: 148 weeks (maximum follow-up from ALTA) + 13 weeks for continued clinical treatment benefit
- 377 weeks: 364 weeks (time at which 1% of people remained on treatment) + 13 weeks (continued treatment benefit as above)
- ***Update: clarification from company that 'tapering' is applied to patients still on treatment at the end of the observed period. Linear decline in proportion on treatment; mortality adjusted accordingly***

[redacted]

ERG comment: Understand the merit of approach but issues remain:
- Both brigatinib and ceritinib should have the same 'tapering' period
- Arbitrary use of decline in mortality rate can be better estimated using available time on treatment curve for brigatinib

Company's overall survival parametric curves



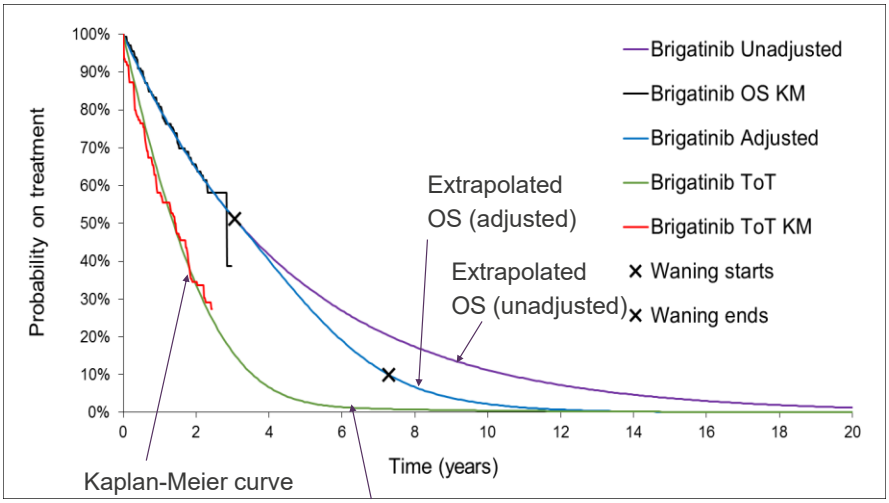
- Tapering from 3.09 to 7.23 years with **exponential curve**
- With exponential curve, 29% and 2% of patients 'surviving' in brigatinib arm at 5 and 10 years, respectively

[redacted]

10

Company clarification of approach to treatment benefit

Observed vs extrapolated overall survival and time on treatment for brigatinib



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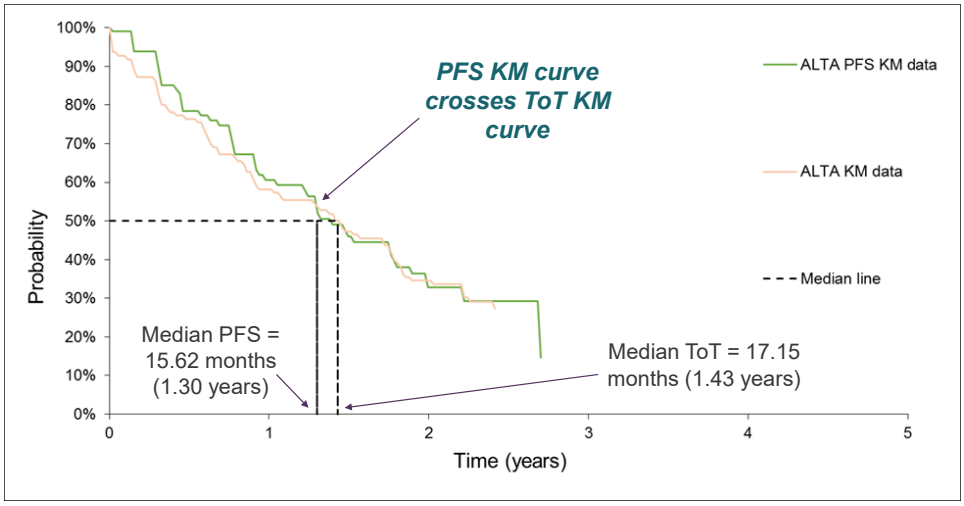
Kaplan-Meier plots of time on treatment (ToT) and progression-free survival (PFS) from ALTA



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Patients on treatment and proportion of hazard ratio applied in company model

Time (years)	Proportion on treatment	% of hazard ratio applied	Company rationale
0	100.00%	100.00%	Hazard ratio (HR) based on trial data.
1	61.92%	100.00%	
2	33.90%	100.00%	
3	16.14%	100.00%	
4	6.77%	78.24%	Reduction in HR/ treatment effect not proportional to time on treatment because average HR has already been diluted by 72.69% of patients discontinuing treatment across the ALTA trial period.
5	2.79%	54.17%	
6	1.43%	30.09%	
7	0.98%	6.02%	
8	0.77%	0.00%	less than 1% of patients on treatment. Survival assumed equal to ceritinib.

ERG critique of company approach

- Rather than arbitrary linear decline, decline in mortality rate should be directly linked to length of time on treatment and adjusted after each model cycle.
- ERG consider that the mortality rate for those surviving beyond the observed period is very uncertain. ERG consider company approach of maintaining mortality rate from observed to extrapolation period may introduce imprecision because the proportion on-treatment diminishes faster than the proportion alive.
- ERG prefer to use mortality rate for best supportive care (BSC) after people come off treatment but company have adjusted the mortality rate relative to ceritinib
- ERG amended approach adjusts tyrosine kinase inhibitor (TKI) mortality rates during the extrapolated period (after week 161) but, rather than a linear decline, retain a direct link between time on treatment (extrapolated from ALTA Kaplan-Meier plot) and then used the BSC mortality rate.

[redacted]

ERG updated base case vs company approach (treatment benefit after treatment stops)

	Company approach	ERG approach
Time-point when mortality rates adjusted	148 + 13 weeks.	Same.
Decline of treatment benefit (brigatinib)	Linear decline in mortality rate (based on proportion of patients on treatment) until <1% of patients on treatment (4.14 years).	Use time on treatment (from ALTA Kaplan-Meier plot) when best supportive care (BSC) mortality rate starts (BSC vs ceritinib HR 0.75**). Rates adjusted at each model cycle.
Decline of treatment benefit (ceritinib)	None.	Same as for brigatinib.
Calculation of cost	Based on time on treatment using progression-free survival (PFS) + 1.53 months* as proxy.	Using time on treatment from ALTA (using Kaplan-Meier plots).

[redacted]

* Calculated based on the difference between the median time on treatment and the median time to progression (based from ALTA).
** Explored in sensitivity analyses

Additional differences between ERG and company approach

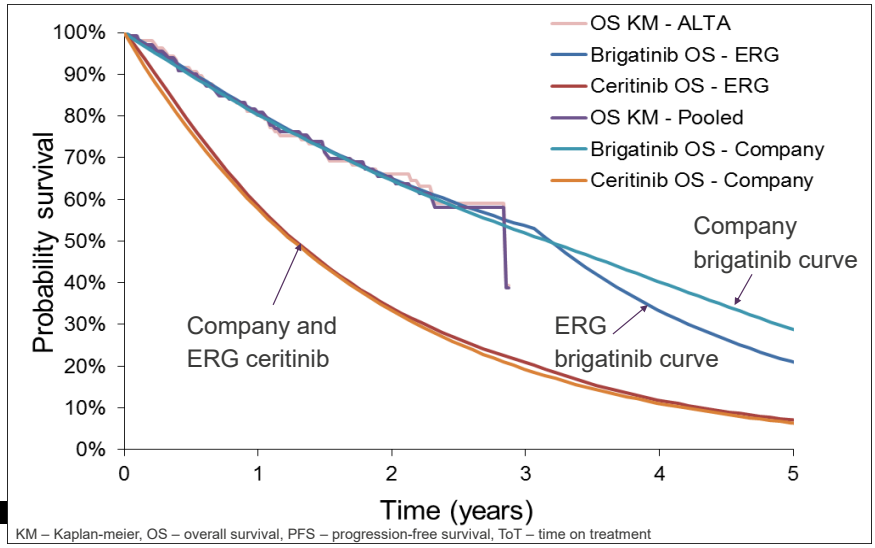
	Company approach	ERG approach
Brigatinib 90 mg tablet cost	Reduced price for cost of 90 mg brigatinib.	Starter park used at £4900 for 1st treatment cycle. **No reduction in price applied**
OS and PFS evidence base in model	Company note that ASCEND-5 chosen over Study 101 for PFS as requested by committee but also for OS. However, study 101 was still in the company base case for both OS and PFS.	Correction made by removing Study 101 from the base case.
Parametric curve choice	PFS – Gompertz OS – exponential	PFS – exponential OS – log-logistic

[redacted]

OS – overall survival
PFS – progression-free survival

16

ERG vs company analyses: overall survival curves incorporating clinical benefit after treatment stops



KM – Kaplan-meier, OS – overall survival, PFS – progression-free survival, ToT – time on treatment

17

Company deterministic and probabilistic ICER (based on list prices)

	Total Costs	Total Life Years	Total QALYs	Inc Costs	Inc Life Years	Inc QALYs	ICER
Original company base case							
Brigatinib	£119,029	3.49	2.45				
Ceritinib	£57,932	1.91	1.32	61,097	1.58	1.12	£54,311
Updated company base case							
Brigatinib	£123,885	3.29	2.23				
Ceritinib	£48,522	1.71	1.11	£75,364	1.57	1.12	**£67,449**

Probabilistic ICER (10, 000 iterations)	**£76,855**

* NOTE: the PSA included altering the choice of distributions for modelling survival

[redacted]

18

Cumulative impact of ERG amendments on company base-case

	Impact	Cumulative ICER
Base case		£67,449
Starter pack cost (no reduction in price for 90 mg dose)	£255	£67,704
Data source for OS and PFS distributions (removed study 101 from base case)	£2,626	£70,324
Method for benefit after treatment stops	£11,530	**£82,274***
PFS distribution (exponential)	£7,868	**£91,531***
OS distribution (log-logistic)	- £9,678	**£80,478***
ToT distribution (ToT distribution used rather than PFS + 1.53 months to estimate costs and benefit discontinuation)	£18,907	**£85,299***
OS HR ceritinib vs BSC (HR=0.75)	£6,211	**£93,283***

[redacted]

* Corrected for error identified in ERG model – values here now correctly apply dose intensity adjustment in line with company model.

ERG base-case ICER (based on list prices)

	Total Costs	Total Life Years	Total QALYs	Inc Costs	Inc Life Years	Inc QALYs	ICER
Brigatinib	£140,697	3.17	2.23				
Ceritinib	£40,442	1.81	1.16	£102,002	1.36	1.07	**£93,283***

Probabilistic ICER (10,000 iterations)	**£97,093***

- ERG conducted a threshold analyses of alternative hazard ratios demonstrating that most ICERs were around100,000 (see table 7 in public version of ERG report)

[redacted]

* Corrected for error identified in ERG model – values here now correctly apply dose intensity adjustment in line with company model.
Also, note that Table 7 in ERG report was previously table 3.

ERG scenario analyses – hazard ratio of brigatinib vs ceritinib for time on treatment (ToT)

- 0.481 may be reasonable alternative to 0.282 (chosen in ERG base case) because the modelled estimates of OS and PFS medians (both company and ERG) tend to be lower than trial medians, and the company's modelled ToT median is only 5.52 months

ToT curve choice	ToT HR brigatinib vs ceritinib	Median ceritinib ToT (months)	ICER (£/QALY) without PAS
Gamma	**0.282** (ERG base case)	**3.68**	**£93,283***
	0.312	4.60	£90,354*
	0.366	5.52	£85,358*
	0.424	6.44	£80,037*
	0.481	**7.36**	**£74,676***
	0.537	8.28	£69,225*
	0.592	9.20	£63,679*

* Corrected for error identified in ERG model

	Median OS (months)	Median PFS (months)	Median ToT (months)
ASCEND-2[1] (INV)	14.9 (95% CI: 13.5-?**)	5.7 (95% CI: 5.4-7.6)	8.8
ASCEND-5[2] (INV)	18.1 (95% CI: 13.4-23.9)	5.4 (95% CI: 4.1-6.9)	6.99
Company BC	15.64	4.60	5.52
ERG BC	15.64	5.52	3.68

[redacted]

**Not evaluable.

21

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