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Single Technology Appraisal

Osimertinib with pemetrexed and platinum-based chemotherapy for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6328]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Osimertinib with pemetrexed and platinum-based chemotherapy for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6328]

Contents:

The following documents are made available to stakeholders:

1. **Comments on the Draft Guidance from AstraZeneca**

2. **Patient group submission** from:
   a. EGFR+ UK

3. **External Assessment Group critique of company comments on the Draft Guidance**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

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Osimertinib with pemetrexed and platinum-based chemotherapy for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6328]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Wednesday 20 November. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	AstraZeneca

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Not applicable
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Not applicable
Name of commentator person completing form:	[redacted], AstraZeneca

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
	As these are detailed technical responses that include tables and figures, full details are presented from Page 4 onwards. A brief list of the key topics covered is provided below.
1	Subsequent treatments in the FLAURA2 trial (Draft Guidance Document section 3.14): It is factually inaccurate that atezolizumab + bevacizumab + carboplatin + paclitaxel (ABCP) was not used in the FLAURA2 trial. There is usage of all the components of ABCP as post study

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	anticancer therapies in the trial however, the recording of the data inhibits the explicit identification of the ABCP regimen.
2	Distribution of subsequent treatments (Draft Guidance Document section 3.14): Systemic Anti-Cancer Therapy Dataset (SACT) data received via freedom of information request present the best distribution input for the cost-effectiveness model and is the scenario which is most representative of both UK clinical practice and the FLAURA2 trial.
2	Approach to overall survival (OS) extrapolations (Draft Guidance Document section 3.7): Further justification for the choice of OS model is provided.
4	Approach to time to treatment discontinuation (TTD) (Draft Guidance Document section 3.8). Further justification for the choice of TTD model and an additional scenario is provided.
5	Utility scores (Draft Guidance Document section 3.9). An additional analysis using multiple imputation to account for missing data was performed and the utility value generated was consistent with the company base case value. An additional utility analysis was conducted to account for treatment-specific disutility during the chemotherapy treatment period and is presented as a scenario. The company's preferred progression-free survival (PFS) utility value is [redacted] in line with the original submission.

Insert extra rows as needed

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- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
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- Do not include medical information about yourself or another person from which you or the person could be identified.
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Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Company response

The company have presented a revised base case analysis to incorporate the following preferred committee assumptions as detailed in Section 3.16 of the draft guidance document):

1. Average starting age of 65.6 years (versus 61 years in the original base case)
2. Progressed disease utility value of 0.678 (versus 0.640 in the original base case)
3. Resource use figures using the company's estimation of outpatient visits and the Evidence Assessment Group (EAG)'s estimations for the other resources
4. 100% carboplatin use for platinum-base chemotherapy (versus 50% in the original base case)
5. Relative dose intensity of 96.4% for carboplatin (versus 100% in the original base case)
6. Revised proportion of patients receiving ABCP (see Section 1 and 2 for details and rationale for updated value)

The revised base case results are presented in Table 3**.**

Furthermore, as requested, an additional subsequent treatment scenario has been performed (see Section 2), additional justification for the company's choice of extrapolation for overall survival is presented (see Section 3), as well a further analysis of the extrapolation of TTD (see Section 4) and additional analyses of the PFS utility value (see Section 5).

1. Subsequent treatments in the FLAURA2 trial

The draft guidance states that ABCP use was not included in the FLAURA2 trial. This is a factual inaccuracy. The use of ABCP as a subsequent treatment was permitted in the trial however, ABCP as a standalone regiment cannot be identified within the current data set. The classification of subsequent treatment use identified treatment classes that components of the ABCP regimen would fall into (taxanes, vascular endothelial growth factor (VEGF) Inhibitor, programmed cell death protein-1/programmed cell death ligand-1 (PD-1/PD-L1) inhibitor, and platinum compounds), but treatments could be counted twice if a patient received more than one post treatment anticancer therapy, inhibiting the identification of the exact usage of the ABCP regimen (see Table 1).

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The taxane, VEGF Inhibitor, PD-1/PD-L1 inhibitor, and platinum compound usage recorded as post treatment anticancer therapy likely represents ABCP use in the trial and is considered to represent the expected efficacy of subsequent treatments in UK clinical practice. Furthermore, the proportion of patients receiving ABCP in the model is small and applied consistently across treatment arms. It is unlikely that any additional survival benefit offered by ABCP would have an impact on the model results; the modelling of subsequent treatment benefit in the company submission was implicitly accounted for in the extrapolated OS data from FLAURA2. The company strongly believes that the costs of ABCP should be included to ensure consistency with the OS extrapolations.

Table 1: Post study treatment anticancer therapy (randomised period – FAS)

	Number (%) patients†	
	Osi + chemo (N=279)	**Osimertinib (N=278)**
Types of post-treatment anticancer therapy received		
Cytotoxic chemotherapy	41 (14.7) [33.3]]	81 (29.1) [53.6
Platinum compounds	19 (6.8) [15.4]	78 (28.1) [51.7]
Folic acid analogues (pemetrexed)	8 (2.9) [6.5]	55 (19.8) [36.4]
Taxanes	26 (9.3) [21.1]	39 (14.0) [25.8]
EGFR-TKI	18 (6.5) [14.6]	39 (14.0) [25.8]
First or second-generation EGFR-TKI	12 (4.3) [9.8]	22 (7.9) [14.6]
Third generation EGFR-TKI	6 (2.2) [4.9]	22 (7.9) [14.6]
Osimertinib	6 (2.2) [4.9]	19 (6.8) [12.6]
Aumolertinib	0	3 (1.1) [2.0]
VEGF Inhibitor – Monoclonal antibody	14 (5.0) [11.4]	38 (13.7) [25.2]
PD-1/PD-L1 inhibitor – Immunotherapy	10 (3.6) [8.1]	22 (7.9) [14.6]
Other	11 (3.9) [8.9]	19 (6.8) [12.6]

† The number of patients is shown with percentages (%) calculated as the proportion of patients in the FAS and secondly [%] as the proportion of patients who discontinued randomised study treatment.
A patient may be counted in multiple rows if they receive more than one post treatment anticancer therapy. Includes anticancer therapies with a start date after the last dose date of study treatment.
Note: Treatment beyond progression is not counted as a subsequent anticancer therapy, this is considered a continuation of first-line therapy.
Abbreviations: EGFR, epidermal growth factor receptor; FAS, full analysis set; Osi + chemo, osimertinib plus chemotherapy; PD-1, programmed cell death protein-1; PD-L1, programmed cell death ligand-1; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.
Source: Planchard et al. (2023);[1] CSR.[2]

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2. Distribution of subsequent treatments

The committee requested a scenario where 7% of participants received ABCP, but the company do not believe the 7% figure is appropriate in the context of the company model. To validate the SACT data verbalised during the committee meeting, AstraZeneca made a freedom of information (FOI) request to National Health Service England (NHSE) to determine the use of atezolizumab in combination with bevacizumab + carboplatin + paclitaxel (code ATE5) according to mutation type. Data were provided for patients with non-small cell lung cancer (NSCLC) who had an actionable mutation for which there is funded NHS England therapy, and the patient has been treated with such targeted therapy prior to the receipt of ABCP. In total, [redacted] patients with activating epidermal growth factor receptor mutations (EGFRm), excluding exon 20 mutations received atezolizumab from Q1-Q4 2023, inclusive.[3] Assuming, a median TTD of [redacted] months based on the FLAURA2 study,[4] the total number of new patient starts on osimertinib for the relevant previous 12 month period (April 2021-March 2022) based on internal AstraZeneca data was [redacted][3] Given that osimertinib monotherapy is the standard of care for EGFRm NSCLC, and atezolizumab is only recommended for use as second line treatment after targeted treatment in combination with bevacizumab, carboplatin and paclitaxel,[5] these patient numbers indicate that 8.2%([redacted]) of people receiving osimertinib monotherapy go on to receive second-line ABCP treatment[3] and therefore inclusion of ABCP costs is reflective of UK clinical practice.

The committee requested a scenario reflecting SACT data in the Draft Guidance Document. The 8.2% value used is the most accurate representation of the scenario referred to in the Draft Guidance Document.

Based on the evidence for use of ABCP in English clinical practice and the likely minimal impact of an additional survival benefit with ABCP, the company does not consider it to be appropriate to exclude ABCP costs from the base case and considers the assumption that 8.2% of patients who receive subsequent treatments would receive ABCP to be appropriate. The company base case has been updated to reflect this. The percentage reduction in ABCP treatment in each arm from the original company base case was reallocated equally between the remaining subsequent treatments; this ensured the proportion of patients receiving subsequent treatments in each arm remained constant ([redacted]% in osimertinib plus chemotherapy arm and [redacted]% in the osimertinib monotherapy arm; Table 2).

Table 3 presents the results of the updated base case.

Table 2: Distribution of patients across second line treatments- revised base case

From ↓To →	PDC	Pemetrexed	Docetaxel	ABCP	Reference in submission
Osimertinib + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	AstraZeneca (2023) FLAURA2 Clinical Study Report[2]
Osimertinib	[redacted]	[redacted]	[redacted]	8%	Clinical expert input NHSE SACT data[3]

Abbreviations: ABCP, atezolizumab + bevacizumab + carboplatin + paclitaxel; NHSE, National Health Service England; PDC, platinum doublet chemotherapy; SACT, systemic anticancer treatment.

NICE National Institute for Health and Care Excellence

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Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Wednesday 20 November. Please submit via NICE Docs.

Table 3: Revised company base case

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Osimertinib + Chemotherapy	[redacted]	[redacted]	[redacted]				
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£36,655**

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

3. Approach to OS extrapolation

The committee concluded that both the company's and EAG's approach to modelling overall survival had methodological strengths and limitations and that either might be appropriate, and further justification for the choice of overall survival model was requested.

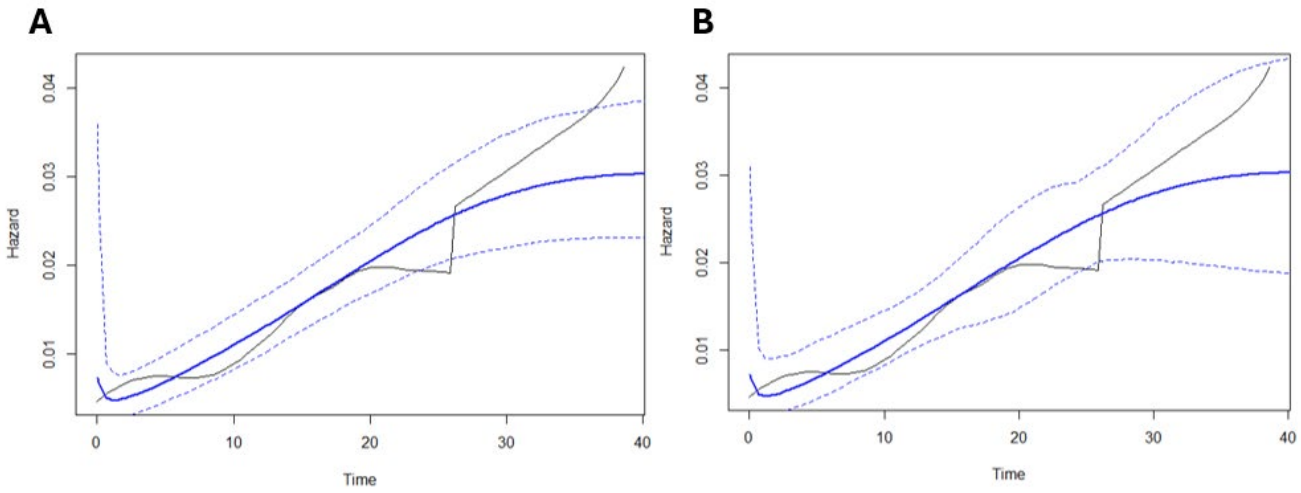
The company submission selected a 2-knot normal model for the osimertinib plus chemotherapy arm as this provided the best within-trial fit (according to Akaike information criterion (AIC)/ Bayesian information criterion (BIC) statistics) and gave a potentially conservative estimate of long-term survival based on clinician feedback. For osimertinib monotherapy, although the one-knot odds spline model provided the best statistical fit, the 2-knot normal model was selected on the basis that it provided a reasonable within-trial fit and aligned closest with the long-term survival estimates of clinical experts consulted during submission development, [6] while the 1-knot model did not produce clinically plausible long-term extrapolations.

The EAG preferred a 1-knot odds model, but the committee stated that the EAG's use of a different number of knots for each treatment arm requires significant justification.[7]
Although the EAG believed that the most suitable extrapolations could have different shapes due to the different mechanism of action, the hazard functions would not be expected to be fundamentally different in real-world use due to the presence of osimertinib in both treatment arms.
As highlighted in NICE Decision Support Unit (DSU) Technical Support Document (TSD)14, NICE considers it preferable to use the same type of model for each treatment arm[8] and therefore the company considers the use of the same number of knots across treatment arms to represent the best practice approach. Using the same number of knots ensures comparability and balance between the treatment arms and provides consistency between the models utilised.

NICE DSU TSD 21 describes that altering the number of knots may have an effect on how the survival function is extrapolated beyond the time horizon of the observed data.[9] Using the 1-knot model may be less accurate at the end of the time horizon in the osimertinib monotherapy arm; as shown in Figure 1, the observed smoothed hazard (in black) is beyond the upper 95% confidence interval of the estimated hazard from the model (the blue lines). In the 2-knot model, the observed hazard function is between the 95% confidence intervals of the estimated hazard function at almost all time points (both the 1-knot and 2-knot model have a small window of time at approximately 25 months where the observed hazard

function lies beyond the estimated lower 95% confidence interval). The company therefore believes that, given the preference to use the same model forms (as stated in NICE DSU TSD 14),[8] and the fact that the 2-knot model for the comparator arm provides a more accurate estimate of the hazard function, the base case approach utilised by the company is appropriate.

Figure 1: Hazard function from 1-knot (A) and 2-knot (B) flexible spline model (odds scale)



4. Time to treatment discontinuation

TTD in the FLAURA2 trial was a post-hoc analysis calculated as time from randomisation to the earliest date of study discontinuation or death. As captured in the draft guidance document, the clinical expert highlighted during the committee meeting that patients receiving osimertinib may continue to receive treatment beyond Response Criteria Evaluation In Solid Tumors (RECIST)-defined disease progression in clinical practice in England.[7] In line with the FLAURA2 study, median TTD was also longer than PFS in the osimertinib treatment arm of the FLAURA study (20.8 months for TTD vs 18.9 months for PFS[10]). Furthermore, treatment beyond RECIST-defined progression is supported by evidence from an Italian real world study of patients with advanced/metastatic NSCLC which reported median TTD of 25.3 months (95% CI 25.3, 25.3) compared with median PFS of 18.9 months (95% CI 11.2, 26.7) with osimertinib.[11] Data from NHSE also indicates that use of osimertinib in clinical practice reflects the treatment duration observed in the FLAURA2 study. Actual osimertinib volumes used from an NHSE FOI data request correlate with AstraZeneca forecasted volumes, which are based on an assumed treatment duration of [redacted] months (compared with 19.9 months PFS for osimertinib monotherapy from FLAURA2) (Figure 2).[3] Therefore, real-world evidence validates the clinical trial findings that patients remain on osimertinib monotherapy beyond disease progression.

Osimertinib with pemetrexed and platinum-based chemotherapy for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6328]

Draft guidance comments form

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Figure 2: Estimated osimertinib volume use versus actualised volumes from NHSE

Abbreviations: NHSE, National Health Service England.

Based on the observed data from FLAURA2, there was a smaller difference between PFS and TTD in the osimertinib plus chemotherapy arm than in the osimertinib monotherapy arm: median PFS was 25.46 months and median TTD was 27.96 months (difference: 2.50 months) in the osimertinib plus chemotherapy arm, whilst median PFS was 16.66 months and median TTD was 21.19 months (difference: 4.53 months) in the osimertinib monotherapy arm. Based on the PFS and TTD curves, there is a different relationship between PFS and TTD in the osimertinib and chemotherapy treatment arm and in the osimertinib monotherapy arm in the earlier months. In the osimertinib plus chemotherapy arm, TTD is initially lower than PFS (up to ~18 months), before crossing the PFS curve and remaining above PFS from ~18 months onwards. However, in the osimertinib monotherapy arm, TTD sits above PFS from approximately 2 months. This difference can potentially be explained by a slightly higher rate of osimertinib discontinuation in the osimertinib plus chemotherapy arm compared with the osimertinib monotherapy arm (10.9% vs 6.2%), with most discontinuations in the osimertinib plus chemotherapy arm occurring during the first 9 months of treatment.[12]

Therefore, the earlier, pre-progression discontinuations due to adverse events (AEs) may be contributing to differences in the observed data. This explains why the difference between median TTD and PFS is lower in the combination arm, despite the fact that the proportion of patients who progress and receive further treatment and the median duration of exposure beyond progression is comparable between the two treatment arms.

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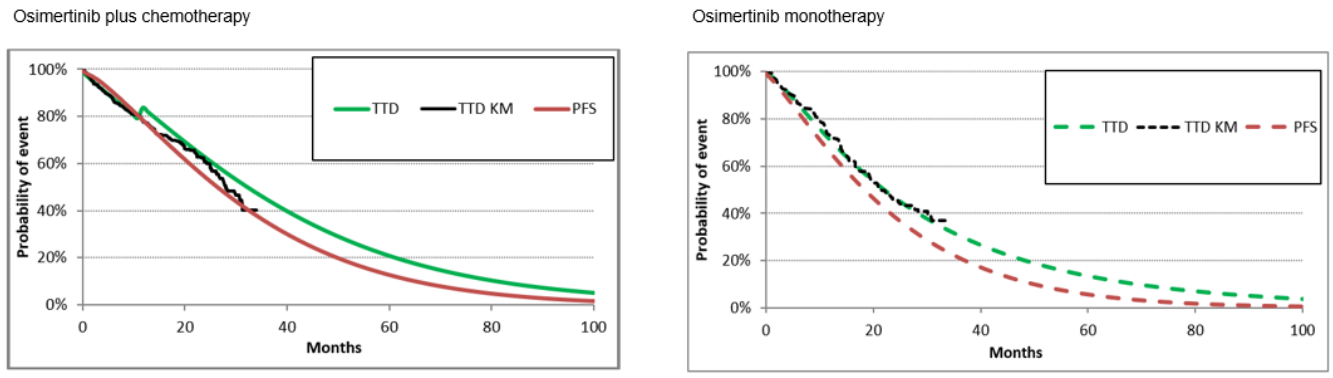
Alternative TTD scenario

As requested by the committee, a scenario in which both treatment arms are modelled to have the same time between progression and treatment discontinuation once pemetrexed and platinum-based chemotherapy have stopped was explored. To derive the TTD curve in the osimertinib chemotherapy arm, the difference between the PFS and the TTD curve in the osimertinib monotherapy arm was added to PFS in the osimertinib chemotherapy arm, at the point where pemetrexed is discontinued. However, this generated a TTD curve which looks implausible compared with the clinical data from FLAURA 2 and sits too far away from the Kaplan-Meier (KM) curve (Figure 3). An alternative TTD scenario was therefore explored.

Figure 3: TTD adjustment to allow for the same time between progression and discontinuation after chemotherapy discontinuation



Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival; TTD, time to treatment discontinuation.

In the committee meeting, the clinical expert stated that TTD was likely to sit between the company and the EAG estimate (Draft Guidance Document section 3.8).[7] Therefore, an analysis has been presented to reflect this assumption using a Weibull extrapolation for the osimertinib monotherapy arm which sits between the company's gamma base case and the EAG Gompertz base case curve (Table 4).

However, as described above, real-world evidence and data on the use of osimertinib from NHSE correlate closely with TTD in the FLAURA2 trial, and the company therefore consider their original base case assumptions to be the most reflective of how osimertinib is used in UK clinical practice (see Table 3).

Table 4: TTD alternative scenario – Weibull extrapolation for osimertinib monotherapy

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Osimertinib + Chemotherapy	[redacted]	[redacted]	[redacted]					

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Osimertinib with pemetrexed and platinum-based chemotherapy for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6328]

Draft guidance comments form

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Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£40,964

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

5. Approach to utilities

The EAG stated that in the osimertinib plus chemotherapy arm, there were a higher proportion of missing data during the first 16 weeks of the trial. However, in FLAURA2, the overall compliance rate for EQ-5D-5L was high and consistent between treatment arms. The number of received questionnaires decreased over time; however, compliance in both arms was [redacted] up to 46 weeks, and [redacted] up to 94 weeks of follow-up (Table 5).[2] Overall treatment compliance rates were also comparable between the treatment arms ([redacted] in the osimertinib plus chemotherapy arm and [redacted] in the osimertinib monotherapy arm).

Table 5: Compliance rate (%) with EQ-5D by visit (FAS)

	Osi + chemo (N=279)	Osimertinib (N=278)
Baseline	[redacted]	[redacted]
Week 4	[redacted]	[redacted]
Week 7	[redacted]	[redacted]
Week 10	[redacted]	[redacted]
Week 16	[redacted]	[redacted]
Week 22	[redacted]	[redacted]
Week 28	[redacted]	[redacted]
Week 34	[redacted]	[redacted]
Week 40	[redacted]	[redacted]
Week 46	[redacted]	[redacted]
Week 52	[redacted]	[redacted]
Week 58	[redacted]	[redacted]
Week 64	[redacted]	[redacted]
Week 70	[redacted]	[redacted]
Week 76	[redacted]	[redacted]
Week 82	[redacted]	[redacted]
Week 88	[redacted]	[redacted]
Week 94	[redacted]	[redacted]

Abbreviations: FAS, full analysis set.
Source: CSR.[2]

Osimertinib with pemetrexed and platinum-based chemotherapy for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6328]

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To address the committee's concerns relating to missing data, an additional analysis using multiple imputation to account for missing data has been presented in Table 6 (AstraZeneca internal data).

The multiple imputation analysis was performed using the mice package in R to impute missing values, using the predictive mean matching (PMM) method. Missing baseline values were imputed as the median of the non-missing baseline values, and all observations that were missing but expected to be present were imputed. Five iterations were used, and imputation was carried out separately by randomised treatment group. Baseline characteristics considered in the imputation process were as follows: race (Asian, non-Asian), Eastern Cooperative Oncology Group (ECOG) performance status (PS) (0, 1), tissue testing method (central, local), age, sex, a flag for whether the subject progressed at some point in the study or not, presence of central nervous system (CNS) metastases, presence of extrathoracic metastases, and presence of bone metastases. To analyse the data, mixed models for repeated measures were used with a term for baseline EQ-5D and progression status. The correlation over time within individuals was modelled with an AR(1) correlation structure i.e., correlation between any two consecutive visits is the same, but diminishes as the gap between visits increases.

The marginal mean progression-free utility value was [redacted], 95% confidence interval ([redacted]). This result is consistent with the progression-free utility value used in the company submission base case ([redacted]).

Table 6: Multiple imputation analysis pre-progression marginal means utility

State	Utility value: marginal means	95% confidence interval
Progression-free	[redacted]	[redacted]

Abbreviation: LCI, lower confidence interval, UPI, upper confidence interval

The committee also noted EAG concerns with the disutility applied to account for chemotherapy-related adverse events. The company base case included all Grade ≥3 AEs occurring in ≥2% of patients in either the osimertinib plus chemotherapy arm or the osimertinib monotherapy arm. The impact of AEs on utility scores in the company base case was accounted for by applying a disutility for the duration over which the AE was assumed to last and applied to the percentage of patients experiencing the AE in the FLAURA2 trial during the first model cycle. This was the same approach as used in TA654.[13] AEs were modelled separately for each treatment arm to account for the differences associated with the addition of chemotherapy to osimertinib.

The EAG recommended using a utility decrement applied to the entire progression-free period in the osimertinib plus chemotherapy arm to account for the impact of chemotherapy on quality of life. However, the company does not consider this to be an appropriate approach as patients did not receive chemotherapy for the full progression-free period. In the osimertinib + chemotherapy arm safety analysis set, the median total exposure to osimertinib was 22.26 months (range 0.1 to 33.8 months) compared with 2.76 months (range: 0.7 to 4.1 months) with cisplatin/carboplatin and 8.28 months (range: 0.7 to 33.8 months) with pemetrexed.[2]

To address the committee's concerns, an additional scenario has been presented that accounted for treatment-specific utility during treatment with chemotherapy. The treatment-specific utility value was derived using a mixed model for repeated measures (MMRM) analysis applied to intention-to-treat (ITT)

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Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Wednesday 20 November. Please submit via NICE Docs.

data from FLAURA2, with a 16-week follow-up data cut-off, consistent with the approach in the company submission. The MMRM analysis used the restricted maximum likelihood method (REML). A model including treatment + progression status as covariates was deemed most appropriate for addressing the committee's concerns. The results of this MMRM analysis are presented in Table 7 and Table 8 (AstraZeneca internal data).

Table 7: Parameter estimates

Parameter	Estimate	SE	p-value	95% CI
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
Osimertinib + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Post progression	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; SE, standard error.

Table 8: Marginal means utility values for treatment and progression status

State	Utility value: marginal means	95% confidence interval
Progression-free (Osimertinib plus chemotherapy)	[redacted]	[redacted]
Progression-free (Osimertinib)	[redacted]	[redacted]
Post-progression (osimertinib plus chemotherapy)	[redacted]	[redacted]
Post progression (osimertinib monotherapy)	[redacted]	[redacted]

Based on the results of the analysis described above, a utility decrement of [redacted] has been applied to the osimertinib plus chemotherapy arm for the duration of chemotherapy treatment (Table 9).

Table 9: Alternative utility scenario – treatment arm as a covariate (decrement of [redacted])

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Osimertinib + Chemotherapy	[redacted]	[redacted]	[redacted]					
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-£119	£36,537

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

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Osimertinib with pemetrexed and platinum-based chemotherapy for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6328]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Wednesday 20 November. Please submit via NICE Docs.

Abbreviations

ABCP	Atezolizumab + bevacizumab + carboplatin + paclitaxel
AE	Adverse event
AIC	Akaike information criterion
BIC	Bayesian information criterion
CNS	Central nervous system
DSU	Decision Support Unit
EAG	Evidence Assessment Group
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
FOI	Freedom of information
ITT	Intention-to-treat
KM	Kaplan-Meier
MMRM	Mixed model for repeated measures
NHSE	NHS England
NSCLC	Non-small cell lung cancer
OS	Overall survival
PFS	Progression-free survival
PMM	Predictive mean matching
PS	Performance status
RECIST	Response Criteria Evaluation In Solid Tumors
REML	Restricted maximum likelihood method
SACT	Systemic anticancer treatment
TSD	Technical Support Document
TTD	Time to treatment discontinuation
VEGF	Vascular endothelial growth factor

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References

1. Planchard D, Jänne PA, Cheng Y, Yang JC, Yanagitani N, Kim SW, et al. Osimertinib with or without Chemotherapy in EGFR-Mutated Advanced NSCLC. The New England journal of medicine. 2023;389(21):1935-48.
2. AstraZeneca. A Phase III, Open-label, Randomised Study of Osimertinib With or Without Platinum Plus Pemetrexed Chemotherapy, as First-line Treatment in Patients with Epidermal Growth Factor Receptor Mutation Positive, Locally Advanced or Metastatic Non-small Cell Lung Cancer (FLAURA2) - Randomised Period. Clinical Study Report 2023;4th Aug 2023 Data on file.
3. AstraZeneca. EGFRm NSCLC market share data and osimertinib TTD data. Data on file. 2024.
4. AstraZeneca. FLAURA2 - PAY0452 - Survival analysis Time to treatment discontinuation. Data on file. 2023.
5. National Institute for Health and Care Excellence. Lung cancer: diagnosis and management. NG122. 2019;Available at https://www.nice.org.uk/guidance/ng122 Accessed 29th February 2024.
6. AstraZeneca. AstraZeneca UK MC: Teleconference clinician interviews to support a HTA submission for osimertinib plus chemotherapy for treatment of untreated EGFR mutation-positive non-small-cell lung cancer. Data on file. 2024.
7. National Institute for Health and Care Excellence. Osimertinib with pemetrexed and platinum-based chemotherapy for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6328]. Draft guidance available at https://wwwniceorguk/guidance/indevelopment/gid-ta11408/consultation/html-content-4. 2024.
8. Latimer N. Undertaking survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. Available from http://wwwnicedsuorguk. 2011.
9. Rutherford M, Lambert P, Sweeting M, Pennington R, Crowther M, Abrams K, et al. NICE DSU Technical Support Document 21. Flexible Methods for Survival Analysis Available from http://wwwnicedsuorguk. 2020.
10. Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, et al. Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. The New England journal of medicine. 2018;378(2):113-25.
11. Lorenzi M, Ferro A, Cecere F, Scattolin D, Del Conte A, Follador A, et al. First-Line Osimertinib in Patients with EGFR-Mutant Advanced Non-Small Cell Lung Cancer: Outcome and Safety in the Real World: FLOWER Study. Oncologist. 2022;27(2):87-e115.
12. Lee CK, Planchard D, Fan Y, Poltoratskiy A, Tran TV, Gálvez ML, et al. Safety and tolerability of first-line osimertinib ± platinum-pemetrexed in EGFRm advanced NSCLC: Data from FLAURA2. Poster presented at the European Lung Cancer Congress 2024 (ELCC) Prague, Czech Republic; 20–23 March. 2024.
13. National Institute for Health and Care Excellence. Osimertinib for untreated EGFR mutation-positive non-small-cell lung cancer. TA654. 2020;Available at https://www.nice.org.uk/guidance/ta654 Accessed 4th March 2024.

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Single Technology Appraisal

Osimertinib with pemetrexed and platinum-based chemotherapy for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6328]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	EGFR+ UK (and the Ruth Strauss Foundation)
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	EGFR+ UK is a patient driven charity established to provide information and support for EGFR mutation positive lung cancer patients, their families and loved ones. We are also dedicated to supporting research and advocacy, and are working to raise awareness of EGFR positive lung cancer and end the stigma associated with lung cancer in general. We currently have approximately 850 members, and are largely funded by fundraising activities, charitable donations, and some grants.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	No

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Patients share their experiences of treatment pathways and drug toleration on our private patient support forum, which is the main vehicle for the exchange of information and support within our charity. As we have approx. 850 members we are able to present a representative view of the experience of living with EGFR mutation positive lung cancer. The charity recently ran a qualitive online consultation with patients in this forum, exploring their experiences with chemo and/or Osimertinib in light of the FLAURA2 results. We also recently ran a survey with our membership exploring the experiences of EGFR+ patients in the UK in terms of their diagnosis, treatment, surveillance and wellbeing (n=234). In this document we summarise both quantitative and qualitative information collected from patients, as well as drawing on personal experience.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Non-small cell lung cancer (NSCLC) with an EGFR mutation is an aggressive disease that has a considerable physical, psychological, economic and social impact on patients and their families. Patients affected by EGFR positive NSCLC are generally younger than typical lung cancer patients, non-smokers, more likely to be female, often still working and with dependent children. The diagnosis therefore is particularly devastating, often coming as a total shock, and with a notable impact on psychological wellbeing. In our annual survey of EGFR+ UK members (n=234), we used standardised measures (the GAD7 and PHQ9) to estimate levels of anxiety and depression in our membership. The results showed that lung cancer causes significant psychological distress, with 1-in-3 of patients scoring over the cut-off for diagnosable anxiety; and 1-in-4 showing likely clinical depression (Harrison, 2024). Both prevalence rates are significantly higher than that seen in the general population. The following quote from one of our members describes just how difficult living with EGFR+ lung cancer can be: *"To look at me without knowing, you could not tell that there is anything wrong with me… BUT there is and it is a challenging life I lead. Currently a good one, but hugely discombobulating where even the most joyous experiences will lead to a wave of sadness as I consider the reality of "will I be here next year" doing this again. Living with the uncertainty of how and when things will change for you is impactful for me and my family… it messes with your head. More emotional support is needed… the psychological impact should be viewed as importantly as the medical."* In addition to being psychologically challenging, EGFR also has a significant social impact. For example, one of our younger patients describes just how isolating having EGFR+ lung cancer can feel: *"I have lots of friends and things, but they just don't get it. I just feel so alone. They don't understand how huge it all is."* The diagnosis also has a significant impact on the family relationship and income. The majority of patients are diagnosed at Stage 4, and are often unable to work as a result. This in itself can be very distressing, and significantly impacts normal family life. Additionally, brain metastases are common with EGFR mutations, which often leads to patients needing to surrender their driving license. This impacts hugely on patient quality of life. For example, one patient said:

	"Losing my license has honestly been one of the hardest things I've had to deal with since my diagnosis. It hasn't just impacted me, but it's impacted our whole family. I can't take our children to parties and clubs and things. I have to rely on my partner to drive them everywhere – and me, which makes me feel like a massive burden. It feels like my freedom has been stripped away from me." Furthermore, fear of progression is enormous, and has a significant psychological burden on the patient and their families. *"I know my treatment is keeping the cancer cells sleeping, but I can't help but wonder when they are going to wake up. I feel like I'm a ticking timebomb – it's only a matter of time before it progresses… and then what? I just want more time."* This quote also highlights the worry patients and loved ones have as a result of the limited number of treatment lines that are available in the UK, and the longevity of those available. It is our hope that more NICE approved treatment lines will become available in the UK, so that patients will be able to live longer and longer, which maintaining active and … lives.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Our abovementioned survey showed that the majority of our members are diagnosed with Exon 19 or 21 mutations, and that 77.7% of respondents were being treated with a TKI – most commonly Osimertinib (in line with current standard or care). In addition, 30.9% of respondents have received chemotherapy as part of their treatment. Osimertinib is generally viewed extremely positively amongst our membership, and it is very well tolerated. Taking a single tablet once a day is seen as convenient and does not disrupt day-to-day life. However, side effects are common. In a recent survey exploring the impact of side effects of TKIs among our members (n=204), we found some of the most common side effects were: dry skin, fatigue, diarrhoea, muscle cramps, rashes/acne, difficulty sleeping, sexual issues, paronychia. Additionally, many of these side effects were seen as significantly distressing: • "The acne is constant and it has really affected my self esteem." • "Mouth ulcers can appear small and insignificant, but can profoundly affect quality of life, enjoyment of food, swallowing and talking." • "The muscle cramps can be very debilitating and incapacitating." However, patients and carers overwhelmingly view Osimertinib in a positive light (many referring to is as their "magic medicine" or "miracle drug") and feel these side effects are worth it, given the extra time and quality of life it affords them. In contrast, many patients dread chemo, partly because it is seen as the last resort and "the beginning of the end", but also because of the side effects. However, there is still a lot of misinformation and misunderstanding about the chemotherapy that EGFR patients would receive. For example, many patients think it will make them lose their hair (which it typically does not), and make them really sick (which modern antiemetics are very effective at treating). But tellingly, several of our patients have had a good response to chemo and have said that they would do it again if it would give them more time. The main concerns that patients and loved ones have (as highlighted above) are in relation to the relatively few treatment options/lines available to them. There is an overwhelming fear about the limited time TKIs give them, knowing that their cancer is likely to develop a resistance mechanism and progress. They hope for more

	treatment lines, and more choice about options that can potentially help to prolong their lives – however, quality of life (not just quantity) is a key priority for patients.
8. Is there an unmet need for patients with this condition?	Yes – despite having Osimertinib as standard of care, EGFR+ lung cancer patients still have relatively few treatment options available to them in comparison to many other cancers. This is despite lung cancer being the most deadly cancer in the UK. Increasing the number of treatment lines for this patient group, and investigating their optimal sequencing, needs to be a priority.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	When discussing the results of FLAURA2, our members felt that the main advantage of this treatment (chemo + osi as first line) is the additional time it would afford patients, and what that means in terms of being able to spend more time with loved ones. Even though chemo is often seen as scary, patients (particularly younger patients and those with young families) felt that they would choose to take this treatment after diagnosis. Three of our members said: *"Chemo scares me, while osi allows you to live fairly normally. But if I had been presented with the [FLAURA2] stats, I would probably opt for chemo and osi."* *"I think when first diagnosed I would have opted for osi and chemo due to being 49 years at the time and in good health. I would have felt time was of the essence and if the TKI did not work then maybe the chemo would"* *"I was diagnosed at 40, and I have two young children. There is nothing I wouldn't do to have more time with them. Taking chemo and osi together would give me that – so it's a no brainer for me"* Interestingly though, whether patients would want to take this combination treatment or not, almost all stated that they wish they had had the choice to have it. *"I think I'd have lots of questions about pros and cons, but would like to have the opportunity to be able to make an informed choice [about whether to take osi alone, or in combination with chemo] especially as it is such a big difference."*

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	The main disadvantage of this treatment relates to the side effects associated with the chemo/osi combination. There is still a lot of fear around chemotherapy, and patients are worried whether the additional time it gives is worth the side effect burden and impact on quality of life: *"Even though I had a great and long response on chemo, if I had a choice I would choose Osi on its own or any TKI as the side effects are much less and it is possible to live a relatively normal life without being tied to the hospital and being sick half the time."* *"I would be reluctant to have chemo alongside Osi. At the moment, I can live a normal life on Osi and the side effects with the chemo added sound quite dire,"* *"If I had been diagnosed in my 40s or 50s, I think I would probably want to take the combination treatment. But I was diagnosed at 72, so I would have to question whether the side effects are really worth it."* However, some patients (who have had chemotherapy) felt that the side effects would be manageable – particularly as the chemo doublet is only taken for a finite period of time. *"I actually found chemo much easier to tolerate than I was expecting. I think knowing you are only taking Carbo for a certain number of cycles can really help. Plus, if the toxicity gets too high, you can always have a break, or drop down to osi only."* Other patients also commented on how the combination treatment would disrupt day-to-day life with hospital appointments for IV administration: *"With osi on its own, I can just take it at home every day – I'm really glad I don't have to be tied to a hospital all of the time."* *"Going to hospital makes me feel like a cancer patient – taking tablets at home almost allows me to forget. Not that you can ever **really** forget."*

	Others expressed concerns about what this combination treatment might mean for treatment options further down the line: *"If I was newly diagnosed and being offered this my concern is if you've used up the platinum doublet chemo at the beginning alongside Osi and then progression happens what can be offered."* Overall, the general feeling was that while many would choose not to take the combination treatment (largely due to toxicity fears and the potential impact on quality of life), they would still like to have been given the choice to have it.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	The combination of Osimertinib and chemotherapy may be too toxic for some patients, so this would need to be carefully managed.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	EGFR affects certain groups more than others (for example, it is more prevalent in women, and in Asian populations). Ensuring access to treatment and information about the treatment is relevant and understandable to these groups is essential.

Other issues

13. Are there any other issues that you would like the committee to consider?	There is still a lot of fear around chemotherapy, and concern about the negative side effects associated with this treatment – particularly from those who have not experienced it. While some of this fear is justified, some of it may not be. For example, some EGFR patients are unaware that Carbo/Pem does not cause hair loss; others worry about debilitating nausea and vomiting, however improvements in antiemetic medications have significantly improved side effects. As such, some myths surrounding chemo need to be dispelled, and that might be reflected in the comments contained within this submission. In addition, there is often an assumption that quality of life and psychological wellbeing will be more affected in those who take chemo in comparison to those who take Osi alone. However, our 2024 members survey does not support that (at least not from a psychological point of view). While we didn't explicitly measure QoL, we did break down anxiety and depression scores for those on chemo, and those who had not had chemotherapy. We found no significant difference between the two groups for either GAD7 (p=.7385) or PHQ9 (p=.279). Unfortunately, we do not have this data for patients on the combination treatment. Finally, while it is clear that there are some significant splits in the EGFR community about whether patients would want to take the combination treatment or not (and a strong debate about quality vs quantity of life is evident in the comments above), almost all patients said that they wish they had had the choice to consider this treatment. This really speaks to the need for more treatment options for EGFR patients.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Being able to take a daily TKI tablet has minimal impact on patients and their loved ones, enabling them to live full and active lives. • Many patients with EGFR dread taking chemo – largely due to the side effects, but the logistics of the treatment and time cost are also a factor. • EGFR patients are quite split in terms of whether they would want to take chemo + osi. This was largely due to the trade off between quantity and quality of life. Typically, younger patients and those with dependents said they would welcome this treatment as an option if it was likely to extend the PFS and OS; while older patients felt quality of life was a priority. • Regardless of whether or not individual patients would want to take chemo + osi as first line treatment or not, almost all patients felt that they would at least like the chance to consider it an option. • Some questions were raised about what subsequent treatment options would be available if a patient had taken chemo + osi as first line treatment.

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Osimertinib with pemetrexed and platinum-based chemotherapy for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6328]

EAG Response to Company Comments on Draft Guidance Consultation

Produced by: Bristol Technology Assessment Group, University of Bristol

Authors: Marques EM, Tomlinson E, Carroll J, Cooper C, Benevente M, Welton NJ, Caldwell DM.

Correspondence to: Deborah M Caldwell, Professor in Epidemiology and Public Health, Bristol TAG, Population Health Sciences, Bristol Medical School, University of Bristol, Bristol

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ABBREVIATIONS

Abbreviation	Definition
1L	First line
2L	Second line
ABCP	Atezolizumab + bevacizumab + carboplatin + paclitaxel
AEs	Adverse Events
EAG	Evidence Assessment Group
EGFR	Epidermal Growth Factor Receptor
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30
EQ-5D-3L	EuroQol 5 dimensions 3 level questionnaire
EQ-5D-5L	EuroQol 5 dimensions 5 level questionnaire
ICER	Incremental Cost Effectiveness Ratio
MMRM	Mixed Model for Repeated Measures
NSCLC	Non-Small Cell Lung Cancer
NHS	National Health Service
NHSE	National Health Service England
NICE	National Institute for Health and Care Excellence
OS	Overall Survival
PD	Progressed Disease
PDC	Platinum Doublet Chemotherapy
PFS	Progression-Free Survival
QALY	Quality-Adjusted Life Year
TKI	Tyrosine Kinase Inhibitors
TTD	Time To Treatment Discontinuation

TABLE OF CONTENTS

LIST OF TABLES

1 INTRODUCTION

This report provides the evidence assessment group (EAG) review of the additional analyses, comments, and results provided by Astra Zeneca in response to the draft guidance consultation for Osimertinib with pemetrexed and platinum-based chemotherapy for untreated EGFR mutation-positive advanced non-small-cell lung cancer. The company has provided an updated base-case and scenario analyses.

2 REVIEW OF COMPANY'S CONSULTATION RESPONSE

The company arranged their response into five issues which we review in turn below.

2.1 Subsequent treatments in the FLAURA2 trial

The company clarifies that atezolizumab + bevacizumab + carboplatin + paclitaxel (ABCP) was likely used as a subsequent treatment in the FLAURA2 trial, but that the recording of the data inhibits the explicit identification of the ABCP regimen. The company argues that since ABCP is used in FLAURA2 which the OS extrapolations are based upon, then the OS benefits of this treatment are to some extent included, and that it should also be included in the costs.

The company's original submission stated, "Clinical experts also advised that 10–20% of patients receiving 2L treatment could receive atezolizumab + bevacizumab + carboplatin + paclitaxel as a subsequent treatment (ABCP), a treatment option not captured in the FLAURA2 trial", which we had interpreted as ABCP not being used in FLAURA2. We therefore thank the company for clarifying that ABCP was likely used.

Ideally both OS extrapolations and costs should reflect the subsequent treatments that are used in NHS practice. We are unable to adjust the OS data to reflect the proportion of patients who would receive ABCP in NHS practice, and as the company note it is not possible to estimate the exact proportion of ABCP use in FLAURA2. The impact of ABCP use on OS therefore remains uncertain. The committee preferred the EAGs base-case where no costs were included for ABCP because this aligned costs and outcomes. However, now that the company has clarified that ABCP was used to some extent in FLAURA2, the EAG agrees with the company that the costs of ABCP use should be included in the model, and that this should be reflective of use in NHS clinical practice (see section 2.2 below).

2.2 Distribution of subsequent treatments

The committee requested a scenario where 7% of participants who receive 2L treatments received ABCP. The company has obtained data from National Health Service England (NHSE) from which they have estimated the proportion of patients receiving ABCP to be 8.2%. This is based on the number of patients accessing ABCP from NHSE (n=[redacted]) and a denominator (n=[redacted]) based on internal company data and the median time-to-treatment

discontinuation from FLAURA2. However, the EAG does not have access to the internal company data to check the calculation used for their denominator.

The company then derived the distribution of patients across second line treatments (Table 1) by reallocating the percentage reduction in ABCP treatment in each arm from the original company base case equally between the remaining subsequent treatments, so that the proportion of patients receiving subsequent treatments in each arm remained constant ([redacted]% in osimertinib plus chemotherapy arm and [redacted]% in the osimertinib monotherapy arm). The company use the distribution in Table 1 (based on NHSE and FLAURA2 data) in their updated base-case rather than the 7% requested by the committee. The EAG has reported the company's figures in Table 1 to one decimal point to match more closely with the values used in the Excel model. The EAG reports the percentages conditional on those who received 2L treatments in Table 1, and notes that the values used by the company in their model are [redacted]% for osimertinib monotherapy and [redacted] for osimertinib plus chemotherapy, rather than 8.2%, due to fixing this percentage for all patients on osimertinib monotherapy, rather than restricting to those who have 2L therapy. The EAG presents a scenario correcting the company's calculations to give 8.2% of those receiving 2L treatment having ABCP, and follows the approach taken by the company to distribute the reduction in ABCP use evenly across the remaining treatments, giving the distributions shown in Table 2.

The EAG agrees with the company that the cost of ABCP use should be included and align with clinical practice in the NHS. As well as providing a scenario correcting the company's 2L treatment distribution (Table 2), the EAG also provides a scenario using 7% ABCP use as requested by the committee. The resulting distribution of 2L treatments was obtained following the approach taken by the company to distribute the reduction in ABCP use evenly across the remaining treatments, giving the distribution of 2L treatments as shown in Table 3. Given that the EAG cannot check the calculation of the denominator for the 8.2% value, the EAG uses the 7% ABCP use requested by the committee (Table 3) in its updated base-case.

Table 1: Distribution of patients across second line treatments- company's revised base case (to 1dp). Normalised proportions of those accessing 2L treatments displayed below in []'s

From ↓To →	PDC	Pemetrexed	Docetaxel	ABCP
Osimertinib + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Osimertinib	[redacted]	[redacted]	[redacted]	8.2% [redacted]

Abbreviations: ABCP, atezolizumab + bevacizumab + carboplatin + paclitaxel; NHSE, National Health Service England; PDC, platinum doublet chemotherapy; SACT, systemic anticancer treatment.

Table 2: Distribution of patients across 2L treatments for those discontinuing 1L treatment, EAG correction to company's updated base-case, assuming 8.2% of those

receiving 2L treatment having ABCP. Normalised proportions of those accessing 2L treatments displayed in []'s

From ↓To →	PDC	Pemetrexed	Docetaxel	ABCP
Osimertinib + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted] [8.2%]
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted] [8.2%]

Abbreviations: ABCP, atezolizumab + bevacizumab + carboplatin + paclitaxel; PDC, platinum doublet chemotherapy

Table 3: Distribution of patients across 2L treatments for those discontinuing 1L treatment, EAG updated base-case with 7% of those receiving 2L treatment having ABCP. Normalised proportions of those accessing 2L treatments displayed below in []'s

From ↓To →	PDC	Pemetrexed	Docetaxel	ABCP
Osimertinib + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted] [7%]
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted] [7%]

Abbreviations: ABCP, atezolizumab + bevacizumab + carboplatin + paclitaxel; PDC, platinum doublet chemotherapy

2.3 Approach to overall survival (OS) extrapolations

The extrapolation of OS is uncertain, and the committee noted that both the company and EAG preferred assumptions had limitations and requested further justification. The company argues that it is not appropriate to use a different number of knots for the OS curves for each treatment, as assumed by the EAG. They provide plots to demonstrate that the empirical hazards lie outside of the credible interval for the 1-knot model towards the end of the curve for osimertinib. They therefore prefer their 2-knot models for both treatment arms.

The EAG recognises that in general it is preferable to use the same family of survival model for each treatment, unless there is reason to expect that the shape of the survival curve might differ between treatments. The spline models are a very flexible class of models, and the shape of the curves and extrapolation can depend on the chosen number of knots. Whilst osimertinib is included in both treatment arms, it does not necessarily hold that the shape of the survival curve would be the same when used in combination with chemotherapy, especially since there is a big difference in the proportions of patients accessing 2L treatments between the treatments. The statistical model fit consistently shows that the fit is better for 2-knot models for osimertinib plus chemotherapy, and better for 1-knot models for osimertinib monotherapy. In addition, the 1-knot model extrapolations were consistent with the data from the FLAURA study on osimertinib

monotherapy (which had longer follow-up than FLAURA2), and registry data for other EGFR TKIs. The EAG notes that the empirical hazards at the end of the curves are based on small numbers of patients, and if the confidence limits around the empirical hazards were displayed on the plots, then there would be substantial overlap with both the 1-knot and 2-knot models for osimertinib monotherapy.

The EAG retains its preference for the 1-knot odds model for osimertinib monotherapy and the 2-knot odds model for osimertinib plus chemotherapy and uses these in its updated base-case.

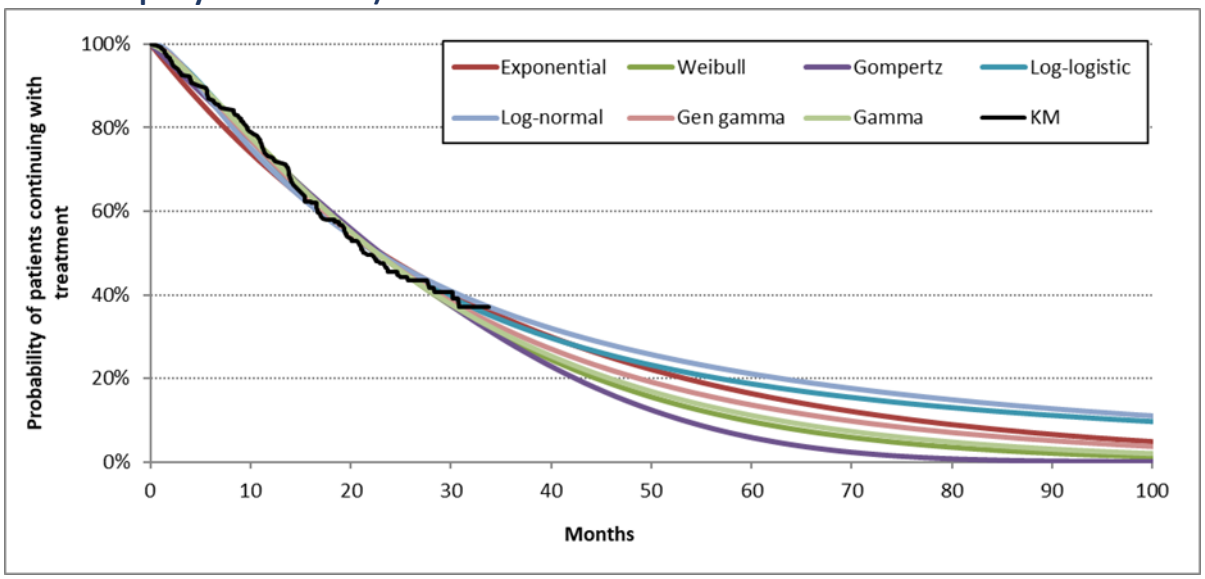
2.4 Approach to time-to-treatment discontinuation (TTD) model

The committee decided there was insufficient evidence to support either the company or EAGs TTD modelling for osimertinib monotherapy and asked the company to provide additional evidence on treatment with osimertinib beyond progression. The company provided data from the osimertinib group of the FLAURA trial showing median TTD (20.8 months) was slightly longer than median Progression Free Survival (PFS, 18.9 months). They also supported this by comparing volumes of osimertinib used from NHSE data with their predictions from FLAURA2.

The committee considered that TTD of osimertinib would be similar for the two treatments after chemotherapy had been stopped and requested a scenario in which both treatment arms are modelled to have the same time between progression and treatment discontinuation once pemetrexed and platinum-based chemotherapy have stopped. The company argued that patients remain on osimertinib for longer following disease progression if they had been taking osimertinib monotherapy compared with if they had been on the combination therapy, and that the reason for this is due to higher discontinuation of osimertinib pre-progression early on due to adverse events for patients taking combination therapy. They present the TTD curves implied by the committee's assumption and argue that the resulting curve is implausible compared with the FLAURA2 data. The EAG agrees with the company that this curve does not fit well to the FLAURA2 study data.

The company retain the gamma distribution for TTD for osimertinib monotherapy in their base-case and present a scenario using the Weibull distribution which they argue provides a compromise between the company's base case (Gamma) and the EAG's base case (Gompertz), as suggested by the committee. The EAG notes however, that the Weibull curve is much closer to the Gamma curve than it is to the Gompertz curve (Figure 1), and so much more similar to the company's base-case than the EAG's base-case. There is no curve provided that lies mid-way between the Gamma and Gompertz, and so the EAG has adapted the company's model to use an average of the Gamma and Gompertz curves and uses this in their updated base-case.

Figure 1: FLAURA2 TTD KM and extrapolations for osimertinib monotherapy (Fig 29 from company submission)



Abbreviations: KM, Kaplan-Meier; TTD, time to treatment discontinuation.

2.5 Utility scores

The company responded to the EAG's critique of the estimation of health-state utilities and provided additional analyses of the utility data from FLAURA2 to address missing data and to estimate the disutility of treatment with chemotherapy. The company's updated base case includes their preferred value for PFS utility (PFS=[redacted]) and individual decrements for each of the serious adverse events during their duration, as per their initial base case, and the committee's preferred assumption for Progressed Disease (PD) utility (PD=0.678). In sensitivity analysis, the company provides a scenario using their estimated disutility values (Disutility=[redacted]) applied to the osimertinib plus chemotherapy group for the weeks of treatment with chemotherapy. The updated economic model also has a functionality to produce an additional scenario using the committee's preferred assumptions for PFS utility (PFS=0.794) and disutility values (disutility= [redacted] during the whole PFS period). The EAG comment on the company's response below.

2.5.1 PFS utility

The committee considered that the company's PFS utility value was too high and agreed that the EAG's preferred value for PFS utility was more realistic (PFS=0.794), albeit with uncertainty. To reduce this uncertainty the committee requested additional analyses that accurately captures the health-related quality of life in the progression-free state. This should include the size and duration of the impact of chemotherapy on health-related quality of life in the osimertinib with chemotherapy group. The committee also suggested further modelling of the PFS utility value to account for missing data and using treatment group as a covariable to produce treatment-specific utility values.

The company argues that the overall level of missing data does not differ between groups, and the EAG does not dispute that. However, the EAG argues that the missing data rates are different in the first 16 weeks of the trial, and lower in the intervention group, where chemotherapy side effects are stronger, and therefore biasing the estimates in favour of the intervention. As shown in the data reported in Table 5 of the company's response document, the completion rates in the intervention group in the first 16 weeks are [redacted]% vs [redacted]% in the control group. This small difference in completion rates may be significant if patients in the intervention group are not completing because they are suffering with side effects of chemotherapy and therefore in worse quality of life. This would be a plausible assumption, especially considering that in no other period of follow-up does the trial observe a [redacted]% difference in completion rates.

The company has presented new analyses applying multiple imputation to address the committees concerns around missing data in the PFS utilities. The EAG previously argued that the mixed model for repeated measures (MMRM) model used to estimate utilities did not account for explanatory variables of missingness and suggested the company to use an imputation model that accounted for these. The company has applied a different imputation model using the Multiple Imputation Chained Equations (MICE) method implemented in R, adjusting for baseline characteristics, and carried this imputation separately per trial group. The EAG considers the company's updated analyses to be more comprehensive than in their original submission but notes that other outcomes at follow-up points are still not part of the multiple imputation model. The missing data mechanism is not missing at random, there is a relationship between utilities at follow-up points and other patient-reported and clinical outcomes and costs at follow-up as well. The imputation model falls short by adjusting for only baseline covariables, and follow-up outcomes should have also been included in the imputation model to estimate the missing utility values. Given the amount of missing data to be imputed, the EAG would also advise using a significantly larger number of imputation sets.

More importantly, the EAG notes that despite the strengths of an appropriate imputation model, the utility values that this model are imputing still lack face validity. The EAG had previously recognised that the Hernandez-Alava (HA) mapping model used to map EQ-5D-5L health states to the EQ-5D-3L utility values is the NICE recommended mapping model but argued that, in this population, is producing values that were higher than the quality of life in the average UK population (0.799 for the average UK population 55-64 years and 0.78 for 65-74 years), for a population with advanced NSCLC, and therefore lacked face validity. Because the imputation model was applied to the values derived using this HA model, the EAG's concerns on face validity remain. Ways to further explore this uncertainty would be, for example, to map values from disease-specific tools such as the EORTC-QLQ-c30 questionnaire to EQ-5D-3L utilities for the FLAURA2 study population, as done previously for the FLAURA population to obtain utilities for TA654. The EAG therefore retains its preferred PFS utility value of 0.794 (used in TA654) in its updated base-case.

2.5.2 Disutilities of adverse events of chemotherapy

The company disagree with the EAG's approach to apply a utility decrement of [redacted] to the osimertinib plus chemotherapy group because it was applied to the entire progression-free period when patients did not receive chemotherapy for the whole period. The EAG would like to clarify that the disutility value of [redacted] applied to the intervention group was estimated using mean utility values estimated for the whole progression-free period, and thus appropriate to apply for its entire duration. The EAG previously noted the [redacted] decrement may still be an underestimation given the potential for bias introduced by missing data, particularly in the first 16 weeks for the osimertinib plus chemotherapy group, when side effects are felt the most.

The committee requested an analysis of the utility values over the first 16 weeks, using treatment arm as a covariable and accounting for missing data. The company conducted an analysis restricting to 16 weeks follow-up using a MMRM model with treatment arm as a covariable and estimated a [redacted] utility decrement.

The EAG appreciate the company providing this analysis but still has concerns. The missing data are likely not missing at random, and the model may not include all the potential explanatory variables for the missing data mechanism. The EAG would have preferred a multiple imputation model, adequately adjusting for baseline characteristics and follow-up outcomes (as per discussion in section 2.5.1 above), and adjusting for baseline utility (Manca et al. 2005) to account for the difference in utility at baseline between groups. The EAG notes that the groups are imbalanced at baseline and that this imbalance is large, with patients in the control group having a mean baseline utility value of [redacted] (SD=[redacted]) compared with a mean of [redacted] (SD=[redacted]) for patients in the intervention group.

The EAG believes that the additional analyses that the company has conducted have not addressed the committee's concerns, and that the [redacted] utility decrement is an underestimation. The EAG retains that a decrement of [redacted] estimated using the difference from baseline between groups in utility values for the PFS period is still the closest approximation to the decrement in utility due to chemotherapy and should be applied for the whole duration of the PFS period, to match the period they are estimated from.

2.5.3 PD utilities

The committee preferred the EAGs utility value of 0.678 from TA654 for patients with PD. The company now use this value in their updated base-case, and the EAG continues to use it in our updated base-case.

3 COMPANY's UPDATED ANALYSES

The company's updated base-case makes the following changes in line with the committee's preferences:

- Average starting age of 65.6 years
- Progressed disease utility value of 0.678
- Resource use figures using the company's estimation of outpatient visits and the Evidence Assessment Group (EAG)'s estimations for the other resources.
- Unit costs to value resource use were corrected to committee's preferred unit costs.
- 100% carboplatin use for platinum-base chemotherapy
- Relative dose intensity of 96.4% for carboplatin

Other assumptions made in the company's base-case on issues raised by the committee:

- Distribution of subsequent treatments based on Table 1 (NHSE and company's data)
- 2-knot normal OS model for osimertinib monotherapy (as in company's base-case)
- Gamma distribution for TTD on osimertinib monotherapy (as in company's base-case)
- PFS utility value [redacted] (as in company's base-case)
- Approach to modelling treatment-related adverse effects of chemotherapy individually (as in company's base-case) rather than a disutility applied to the osimertinib plus chemotherapy group.

The deterministic results from the company's updated base-case are given in Table 4 and the probabilistic results are given in Table 5.

Table 4: Company's updated base-case: deterministic results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Osimertinib + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£36,655
Osimertinib	[redacted]	[redacted]	[redacted]				

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 5: Company's updated base-case: probabilistic results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Osimertinib + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£39,455
Osimertinib	[redacted]	[redacted]	[redacted]				

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years. Probabilistic analysis after 50,000 iterations run

The company ran two scenarios:

- Using the Weibull TTD model for osimertinib monotherapy (results in Table 6 below)
- Using a [redacted] utility decrement for osimertinib plus chemotherapy for the period when chemotherapy is given (results in Table 7 below)

Table 6: Scenario analysis: company's updated base-case with Weibull TTD model for osimertinib monotherapy (deterministic analysis)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Osimertinib + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£40,964
Osimertinib	[redacted]	[redacted]	[redacted]				

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 7: Scenario analysis: company's updated base-case with utility decrement of XXXX using treatment arm as a covariable (deterministic analysis)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Osimertinib + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£36,537
Osimertinib	[redacted]	[redacted]	[redacted]				

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

4 EAG's UPDATED ANALYSES

4.1 Scenario analyses undertaken by the EAG

The EAG's scenario analyses were applied to the company's updated base-case model received by the EAG on 21/11/2024. The EAG conducted the following scenarios analyses:

- Scenario 1a: Using the distribution of 2L treatments based on Table 2 with 8.2% ABCP use (i.e., correcting the company's calculations)

Scenario 1b: Using the distribution of 2L treatments based on

- Table 3 with 7% ABCP use (as requested by the committee)
- Scenario 2: Using an average of the Gompertz and Gamma TTD models for osimertinib monotherapy (reflecting committee's view)
- Scenario 3: Using 1-knot odds model for osimertinib monotherapy, and 2-knot odds model for osimertinib plus chemotherapy (as a plausible alternative to company's assumption)
- Scenario 4: Using PFS utility value of 0.794 used in TA654 (considered more plausible in comparison with general population values)
- Scenario 5: Using utility decrement of [redacted] for chemotherapy applied over the PFS period (as best data available to inform the decrement in utility due to chemotherapy)

The results from the EAGs scenario analyses are shown in Table 8**Error! Reference source not found.**.

Table 8 EAG's additional scenario analyses applied to the company's updated base-case (deterministic analysis)

No.	Scenario	Incremental Costs	Incremental QALYs	ICER
0	Company's updated base case	[redacted]	[redacted]	£36,655
1a	Using the distribution of 2L treatments based on Table 2 with 8.2% ABCP use	[redacted]	[redacted]	£37,146
1b	Using the distribution of 2L treatments based on Table 3 with 7% ABCP use	[redacted]	[redacted]	£38,131
2	Using an average of the Gompertz and Gamma TTD models for osimertinib monotherapy	[redacted]	[redacted]	£43,311
3	Using 1-knot odds model for osimertinib monotherapy, and 2-knot odds model for osimertinib plus chemotherapy	[redacted]	[redacted]	£44,317
4	Using PFS utility value of 0.794	[redacted]	[redacted]	£38,730
5	Using utility decrement of [redacted] for chemotherapy applied over the PFS period	[redacted]	[redacted]	£40,835

4.2 EAG's updated base-case

The EAG's preferred assumptions are:

- Using the distribution of 2L treatments based on Table 3 with 7% ABCP use (scenario 1b)
- Using an average of the Gompertz and Gamma TTD models for Osimertinib monotherapy (scenario 2)
- Using 1-knot odds model for osimertinib monotherapy OS, and 2-knot odds model for osimertinib plus chemotherapy OS (scenario 3)
- Using PFS utility value of 0.794 (scenario 4)
- Using utility decrement of [redacted] for the osimertinib plus chemotherapy group applied over the whole PFS period (scenario 5)

The results for the EAG's preferred assumptions are shown in Table 9 for deterministic results, with each assumption added incrementally to give the EAG's updated base-case cost-effectiveness results in Table 10. The probabilistic cost-effectiveness results for the EAG's updated base-case are given in Table 11.

Table 9 EAG's updated base-case with incremental scenario results applied to the company's updated base-case (deterministic analysis)

No.	Scenario	Incremental Costs	Incremental QALYs	ICER
0	Company's updated base case	[redacted]	[redacted]	£36,655
1b	Using the distribution of 2L treatments based on Table 2 with 7% ABCP use	[redacted]	[redacted]	£38,131
1b+2	+Using an average of the Gompertz and Gamma TTD models for osimertinib monotherapy	[redacted]	[redacted]	£44,788
1b+2+3	+Using 1-knot odds model for osimertinib monotherapy, and 2-knot odds model for osimertinib plus chemotherapy	[redacted]	[redacted]	£54,488
1b+2+3+4	+Using PFS utility value of 0.794	[redacted]	[redacted]	£58,402
1b+2+3+4+5 **EAG's updated base-case**	+Using utility decrement of [redacted] for chemotherapy applied over the PFS period	[redacted]	[redacted]	£67,691

Table 10 EAG's updated base-case: deterministic results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Osimertinib + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£67,691
Osimertinib	[redacted]	[redacted]	[redacted]				

Table 11 EAG's updated base-case: probabilistic results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Osimertinib + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£67,768
Osimertinib	[redacted]	[redacted]	[redacted]				

Probabilistic analysis after 50,000 iterations run

5 SEVERITY

The company states the severity modifier was not applicable for this submission.

6 REFERENCES

Manca A, Hawkins N, Sculpher MJ. Estimating mean QALYs in trial-based cost-effectiveness analysis: the importance of controlling for baseline utility. Health Econ. 2005. 14(5):487-496.