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

2nd appraisal committee meeting

Committee D
Lead team: David Bowen, Rob Hodgson and Rebecca Harmston
ERG/AG: PenTAG
NICE technical team: Heather Stegenga, Emily Eaton-Turner, Christian Griffiths
Company: Takeda
8 November 2018

Key issues for consideration

- Does the committee agree with the new company's base-case with respect to:
  - Modelled treatment benefit after treatment stops
  - Utility values used for progressed disease off-treatment
  - Administrative costs – potential double-counting
- Ceritinib SPC changed in April 2018 – dosage has decreased from 750 mg to 450 mg
- Effect of updated PAS on ICER
  - What is the most plausible ICER?
- Cancer drugs fund – committee did not think that clinical uncertainty could be addressed through collection of data
  - Company have noted they are willing to consider

[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]

Note: Since publication of the ACD, the NHS list price for the lower dosage forms (excluding the starter pack for 1st 28 days) has been reduced

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Committee's considerations in the appraisal consultation document (1)

Issue	Committee's consideration
Clinical efficacy (compared with ceritinib)	• Brigatinib improves OS and PFS • Accepted company's approach to indirect comparison (unanchored ITC and MAIC) taken as only 'single-arm' data available • Meta-analysis is uncertain because of single-arm studies but acceptable for decision-making • For PFS used in the model, preferred use of ALTA only (excluding Study 101) for brigatinib and ASCEND-5 for ceritinib in PFS * Slide 14
Extrapolation of survival curves	• Accepted OS and PFS extrapolation approach
Clinical benefit after treatment stopped	• Did not accept that lifetime benefit is clinically plausible • ERG's approach (shortened benefit) might be suitable if model outputs were clinically plausible (but they were not) * Slides 14, 16-19

*Company amended its approach in response to the ACD

Committee's considerations in ACD (2)

Issue	Committee's consideration
Treatment after progression	• Accepted 1.53 months on treatment for both treatments for clinical effects beyond radiological progression
Utility values	• Accepted 0.793 for progression-free health state • Considered that 0.643 for progressed disease is too high when off-treatment (but reasonable when on-treatment) * Slide 15, 24
Drug wastage	• Preferred ERG approach (50% of costs from unused packs could be recovered) * Slide 15
Administrative costs	• Admin costs of £120 per treatment cycle and delivery cost for 70% of treatments should be included
End of life criteria	• End of life criteria met; life expectancy with standard care around 24 months & extension to life >3 months (22.49)

* Company amended its approach in response to the ACD

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Committee's considerations in ACD (3)

Issue	Committee's consideration
Innovation	• Brigatinib may be innovative but no additional evidence of benefits that had not been captured through quality adjusted life years and resulting cost effectiveness estimates
Cancer Drugs Fund	• Did not acknowledge any possibility that clinical uncertainty could be addressed through collection of data from patients having brigatinib through the cancer drugs funds
ICER	• Most plausible incremental cost-effectiveness ratio (ICER) was above £50,000 per QALY gained

ACD conclusion: Brigatinib not recommended for routine use or for use within the cancer drugs fund

ACD consultation responses

- Consultee comments from:
  - Takeda (the company)
  - Royal College of Physicians (RCP)/ Royal College of Radiologists (RCR)/National Cancer Research Institute (NCRI)*/British Thoracic Oncology Group (BTOG)/ Association of Cancer Physicians (ACP)
  - Roy Castle Lung Cancer Foundation
- Comments from 1 clinical expert
- Web comments from:
  - 2 consultant physicians
  - 9 patients (1 representing ALK Positive UK), 6 carers
- Comments from NHSE

* National Cancer Research Institute (NCRI) are a commentator

[redacted]

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Responses to consultation – Company (Takeda)

- Disagree with recommendation and do not consider it to be a sound and suitable basis for guidance to the NHS
- Takeda has improved its confidential discount (patient access scheme)
- Updated their base case analysis to address committee's concerns:
  - Sources included in the indirect treatment comparisons
  - Duration of treatment benefit beyond treatment discontinuation
  - Separate utility values for progression-free, progressed disease on-treatment and progressed disease off-treatment phases and
  - Drug wastage

(see later slides for further details)

[redacted]

Takeda response continued

Takeda highlight benefits of brigatinib vs ceritinib:

- Increased efficacy (PFS an OS) in this indication demonstrated by the indirect treatment comparisons
- Increased efficacy in the central nervous system
- Improved tolerability, with less need for dose reduction or drug discontinuation (particularly in relation to gastrointestinal side-effects)
- More convenient dosing for patients (i.e. one tablet, once-daily with or without food, whereas ceritinib requires multiple capsules to be taken once-daily and with food)
- Willing to consider funding via the Cancer Drugs Fund (CDF), if required

[redacted]

RCP/RCR/NCRI/BTOG and Roy Castle Lung Cancer Foundation

- Disappointed it did not meet cost-effectiveness threshold → encourage NICE & the manufacturer to agree a price to allow availability
- Small population since ceritinib and alectinib are now available, some people responding to crizotinib who will relapse.
  - Only option for these people is ceritinib, with more toxicity and less effect on survival
- Disappointed manufacturer did not express interest for use within the Cancer Drugs Fund

Clinical expert

- Recommendation will deny people access to one of the **most effective treatments for ALK+ve NSCLC with brain metastases**
- Guidance applies to a small population who only have access to ceritinib after crizotinib
- Patients only have access to more toxic treatment with more debilitating symptoms, poorer quality of life and shorter survival than patients having 1st line alectinib

[redacted]

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Summary of web comments

- ALK+ NSCLC affects younger people than other types of NSCLC
- Positive benefits on every day living and quality of life; benefits of knowing there is another treatment if these fail
  - especially as less toxic
  - more available options can change from terminal to chronic illness
  - experience shows that people can return to everyday lives
- One consultant noted ease of administration
- One consultant disagreed with the committee that utility value of 0.643 is unreasonable for progressive disease (see slide 24 for company's amendments to utility values)

NHSE submission

- Eligibility of the treatment (and marketing authorisation) is only 2nd line after crizotinib – NHSE does not commission crizotinib after ceritinib or alectinib, or anything other than ceritinib after crizotinib.
- Reiterates population has diminished with new 1st line agents but welcomes Takeda's submission as brigatinib is likely to be better tolerated and notes that main focus will be on first line use.
- Current comparator is ceritinib which is currently supplied in 150 pill pack (at 750 mg/d for 30-day supply), but this will be replaced by a 90 pill pack at the new licensed dose of 450 mg/d late 2019.
- Admin costs of £217 (used by Takeda) seems in excess of £120 tariff – thus, seems reasonable as long as applied to both arms
- Treatment with brigatinib after crizotinib is not worthwhile use of cancer drugs fund resources because use of 2nd line treatment after crizotinib will be clinically redundant before uncertainties have been resolved (population eligible will have mostly relapsed and receive another 2nd line agent).

[redacted]

Updated company base case (1)

Issue	Company amendments
Administrative costs	• **Committee**: Admin costs of £120 per treatment cycle and delivery cost for 70% of treatments should be included • **Company**: Assume administration and delivery costs are already accounted for within the base case model as part of £217 applied per administration * ✗ **No changes made**
Additional changes that were not in response to committee comments	
Minor corrections	• Corrections to 2 PFS and 2 adverse events • Reduced NHS list price relating to 90-mg dose of brigatinib (from £4,900 per 28-tablet pack to £3,675 per 28-tablet pack)

[redacted]

Updated company base case (2)

Issue	Company amendments
Changed in response to committee concerns	
Clinical input into model	• **Committee**: Preferred PFS data from ASCEND-5 (independent review committee-assessed) over study 101 (investigator-assessed) • **Company:** Removed study 101 and used ASCEND-5 (also applied principles to OS)
Clinical benefit after treatment stopped	• **Committee:** Did not accept company's lifetime benefit or ERG's approach as neither were clinically plausible • **Company:** Modelled a reduced treatment benefit following treatment discontinuation, with tapering starting at 161 weeks (3.07 years) applied in brigatinib arm only

* Slides 17-19

* Main point of discussion for today

[redacted]

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Will elaborate on the middle two points in the following slides

Updated company base case (3)

Issue	Company amendments
Changed in response to committee concerns	
Utility values	• **Committee**: Did not expect utility value of 0.643 to persist for progressed disease until death; preferred 2 different values for people with progressed disease 'on-treatment' and 'off-treatment' • **Company**: Created 2 different values for progressed on- and off-treatment
Drug wastage	• **Committee**: Preferred ERG's approach to assume that half of costs incurred through unfinished packs could be saved by NHS and half would be wasted • **Company**: Implemented as per committee's preference

* Slide 24

* Main point of discussion for today

[redacted]

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Will elaborate on the middle two points in the following slides

From previous meeting

Duration of clinical benefit after treatment stops

- Previously, company assumed a lifetime **continued treatment benefit** (overall survival and progression free survival) for brigatinib and ceritinib
- **NICE clinical expert submission**: did not anticipate significant benefit beyond discontinuation, but in those who may discontinue for reasons other than progressed disease it maybe a month or two
- Expert clinical opinion on ceritinib (TA395) noted benefits of treatment unlikely to persist beyond treatment
- ERG: compared each strategy with BSC and used the point at which the rate of decline of treatment benefit was higher for brigatinib than best supportive care as the time point for when treatment effect was lost from start of treatment (1.46 yrs brigatinib, 1.07 yrs ceritinib). Analysis did not give clinically plausible outputs of survival after 3 years (treatment effects were too low).

[redacted]

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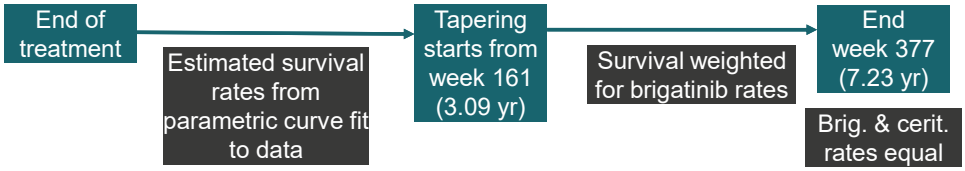
Company's revised approach: duration of clinical benefit after treatment stops

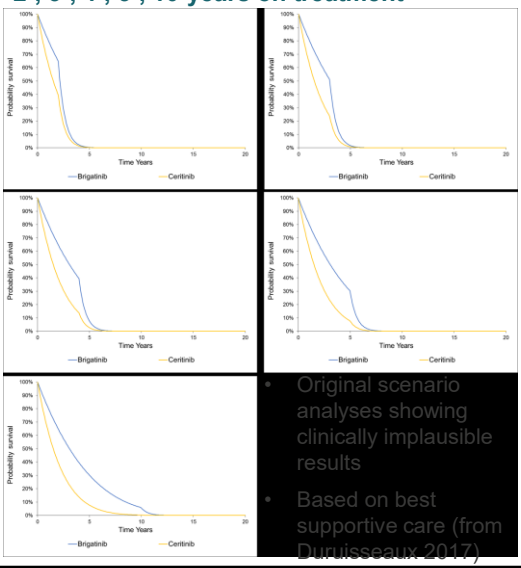


- 161 weeks: 148 weeks (maximum follow-up from ALTA) + 13 weeks (continued clinical treatment benefit based on clinical experts at 1st committee meeting)
- 377 weeks: 364 weeks (time at which 1% of people remained on treatment) + 13 weeks (continued treatment benefit as above)
- Note: ALTA median follow-up was 24.3 months (Sept 2017 cut-off); in study 101, median time on treatment was 20.0 months (May 2016 data cut off).

- *Should the maximum follow-up from ALTA be used to assume the duration of full treatment benefit?*
- *Is the company's tapering approach acceptable or should effectiveness with best supportive care be used beyond the trial data?*

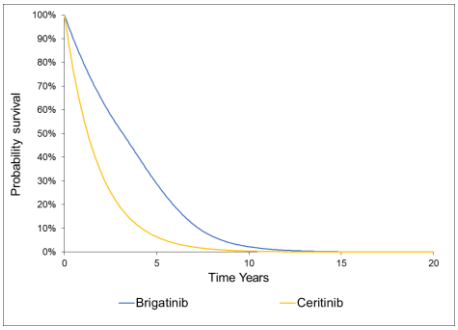
Company's overall survival parametric curves

Original submission scenario analysis at 2-, 3-, 4-, 5-, 10-years on treatment



- Original scenario analyses showing clinically implausible results
- Based on best supportive care (from Duruisseaux 2017)

Updated base-case



- Updated base-case using gradual tapering from 3.09 to 7.23 years with exponential curve.

Proportion of patients surviving in model

	3-years	5-years	10-years	20-years
Clinical experts average	50.00%	28.50%	5.83%	0.00%
Exponential (company's chosen base-case)	52.01%	28.99%	2.28%	0.01%
Gamma	51.29%	27.27%	1.67%	0.00%
Log-normal	55.14%	39.27%	13.77%	3.13%
Log-logistic	52.82%	33.99%	8.84%	1.53%
Weibull	51.20%	26.87%	1.46%	0.00%
Gompertz	51.05%	25.21%	0.54%	0.00%
Generalised gamma	51.46%	27.96%	2.03%	0.01%

- *Is an estimate of 2.28% of people surviving at 10 years clinically plausible?*

[redacted]

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ERG critique of company's approach to clinical benefit after treatment stops

- With respect to 2 components of ERG's approach at previous meeting (which was preferred by committee if had clinical plausible results):
  1. Rule determining time which mortality rate changes from treatment drive rate (for both brigatinib and ceritinib)
     - Only introduced for brigatinib
     - Used maximum follow-up from ALTA – rationale unclear
  2. Change in mortality rate (at above determined time-point) based on rates with best supportive care (BSC)
     - Used rate on ceritinib but incidentally not an issue since ASCEND-5 showed no difference between ceritinib and BSC (hazard ratio was 1)
     - Generous tapering of effect for 4.14 years (from 3.09 to 7.23 yrs)
     - One time-point for full benefit used for all patients does not take into account those finishing earlier or later
- Conclusion: ICER underestimated. Large uncertainty with aspects of modelling and strong assumptions could introduce inaccuracy in either direction.

[redacted]

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ERG critique updated – see slides from 6th December 2018

ERG approach to clinical benefit after treatment stops (1)

	ERG approach (Cohort)	Company approach (Whole population)
Time-point when mortality rate declines (i.e. loss of effect)	Time on treatment (variable)	Longest follow-up period of one patient in ALTA trial (148 weeks)
Measurement of time on treatment (i.e. determining who is on/off treatment)	Proxy of progression-free survival curve – 1.53 months (incorporates population on/off treatment as it changes over time)	Relevant only to estimate time when only 1% of patients remain on treatment (marking the time chosen at which mortality rates should equalise [7.2 years from treatment commencement]).
Period of full effect after treatment discontinuation	13 weeks	161 weeks (148 + 13)
Population with full effect after treatment discontinuation	Those who progress and discontinue treatment	An average is used to represent all patients

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ERG approach to clinical benefit after treatment stops (2)

	ERG approach (Cohort)	Company approach (Whole population)
Mortality rate used for *brigatinib* at the point of loss of effect	Best supportive care	Ceritinib
Mortality rate used for *ceritinib* at the point of loss of effect	Best supportive care	Not applicable. Rate remains consistent.
Period of tapering to new mortality rate	None. Best supportive care immediately adopted.	Tapered until only 1% of patients remain treated with brigatinib.*
Curve convergence	Survival curves for strategies converge but will not intercept. The absolute effect of treatment on the population is persistent, albeit reducing with time.	
Parametric curve choices for OS at 5 and 10 years	PFS = Exponential OS = Log-Logistic ToT = PFS + 1.53months	PFS = Gompertz OS = Exponential ToT = PFS + 1.53 months

(OS: overall survival, PFS: progression-free survival, ToT: time on treatment)

* Updated following the committee meeting to correct for factual inaccuracy

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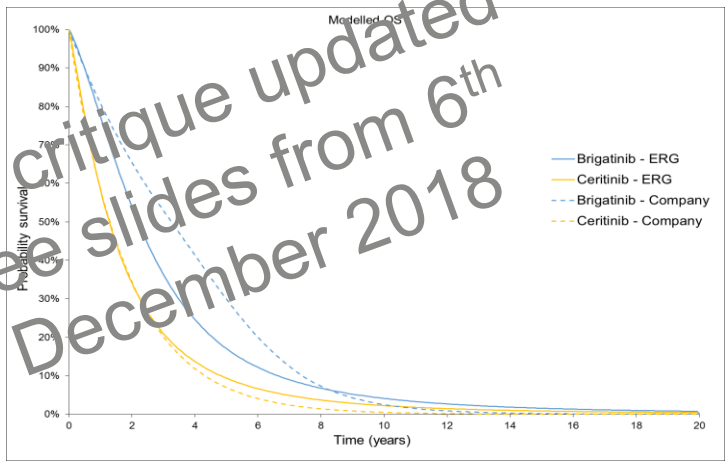
ERG vs company analyses: overall survival clinical benefit after treatment stops

- Note: as mortality rate of BSC strategy is the same as the ceritinib strategy (HR BSC v ceritinib = 1.0, ACSEND-5), it is not visible.



ERG critique updated – see slides from 6th December 2018

[redacted]

Updated utility: split progressed disease stage

Phases	Utility value	Note
Pre-progression on-treatment	0.793	Accepted by the committee at first meeting
Progressed disease on-treatment (updated in company's revised base-case)	0.732	Derived from progressed utility values from ALTA, reflecting patients who have just progressed (includes patients on- and off-treatment). Patients in this stage for only 3 months.
Progressed disease off-treatment (updated in company's revised base-case)	0.582[1]	Utility decrement of 0.15 obtained from Chouaid et al. (2013) applied to progressed disease on-treatment value (0.732)
Note: 1. Values adjusted in model by decrements associated with age and adverse events. 2. Two clinical experts have noted the approach and values are reasonable.		

[1] 0.59 for 2nd line treatment in Chouaid (2013) in wider NSCLC population. Company note ALK+ population often younger and healthier – utility decrement may be similar but absolute value may be higher

[redacted]

⊙ *Is a 0.582 utility value more acceptable than original value (0.643) for people who progressed off-treatment?*

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ERG critique (general)

- Content with approach to utility values, drug wastage, drug administration costs.
- Agree with company approach to be consistent in use of data (re: removing study 101 from both progression-free and overall survival analyses), but would prefer company to have removed study 101 from the baseline calculation in addition to the derivation of the hazard ratio. Removing this decreases the company ICER by £2,500 per QALY.

[redacted]

Company incremental updated base case

	Cumulative ICER
Original base case	£54,311
Correction of minor errors	£54,628
Updated list price	£54,390
Exclusion of Study 101 from OS and PFS outcomes	£55,766
Reduced treatment benefit in brigatinib arm only using maximum follow-up in ALTA	£63,058
Utility value amendments	£64,940
Drug wastage amendments (half unfinished packs saved by the NHS)	**£67,449**

[redacted]

Company deterministic and probabilistic ICER based on list price

	Total Costs	Total Life Years	Total QALYs	Inc Costs	Inc Life Years	Inc QALYs	ICER
Previous 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]

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ERG base-case ICER

	Total Costs	Total Life Years	Total QALYs	Inc Costs	Inc Life Years	Inc QALYs	ICER
Brigatinib	£141,195	2.83	2.03				
Ceritinib	£51,538	1.95	1.50	£89,657	0.89	0.53	**£169,366**

ERG critique updated – see slides from 6th December 2018

Note: company identified error in the ERG's amended model. In attempting to derive PFS estimates for ceritinib, the model omitted applying hazard ratio to brigatinib data. Correcting this error, resulted in an **ICER of £110,342**

- ERG conducted a threshold analyses of alternative hazard ratios demonstrating that most ICERs were above 100,000 (see table 3 in public version of ERG report)

[redacted]

ERG scenario analyses

- Explored time on treatment (ToT) using the ToT curve from ALTA to attempt to better represent the costs associated with treatment with patients starting or finishing at different time points on the curve.
- Choice of ToT method makes impact on ICER as ToT drives costs.

OS curve choice	PFS curve choice	Time on treatment (ToT) method for brigatinib *	5 year OS brigatinib	10 year OS brigatinib	ICER (£/QALY) without PAS with 90mg ceritinib	Correction of error
Log-logistic	Exponential	PFS+1.53 months (ERG base-case)	17.90%	4.44%	£169,366	£110,342
		ToT Gamma	17.66%	4.39%	£125,779	£83,769
		ToT Exponential	17.53%	4.31%	£118,299	£79,039
		ToT Weibull	17.62%	4.43%	£125,266	£83,567
		ToT Gen. Gamma	17.37%	4.22%	£124,407	£82,571
		ToT Gompertz	17.65%	4.46%	£120,718	£80,794

[redacted]

* Note: approach is similar for ceritinib with hazard ratio for PFS applied

ERG critique updated – see slides from 6th December 2018

Key issues for consideration

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  - How treatment benefit is modelled after treatment stops
  - Utility values used for progressed disease off-treatment
  - Administrative costs – potential double-counting
- Ceritinib SPC changed in April 2018 – dosage has decreased from 750 mg to 450 mg
- Effect of updated PAS on ICER
  - What is the most plausible ICER?
- Cancer drugs fund – committee did not think that clinical uncertainty could be addressed through collection of data
  - Company have noted they are willing to consider

[redacted]