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

A Single Technology Appraisal

Erratum, following Company fact check

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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 19). 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)

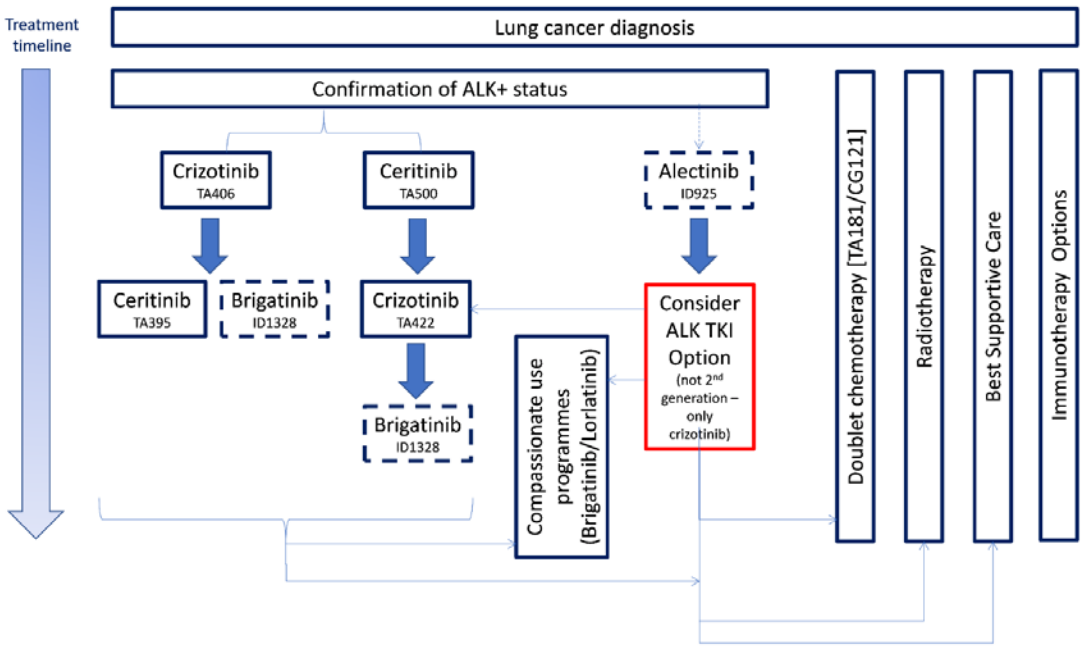
ERG opinion:

- 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 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 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 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 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 (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

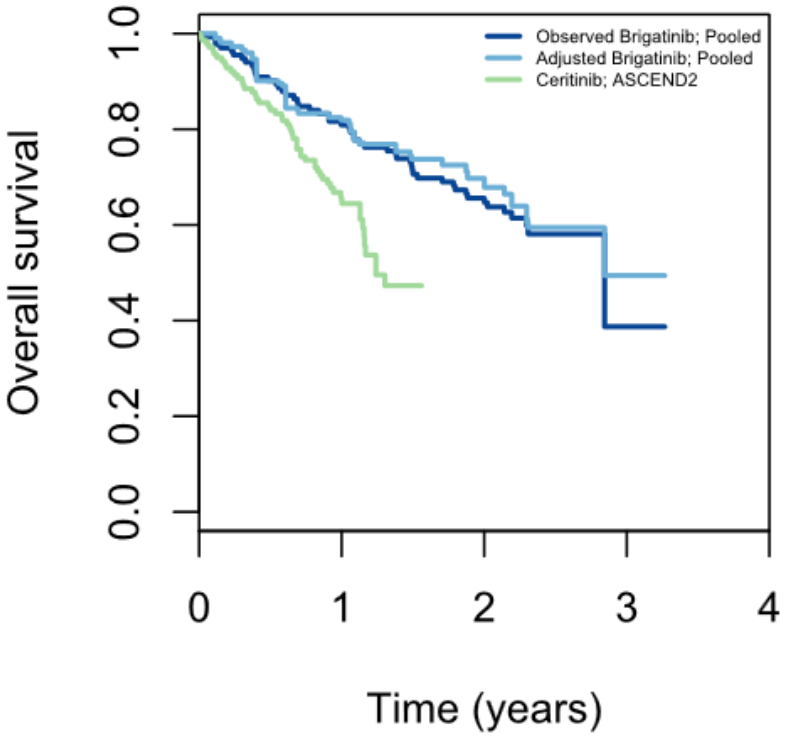
trials (See Section 4.4). The base case used the full set. As expected both the unadjusted and adjusted pooled brigatinib curves showed superior survival versus ceritinib. The company scenario analysis for the OS HR that used the meta-analysis of unadjusted pooled brigatinib outcomes (naïve analysis), 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 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 MAIC method, and CS p109 Table 38 for full details of ITC scenario analyses.

Issue 14

ERG opinion:

- 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 37).

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

Issue 15

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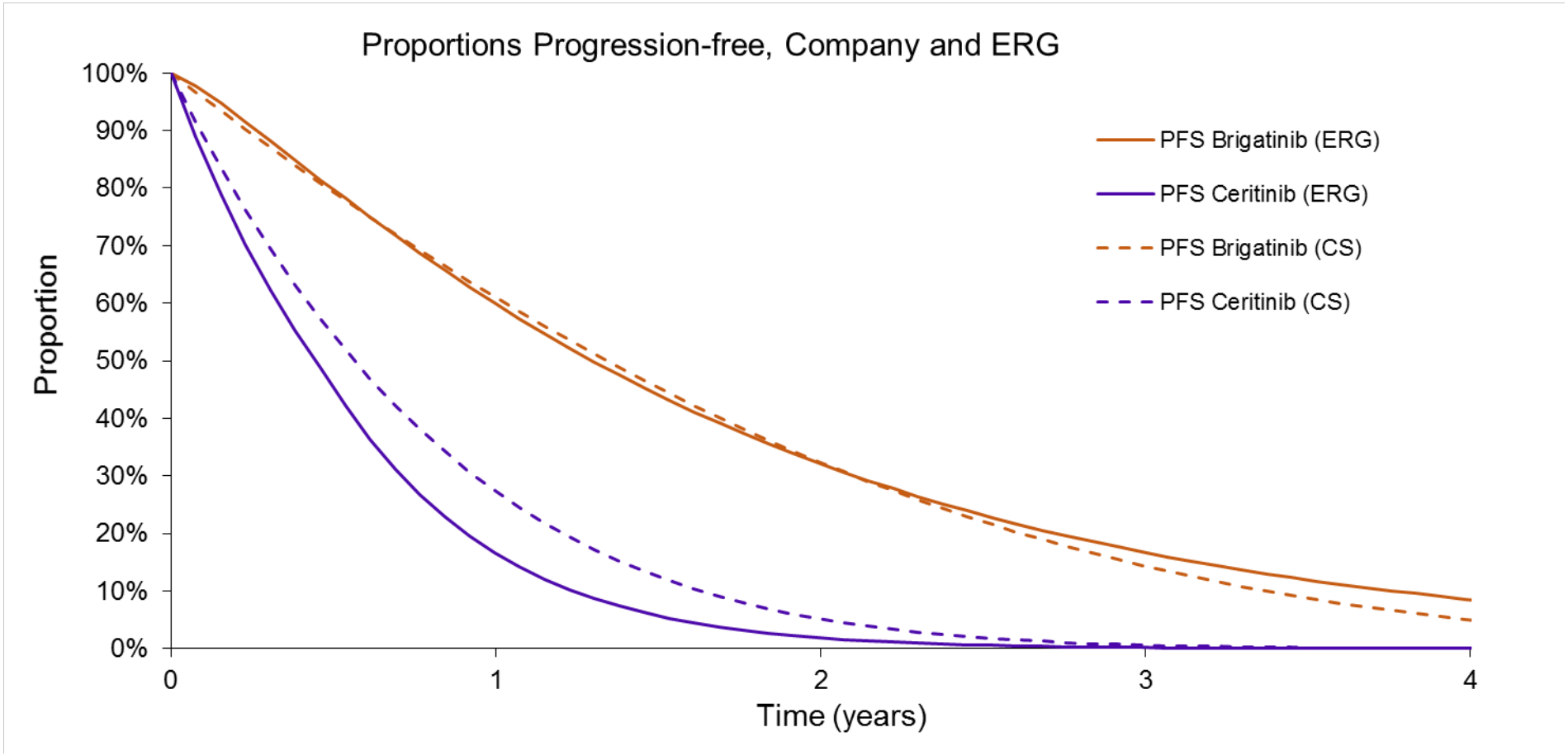
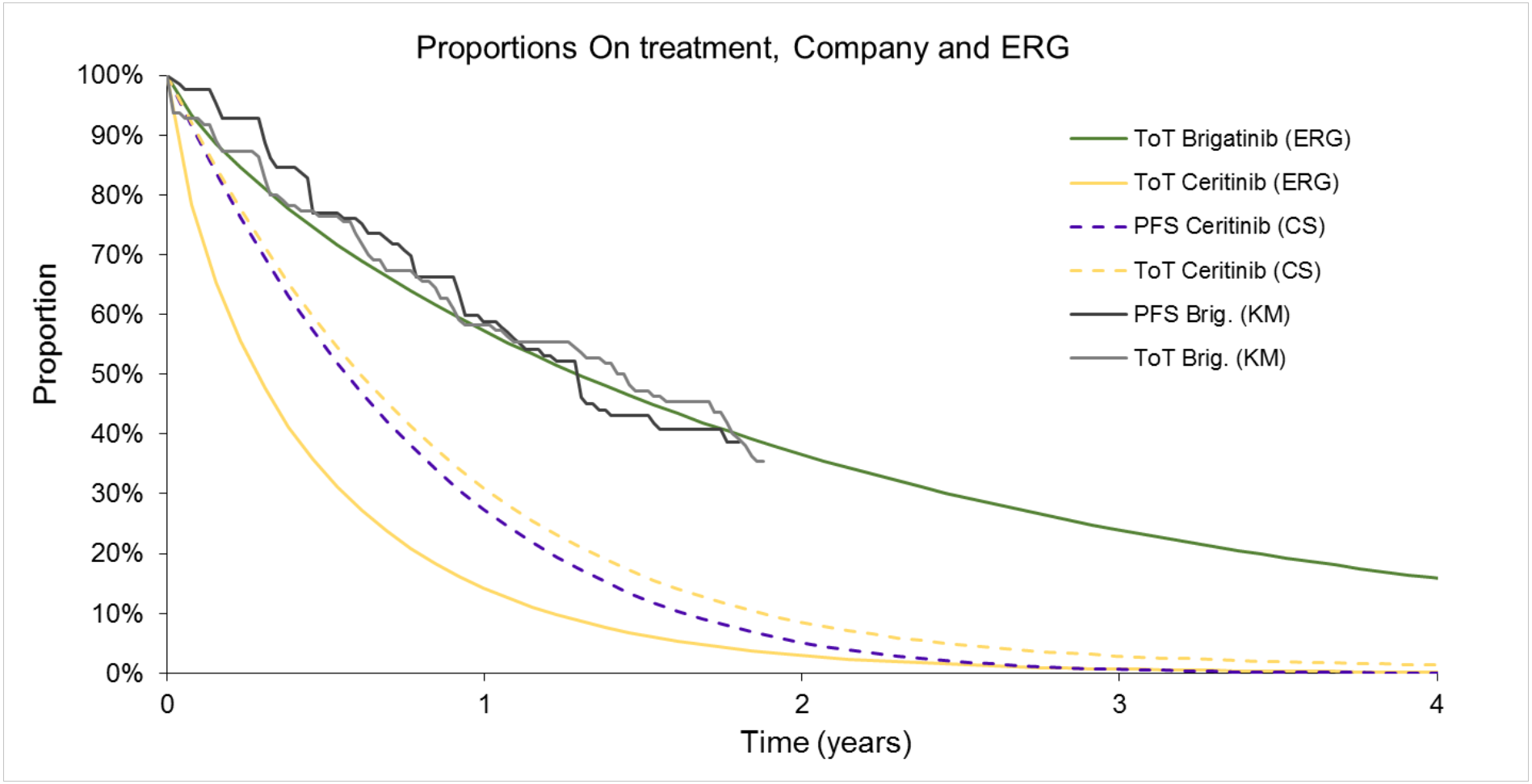
Figure 3 Long-term PFS estimates for strategies, company and ERG



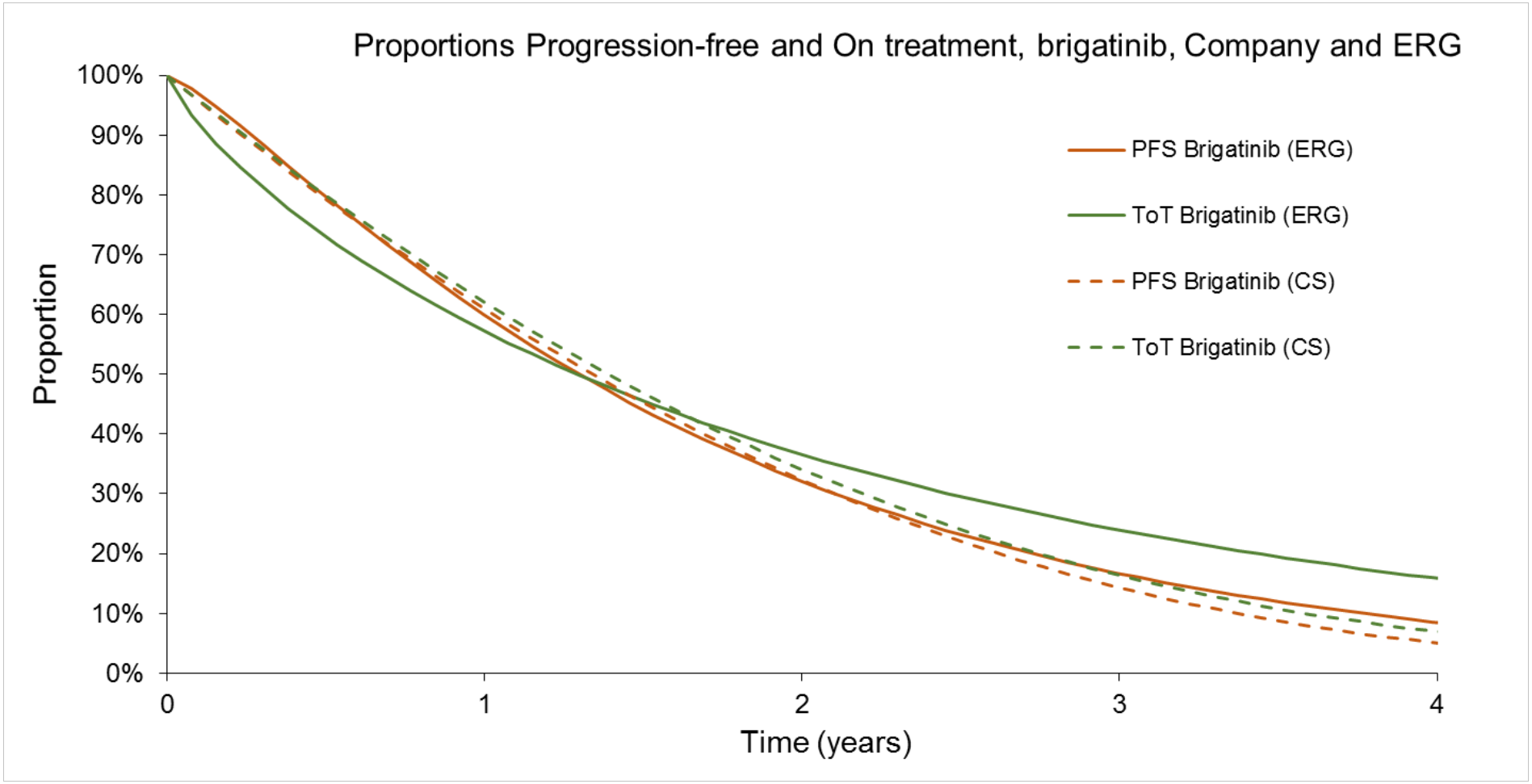
The combined effect of ERG base case changes 1 and 2 is to reduce the long-term estimate of PFS on ceritinib; with a slight change to the brigatinib estimate.

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.

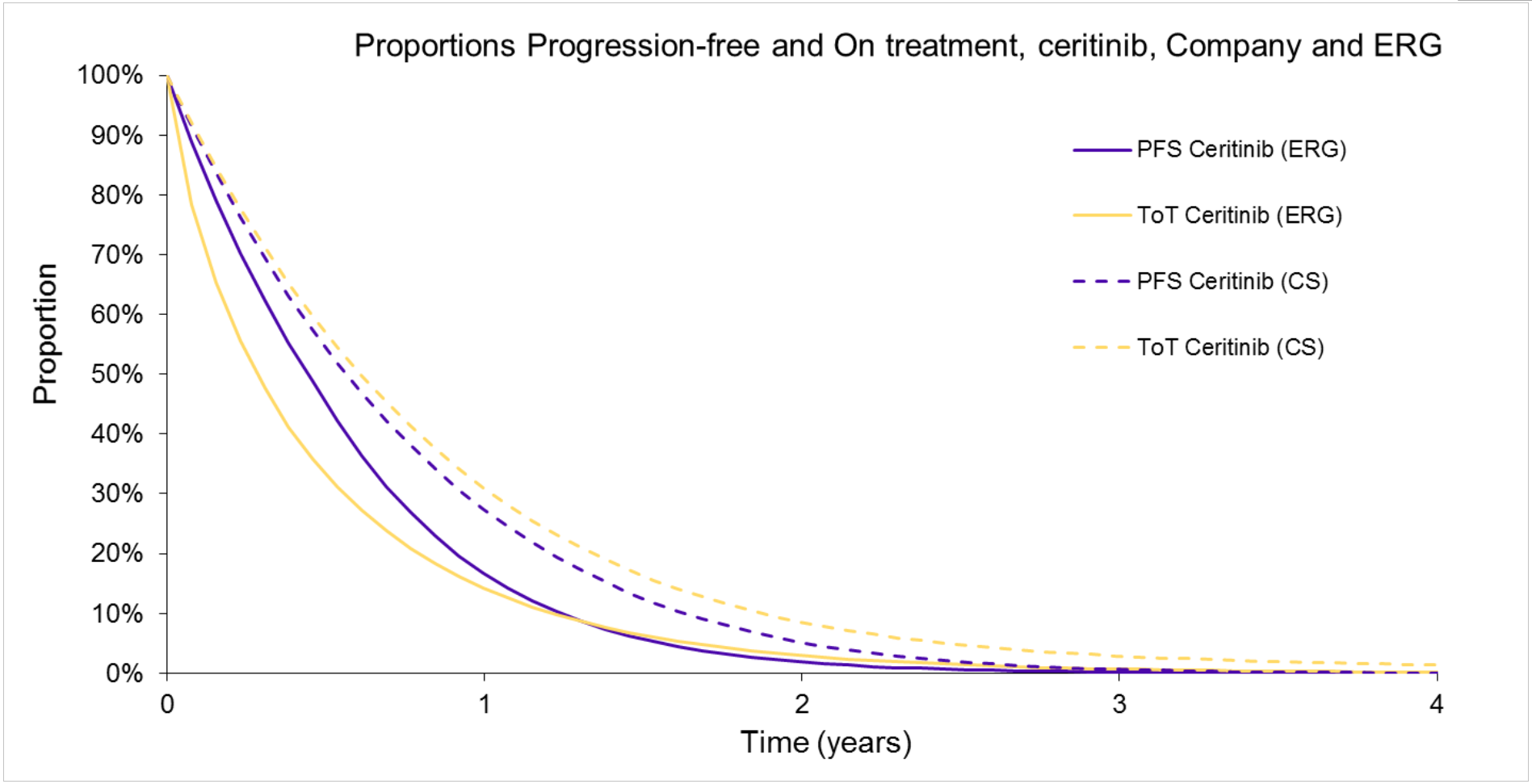
Figure 5 Brigatinib TOT and PFS as a proportion of patients on treatments or progression-free, Company and ERG estimates



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).

Issue 16

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 51 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 presents the summary results of the ERG base case.

Table 4 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'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%

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*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 54 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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