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

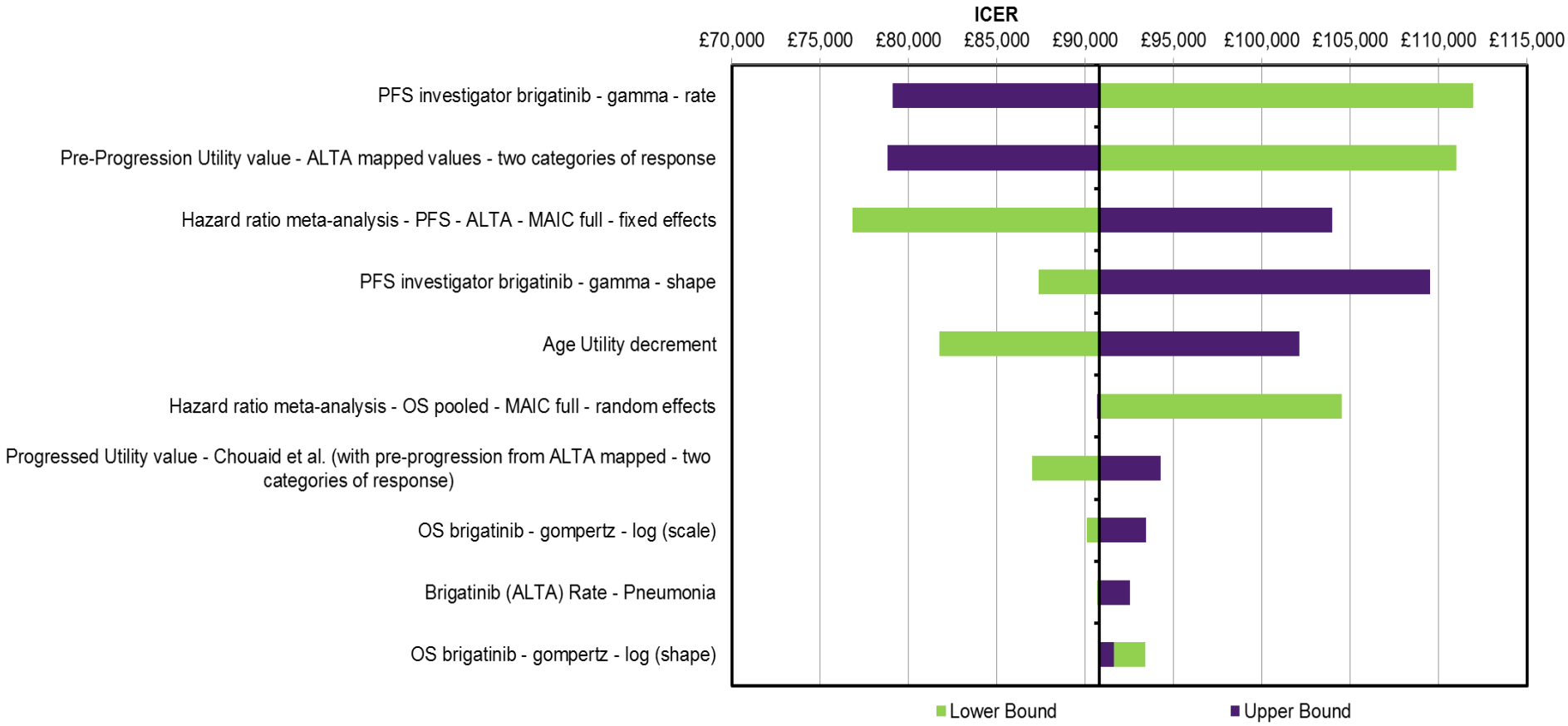
Health State	Cost (£) brigatinib	Cost (£) ceritinib	Increment (£)	Increment as % of total increment
Progression-free state	£71,887	£32,960	£38,927	126.6%
Progressed disease state	£9,673	£17,828	-£8,155	-26.5%
End of Life	£1,611	£1,638	-£26	-0.1%
Total	£83,171	£52,425	£30,746	100.0%

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

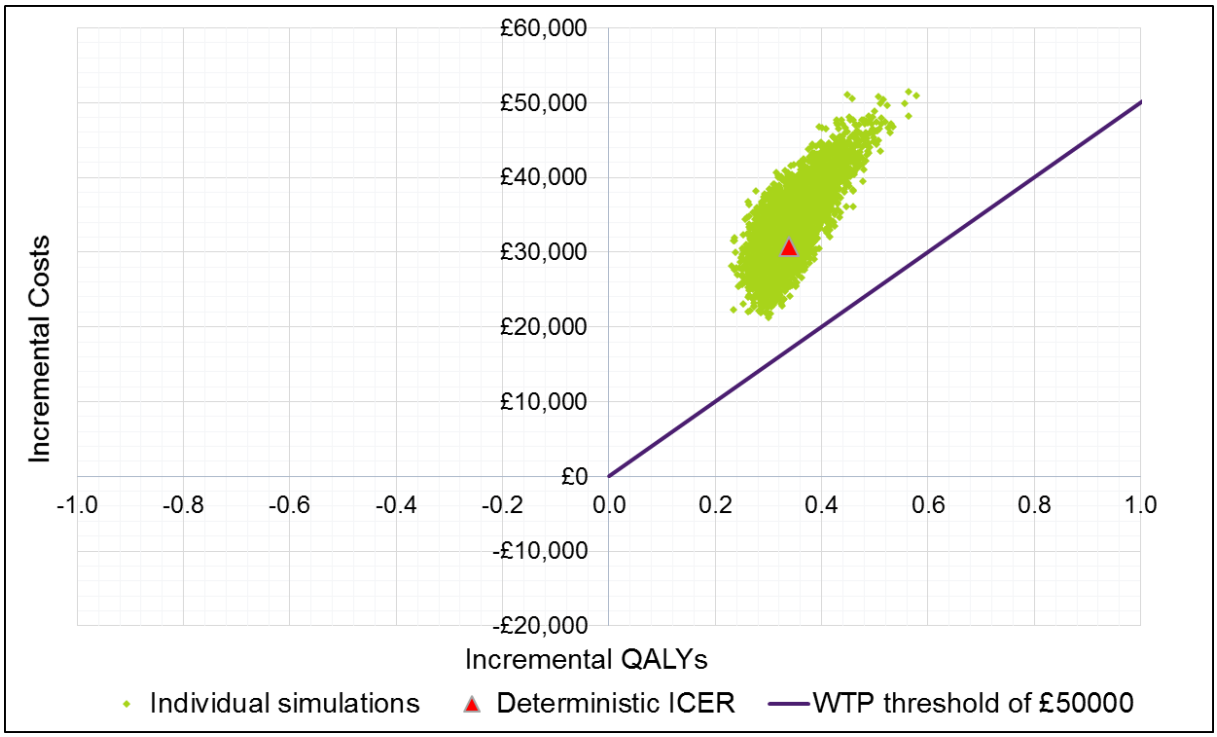


Abbreviations: ICER, incremental cost-effectiveness ratio; OS, overall survival; HR, hazard ratio; PFS, progression-free survival

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)

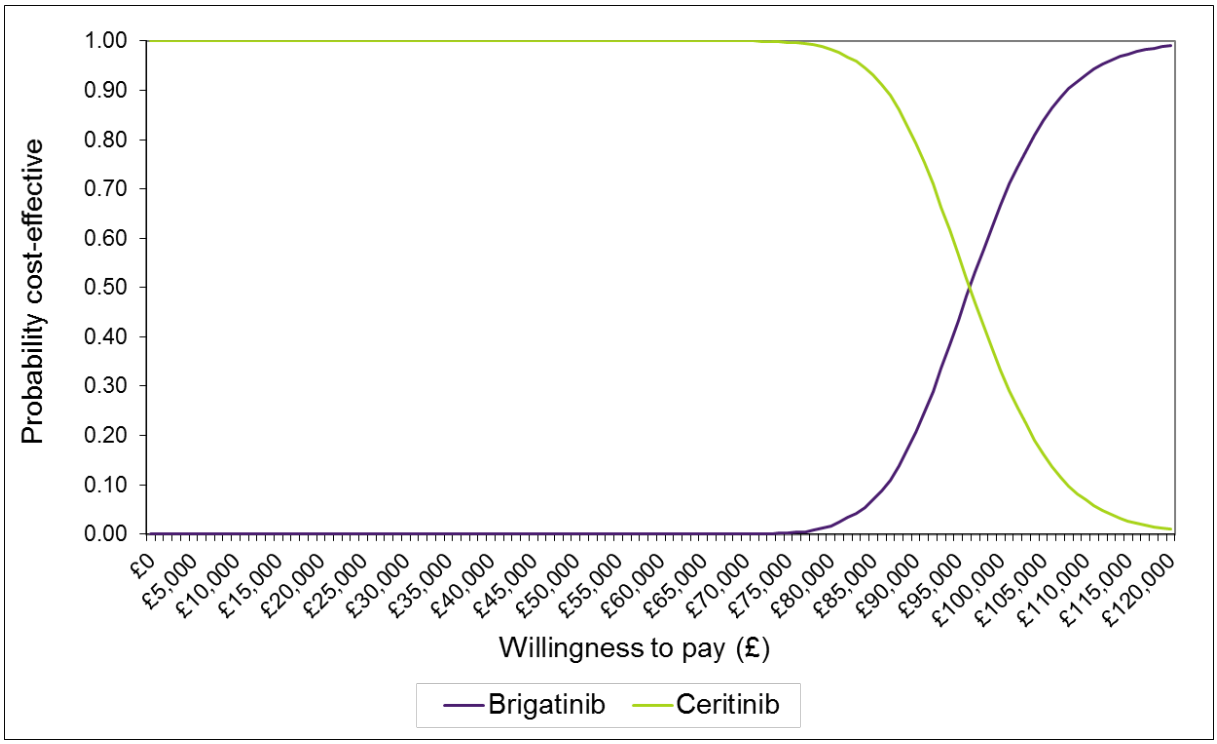
Table 6 Probabilistic base case results

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.