Single Technology Appraisal

Osimertinib for maintenance treatment of EGFR mutation-positive unresectable locally advanced non-small-cell lung cancer after platinum-based chemoradiotherapy [ID6223]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Osimertinib for maintenance treatment of EGFR mutation-positive unresectable locally advanced non-small-cell lung cancer after platinum-based chemoradiotherapy [ID6223]

Contents:

The following documents are made available to stakeholders:

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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Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Thursday 18 September 2025. 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.	[Insert disclosure here]

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[Insert disclosure here]
Name of commentator person completing form:	[redacted]
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.
1	**Summary** AstraZeneca UK (AZUK) is disappointed that the committee decided not to recommend osimertinib for maintenance treatment of EGFR mutation-positive locally advanced unresectable non-small-cell lung cancer (NSCLC) after platinum-based chemoradiation. This is despite the proven statistically significant progression-free survival (PFS) benefit demonstrated by osimertinib compared to placebo in the LAURA trial (hazard ratio [HR]: 0.16 [95% confidence interval, CI: 0.10, 0.24])(1) , and the current lack of effective treatment options for this patient population, imposing a significant psychological burden on patients who feel like they are currently 'doing nothing' when going through active surveillance following chemoradiation. The benefits for patients of remaining progression-free cannot be understated, with the progression to metastatic disease and associated increase in symptom burden being associated with an immense psychological burden, including death anxiety and demoralisation (2). The committee further acknowledged the efficacy of osimertinib in significantly reducing the burden of CNS disease (CNS PFS HR: 0.17 [95% CI: 0.09, 0.32]) (3)and potential for improving overall survival for patients (updated OS HR: 0.67 [95% CI 0.40, 1.14])(4), the committee preferred assumptions led to the cost-effectiveness model estimating a lower proportion of patients alive when treated with osimertinib compared to best supportive care following chemoradiation after 72 months, which was not considered clinically plausible. This response to the draft guidance will focus on: • Implausibility of crossing OS curves (response 2); • Request for crossover adjustment (response 3); • Clinical plausibility of treatment duration estimates (response 4), and • Appropriateness of model structure (response 5).

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2	**The committee's preferred assumptions led to the crossing of OS curves for osimertinib and placebo, which is clinically implausible. In response to the committee request, we have explored scenarios with various combinations of clinically plausible extrapolations, almost all of which result in ICERs below the £30,000 willingness-to-pay threshold.** The latest overall survival (OS) data cut (data cut-off [DCO] date: 29 Nov 2024) was provided as an addendum to the submission and clearly shows separation between the osimertinib and placebo arms, despite almost two-thirds of all patients randomised to the placebo arm receiving osimertinib as a subsequent therapy in the trial (as of DCO 29 Nov 2024)(4). This benefit was maintained once patients who had received subsequent osimertinib in the osimertinib arm had been adjusted for (see response 3) and demonstrates that there is an OS benefit from moving osimertinib earlier in the treatment pathway, before patients progress to metastatic disease. Moreover, the growing body of evidence from recent osimertinib monotherapy studies in NSCLC (AURA, ADAURA, FLAURA) have consistently demonstrated that delaying disease progression not only postpones the onset of more advanced disease but frequently leads to improved survival outcomes (5-7). This growing body of trial data from first line, second-line and adjuvant settings reinforces the clinical expectation that moving osimertinib earlier in the treatment pathway will also provide benefits for patients beyond disease control, substantiating its role in optimising long-term outcomes in EGFRm NSCLC. In contrast, the combination of curves selected by the committee result in the osimertinib and placebo OS curves crossing at 72 months which implies that patients initially receiving placebo after chemoradiation would experience better long-term survival outcomes than those treated with osimertinib. This scenario was not discussed in the public committee meeting thus feedback was not obtained on the plausibility of this scenario from clinicians, patient experts, the company or the EAG. Nevertheless, since the appraisal meeting, AZUK have conducted additional interviews with five UK clinical experts who unanimously described the crossing curves as clinically implausible, with one adding that it "defied biology"(8). Whilst the committee's preferred assumptions led to a crossing of OS curves, further analyses of the combinations of time to progression (TTP), progression-free survival (PFS) and post-progression survival (PPS) extrapolations, considering the resulting OS predictions, were also requested. In this response, we first describe the extrapolations explored, then provide the resulting combinations of extrapolations for consideration by the committee. *TTP and PFS for osimertinib* • The Weibull curve provided a reasonable statistical and visual fit to the Kaplan-Meier (KM) and hazard curves and was considered the most clinically plausible long-term extrapolation of TTP based on clinical expert opinion. During one-to-one interviews with UK clinical experts with experience in treating NSCLC, four out of five clinicians considered the Weibull curve the most clinically plausible extrapolation of TTP in the osimertinib arm (9). One clinician preferred the more optimistic log-normal curve, which was also considered as a plausible alternative by another clinician. Weibull was therefore considered to be well justified in the base case and potentially conservative compared to other plausible distributions.

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	• Whilst the EAG commented that the Osimertinib [redacted], this observation is based on a low number of patients at risk (n=9 at 42 months), and the tail of the curve could potentially be overinterpreted. This observation may also be visually exaggerated by the y-axis scale of the hazard plot, as the [redacted]. As a result of this observation, the EAG conducted an exploratory scenario using the exponential distribution, describing it in their report as, "the most pessimistic of the seven standard distributions". The EAG ultimately retained the Weibull distribution in their base case analysis, and did not claim to have selected the exponential curve based on clinical plausibility or goodness of fit to the data. • The committee preferred base case differed from the company and the EAG, opting for the exponential model because they believed the Weibull distribution overestimates long-term PFS. The figures quoted in the Draft Guidance were from a global advisory board, which did not constitute a formal validation of the modelled curves. The conversation was broad and global in scope, covering numerous topics rather than focusing specifically on long-term outcomes or curve selection. In contrast, the UK clinical validation exercise was conducted specifically to inform the NICE submission. Given its relevance and focus, the UK validation exercise should take precedent when considering clinical validation of the modelled survival curves. • The exponential distribution does not provide a superior fit to the data compared to the Weibull distribution, nor is it supported by clinical opinion. Therefore, we do not consider this distribution to be representative of long-term TTP/PFS. However, in response to the request made by the committee, we have included it in the combination scenarios with other curve selections alongside the retained company base case (Weibull). We have also included scenarios with the gamma distribution, as this is the only distribution to fall between the Weibull and exponential. • The EAG and company agree that using the same distribution to model both TTP and PFS is a reasonable approach, and this assumption been retained in the scenarios tested. *TTP and PFS for placebo* • The generalised gamma distribution was retained to extrapolate TTP and PFS for placebo as there was alignment of this distribution across the Company, EAG and committee. *PPS for osimertinib* • In the Company base case, the Gompertz distribution was selected as it provides a good statistical fit to the osimertinib data from the LAURA, reflects the [redacted] of post-progression death and was considered the most clinically plausible by UK clinical experts (n/N= 3/5)(9). Some of the clinicians consulted commented that the decline in survival may be too rapid, and two clinicians considered the lognormal curve could be a reasonable approximation as it allowed for some long-term survivors. These same two clinicians also selected a more optimistic extrapolation for the placebo arm (see *PPS for placebo*).

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	• The NICE committee and the EAG agree that Gompertz should be used to model PPS for osimertinib, although also said that exponential is a 'useful scenario' given that Gompertz could be considered pessimistic if some long-term survival occurs. • For the scenarios requested by the committee, combinations testing Gompertz and exponential have been included. As two clinicians interviewed by the Company also explicitly preferred lognormal, this has also been included but only when in combination with using Weibull to model PPS for placebo, as this reflects these clinicians' tendency to favour less conservative survival projections for both arms and retains internal consistency with the distributions selected. *PPS for placebo* • In the Company base case, the Gompertz distribution was selected as it provides a good statistical fit to the placebo data from the LAURA, reflects the [redacted] of post-progression death and was considered the most clinically plausible by UK clinical experts (n/N= 3/5)(9). Similar to the comments made about selections for the osimertinib arm, three of the clinicians consulted thought a more optimistic distribution were plausible (Weibull). Two of these three clinicians also selected a more optimistic extrapolation for the osimertinib arm. • The EAGs commentary on why the Gompertz distribution may not be appropriate was focused on a comparison between mean PPS in LAURA to mean OS from FLAURA (osimertinib in untreated locally advanced or metastatic EGFR-positive NSCLC, appraised in TA654). As stated in the committee meeting, this comparison lacks validity as: o All patients in the osimertinib arm in FLAURA received osimertinib, versus only 82% (51/62) of the patients in the LAURA PPS data (N= 62, as per DCO 5th January 2024), with the remaining patients receiving either no active treatment or a less efficacious subsequent treatment (predominantly 2nd generation TKIs or chemotherapy). This is a critical difference, and contrary to what is stated in the draft guidance, this was not adjusted for in the EAGs comparison. o Not only are the treatments received different across these trials, but patient characteristics differ, some of which are considered prognostic (e.g., prior chemoradiation, disease stage), making a comparison of absolute survival outcomes unreliable. o This interpretation was unanimously supported by UK clinicians (N= 5) consulted during this appraisal who clearly stated that this comparison was inappropriate[i](9). The EAGs rationale for disagreeing with the clinical expert's opinion is not stated. o Notably, this comparison did not inform the long-term extrapolation choices for the osimertinib monotherapy arm in the recent FLAURA-2 appraisal (TA1060) highlighting an inconsistency in approach across appraisals. • Whilst we do not agree with the rationale of selecting Weibull based on attempting to align the LAURA PPS for placebo with the FLAURA OS for osimertinib, we recognise that some of the UK clinicians interviewed preferred a distribution with a tail to reflect patients who experience long-term survival. As explained above (in *PPS for*

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	osimertinib), there was a large degree of overlap between clinicians that favoured a more optimistic distribution for osimertinib in PPS and those that favoured a more optimistic distribution for placebo in PPS. Therefore, we have presented scenarios using Weibull when selecting lognormal for osimertinib. As generalised gamma falls between the Company base case and the EAG and Committee preference, this has also been included in the scenarios. *Results* • The results of these curve combinations are presented in Appendix A Table 1. All analyses are presented using the committee preferred utility values, subsequent treatment proportions and the removal of a maximum treatment duration of 10 years. We have retained the exponential distribution to model time to treatment discontinuation (TTD), as explained in response number 4. • A systematic selection process towards testing the combinations of curves has been adopted, following the guidance outlined in the NICE TSD DSU 14(10) , whilst responding to the request by the committee to perform "further analyses of PFS and TTP extrapolations, taking into account PPS extrapolations and resulting OS predictions". • Results of clinically plausible selections show that osimertinib represents a cost-effective treatment option at a £30,000/QALY willingness-to-pay threshold in almost all scenarios. In the single outlier scenario where the ICER exceeds £30,000, the model essentially predicts no long-term benefit of using osimertinib earlier in the treatment pathway. Given the unprecedented PFS and CNS PFS benefit demonstrated in the LAURA clinical trial, this result should be considered implausible and has been included for completeness only.
3	**Crossover adjustment for subsequent osimertinib in the patients randomised to osimertinib reinforces an overall survival benefit versus placebo in the LAURA trial and further supports the relevance of trial findings for UK clinical practice.** • In the LAURA trial, a small number of patients (N=15 in the first data cut) randomised to osimertinib received subsequent osimertinib treatment after progression. This treatment sequence would not occur in UK clinical practice. Crossover analysis to adjust for this was not explicitly discussed during the public part of the appraisal committee meeting meaning the company, EAG, clinicians and patient experts did not have opportunity to comment on the appropriateness of such an analysis. • Furthermore, the draft guidance states that the "EAG suggested that a crossover adjustment could have been applied to mitigate this issue, but the company did not include one in its submission". This request was not made during the clarification questions and does not feature in the EAG report. [redacted]Given the limited incidence of subsequent osimertinib use in the osimertinib arm in the trial, it was reasonable to expect no meaningful impact on overall survival outcomes. However, in response to the request by the committee in the draft guidance, we have conducted a crossover adjustment analysis, [redacted]

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	[redacted] • The crossover adjustment methodologies considered were the rank preserving structural failure time (RPSFT) method, two-stage estimation (TSE), and inverse probability of censoring weighting (IPCW). IPCW and TSE allow adjustment for treatment switching/subsequent therapy using data solely from the osimertinib arm. The IPCW method requires longitudinal data on prognostic factors, however these data were considered insufficient, particularly following disease progression, and therefore the method could not be implemented. For a TSE approach, it is necessary to identify a disease-related timepoint at which treatment switching occurs, referred to as the 'secondary baseline.' The use of progression as a secondary baseline was considered inappropriate given the lag between progression and subsequent therapy receipt; alternatively, defining a secondary baseline at time of subsequent therapy receipt would then lack the necessary patient covariate data required to account for difference between groups from this point. In addition, the sample sizes and event numbers available at the time of either secondary baseline option for estimation of the acceleration factor were too small. To apply the RPSFT method, the estimated acceleration factor would be utilised to adjust the time on subsequent osimertinib for relevant patients on the osimertinib arm. However, due to the inability to apply IPCW and TSE to account for subsequent osimertinib receipt in the osimertinib arm, the RPSFT method was considered a viable alternative. [redacted]Full methodological details and detailed results are provided in Appendix B. In summary, [redacted] as illustrated in the Kaplan Meier plots (Figure 1 and Figure 2 in Appendix B). For example [redacted]
4	**The company approach to modelling treatment duration for osimertinib is intended to reflect trial evidence and clinical expert consensus , and is considered a pragmatic approach that predicts time on treatment in line with expected UK clinical practice.** • The approach adopted in the company base case was considered to best capture the time on treatment within the LAURA trial whilst extrapolating appropriately and aligning with clinical expectations. Whilst osimertinib is a treat-to-progression regimen, during an online clinical advisory board with eight clinicians, it was discussed that an indefinite duration of osimertinib treatment is unlikely to occur in practice(9). Although osimertinib is considered to have a tolerable safety profile, it is not without toxicity, and clinicians referenced expecting 3-5 years of treatment after which patients may be taken off treatment even if progression-free. The exponential model was considered to capture this gradual decline. However, as this curve provides a poor visual fit to the TTD KM data, a piecewise approach was adopted whereby the observed TTD KM was used directly up to a timepoint where there were

	a small number of patients at risk (month 36). The EAGs claim that this assumption is not supported by the LAURA trial PFS and TTD Kaplan–Meier data does not hold, as the modelling is directly supported by the trial data until 36 months and from an extrapolation derived from the trial data thereafter. • The committee acknowledged that, given the limited availability of long-term data and the clear clinical rationale for not assuming indefinite treatment, the company's piecewise approach may also be plausible for modelling time on treatment. This supports the view that incorporating clinical expert opinion is reasonable and improves the generalisability of the model to anticipated clinical practice. • In addition, to reflect the feedback that patients are unlikely to remain on treatment indefinitely, a maximum modelled treatment period of 10 years was applied. Without this pragmatic assumption, the exponential model used in the company base case predicts that 11% of patients would still be receiving treatment at 10 years, while use of the EAG's preferred Weibull distribution would increase this proportion to 20%. These estimates do not reflect anticipated clinical practice and are therefore considered clinically implausible. • The EAG noted that the maximum modelled treatment period applied in the model only affected treatment costs, and not outcomes. However, the impact on the ICER of adjusting efficacy to reflect this at 10 years is expected to be minimal. • In response to committee and EAG feedback, the scenario results provided in the Appendix were produced adopting an approach without a maximum modelled treatment period, therefore removing the 10-year cap. However, we have maintained the exponential distribution for extrapolating time on treatment beyond the observed trial data. This distribution was selected based on its ability to capture the anticipated gradual decline in treatment duration as noted by clinical experts whilst remaining directly informed by the available trial data. Retaining the exponential distribution ensures that our estimates for time on treatment and associated costs remain more clinically relevant and consistent with the evidence provided by the LAURA trial and expert consultation, although the ICERs provided in the scenarios should be considered conservative and anticipated to overestimate costs given the removal of the maximum treatment duration.
5	**Changing the model structure based on currently available data is not appropriate and would not resolve uncertainty.** • The committee suggest that allowing observed OS data to be directly incorporated into the model, rather than relying on indirectly modelled survival estimates, would reduce uncertainty in modelling assumptions. The draft guidance says that a scenario was requested in which OS is directly modelled using observed OS data (including crossover adjustment), however, this was not raised during the public section of the committee meeting, and there was no discussion on the appropriateness of changing model structure based on the existing evidence base. • Furthermore, the committee concluded that the 3-state semi-Markov model provided by the Company was "reasonable and consistent with models used in other oncology NICE technology appraisals guidance at this line of treatment". The EAG report also stated that the semi-Markov model structure was appropriate.

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	• Changing the model structure to rely on relatively immature OS data would not reliably reduce overall uncertainty. A strength of the semi-Markov structure is that it allows for the OS endpoint to be extrapolated as a function of TTP and PPS, introducing a structural link between mortality and earlier non-fatal events. Furthermore, an STM structure ensures consistency in the long-term model predictions and avoids logical inconsistencies (i.e. PFS and OS crossing), which are common when low maturity data are extrapolated independently in a PSM approach. As provided in the Company Submission (Section B.3.2.2.1), a review of previous NICE technology appraisals shows that a semi-Markov structure is common when OS data is immature. Therefore, we maintain that the semi-Markov structure currently adopted remains the most appropriate approach for addressing these challenges.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- Do not include medical information about yourself or another person from which you or the person could be identified.
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Appendices

Appendix A: Curve selection

The Company base case curve selection is in the top row, indicated by the cells shaded in grey.

Table 1 Curve selection scenarios

PF to PD - Osi	PF to PD - Pbo	PD to Dead - Osi	PD to Dead - Pbo	Incr cost	Incr LY	Incr QALY	ICER
Weibull	Gen gamma	Gompertz	Gompertz	[redacted]	[redacted]	[redacted]	£21,629
Weibull	Gen gamma	Gompertz	Gen gamma	[redacted]	[redacted]	[redacted]	£25,083
Weibull	Gen gamma	Exponential	Gompertz	[redacted]	[redacted]	[redacted]	£18,783
Weibull	Gen gamma	Exponential	Gen gamma	[redacted]	[redacted]	[redacted]	£21,045
Weibull	Gen gamma	Log-normal	Weibull	[redacted]	[redacted]	[redacted]	£21,736
Exponential	Gen gamma	Gompertz	Gompertz	[redacted]	[redacted]	[redacted]	£28,778
Exponential	Gen gamma	Gompertz	Gen gamma	[redacted]	[redacted]	[redacted]	£36,095
Exponential	Gen gamma	Exponential	Gompertz	[redacted]	[redacted]	[redacted]	£23,382
Exponential	Gen gamma	Exponential	Gen gamma	[redacted]	[redacted]	[redacted]	£27,417
Exponential	Gen gamma	Log-normal	Weibull	[redacted]	[redacted]	[redacted]	£28,299
Gamma	Gen gamma	Gompertz	Gompertz	[redacted]	[redacted]	[redacted]	£23,693
Gamma	Gen gamma	Gompertz	Gen gamma	[redacted]	[redacted]	[redacted]	£28,077
Gamma	Gen gamma	Exponential	Gompertz	[redacted]	[redacted]	[redacted]	£20,191
Gamma	Gen gamma	Exponential	Gen gamma	[redacted]	[redacted]	[redacted]	£22,930
Gamma	Gen gamma	Log-normal	Weibull	[redacted]	[redacted]	[redacted]	£23,706

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ICER: incremental cost-effectiveness ratio; Incr: incremental; LY: life year; PD: progressed disease; PF: progression free; QALY: quality adjusted life year

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Appendix B: Crossover adjustment

Methodology

In the LAURA study, patients were randomised 2:1 to osimertinib or placebo. In both treatment groups, a number of patients received subsequent treatment with osimertinib. Overall survival and data on subsequent treatments from LAURA used for this analysis are from the most recent data cut-off (DCO, dated 29 Nov 2024); Table below summarises the use of osimertinib as a subsequent therapy by randomised treatment group.

Table 2 Use of osimertinib as a subsequent therapy by randomised treatment group (DCO: 29 Nov 2024)

Randomised treatment arm	n (% total subjects randomised)*
Osimertinib	[redacted]
Placebo	[redacted]

*includes patients receiving osimertinib as a first or second subsequent treatment

As noted in the committee draft guidance, this treatment sequence is reflective of the treatment pathway in the NHS for patients in the placebo arm of the LAURA trial. The proportion receiving subsequent osimertinib in the placebo arm was considered reflective of UK clinical practice. However, as indicated by UK clinical experts and the current treatment restrictions for patients who have been previously treated for locally advanced/metastatic disease, osimertinib will not be given following progression in patients who received osimertinib treatment following chemoradiation. The committee expressed an interest in the draft guidance on estimating a treatment effect in the absence of subsequent therapy with subsequent osimertinib in the osimertinib arm.

[redacted]

To estimate the effect of subsequent treatment with osimertinib, the rank-preserving structural failure time (RPSFT) method was used. In this case, the estimated acceleration factor for the impact of receiving subsequent osimertinib was estimated using standard RPSFT approaches utilising data from both the placebo and osimertinib arms, and the resulting acceleration factor was then applied to post-switch times for subsequent osimertinib receipt in the intervention arm. The analysis was performed in R and utilised the rpsftm (1.2.9) package. For this method, the causal effect of treatment is estimated using a counterfactual framework, where counterfactual survival times are those that would have been observed if treatment switching, or in this case subsequent treatment with osimertinib, had not occurred. The counterfactual survival times for osimertinib without subsequent osimertinib are equivalent to the time spent on osimertinib plus the time spent on subsequent osimertinib multiplied by an ‘acceleration factor’. This acceleration factor is the degree to which being on subsequent osimertinib changes survival. The RPSFT method assumes a common treatment effect.
Firstly, to estimate the proportion of time on osimertinib for each patient:

- For patients randomised to placebo who did not receive subsequent therapy with osimertinib, the proportion of time on osimertinib is set to 0;

- A 'treatment group' approach was used whereby subjects were considered to be on treatment until death/censoring for OS.
    - For patients randomised to placebo who did receive subsequent therapy with osimertinib, the proportion of time on osimertinib is calculated as (OS time - time prior to subsequent therapy) / OS time;
    - For patients randomised to osimertinib, the proportion of time on osimertinib is set to 1.

Secondly, the acceleration factor (or psi Ψ) is estimated. The exponential of psi is the amount that we multiply post-switch times by to 'accelerate' them to account for survival having been extended by the receipt of subsequent therapy. For patients randomised to osimertinib, the post-subsequent therapy times are adjusted using the psi parameter, and then the adjusted KM curves are generated.

The analysis is conducted both with and without recensoring. For patients receiving subsequent therapy who are censored for overall survival (i.e., alive at the data cut-off), censoring times must be adjusted. This selective adjustment induces informative censoring, violating the standard assumption of non-informative censoring in survival analysis. To address this, recensoring is applied whereby the acceleration factor is used to modify the administrative censoring time (from randomisation to data cut-off). Patients with events or censoring beyond this recalibrated time are administratively censored at their new accelerated censoring point.

Results

The acceleration factor (psi) is provided in Table . For patients randomised to osimertinib, the post-subsequent therapy times are adjusted using the exp(psi) parameter.

Table 3 Acceleration factor, psi (Ψ)

Method	psi (95% CI)	exp(psi) (95% CI)
Without recensoring	[redacted]	[redacted]
With recensoring	[redacted]	[redacted]

CI: confidence interval

The resulting KM OS curves showing osimertinib with and without adjustment, alongside the placebo arm, are provided in Figure 1 (without recensoring) and Figure 2 (with recensoring).

Figure 1 LAURA FAS OS with and without adjustment for subsequent osimertinib in the osimertinib arm (no recensoring)

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Figure 2 LAURA FAS OS with and without adjustment for subsequent osimertinib in the osimertinib arm (with recensoring)

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	EGFR+ UK

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Name of commentator person completing form:	[redacted]

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.
Example 1	We are concerned that this recommendation may imply that ……..

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1	It seems clear to us that maintenance Osimertinib following chemoradiation can extend PFS and reduce CNS disease burden in patients, while having predictable and manageable side-effects that minimally interfere with patients' ability to life 'normal' lives – something which is of the utmost importance to patients.
2	We are worried that the significant impact that this guidance is likely to have on the wellbeing of patients who find themselves in this situation has not been fully taken into account. Not having access to maintenance treatment that has been showed to prolong PFS is hugely upsetting for EGFR patients in this situation, and the impact on Quality of Life is significant. Furthermore, the fear associated with recurrence/progression should not be underestimated – something maintenance treatment can help reduce by giving patients a sense of control (i.e. that they are doing something to prevent this happening) and alleviate some of their psychological distress. This is perhaps best illustrated by the following testimony from one of our patients: *I was 40 when I was diagnosed with EGFR+ lung cancer. I had recently moved in with my partner and we were considering starting a family. I had* [redacted] *At the time of diagnosis I was told I was stage 3b and so prescribed a radical course of chemoradiation. This brutal regime knocked me for six; the consequences of the side effects meant I lost my job, and stopped running. During this treatment I was also given Zoladex to protect my ovaries. After the radiotherapy, and because the cancer I have is PD-L1 positive, I was offered immunotherapy. This is despite trials showing no significant difference in outcomes compared to chemoradiation alone in EGFR+ patients. My thinking at the time, however, was to go along with the 'belt & braces' approach explained by my oncologist. And so last August I began a year of monthly Durvalumab infusions.* *After only six months, an MRI to my brain revealed an 8mm lesion - stage 4, incurable.* *I began on Osimertinib immediately followed by consolidative gamma knife therapy two weeks later - that was January this year. Thankfully, since then my scans have shown been stable. Osimertinib is working. This tells me that if I had started Osimertinib after chemoradiation, I would be living with a curative prognosis - without any brain progression. Me and my partner could make plans for our future - a family, work, marathons. A stage 4 diagnosis has changed everything.* *I saw a friend recently who was diagnosed at stage 3 and offered Osi for 3 years (after localised treatment - a lobectomy as opposed to my radiation). She is almost at the end of her 3 years, which is of course, terrifying, but her view of the future is one full of curative hope. Very different to mine.* *The idea that Osimertinib may not be made available to patients who will find themselves in the same situation as me triggers many upsetting emotions. I know I can not live in 'what if's' for my own sake, but am forced to ask the painful question to stop it happening to others.*

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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.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Liverpool Reviews and Implementations Group (EAG)

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None.
Name of commentator person completing form:	[redacted]

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.
1	The EAG has identified an inaccuracy in section 3.9: Original "..with a mean **PPS** of around 56 to 60 months in TA654." Suggested correction "..with a mean **survival** of around 56 to 60 months in TA654."

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2	The EAG also suggests two amendments to improve accuracy and clarity: *Section 3.9* Original "…in line with OS seen in previous relevant NICE's technology appraisals guidance such as on osimertinib for untreated EGFRm-positive NSCLC (from here TA654)." Suggested amendment "…in line with modelled OS estimates in previous relevant NICE's technology appraisals guidance such as on osimertinib for untreated EGFRm-positive NSCLC (from here TA654)." *Section 3.12* Original "In the EAG's base case, osimertinib drug acquisition costs were calculated using the minimum of PFS and TTD." Suggested amendment "In the company and EAG's base cases, osimertinib drug acquisition costs were calculated using the minimum of PFS and TTD."
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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments

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without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.

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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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Name of commentator person completing form:	[redacted]
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.
1	**Summary** AstraZeneca UK (AZUK) is disappointed that the committee decided not to recommend osimertinib for maintenance treatment of EGFR mutation-positive locally advanced unresectable non-small-cell lung cancer (NSCLC) after platinum-based chemoradiation. This is despite the proven statistically significant progression-free survival (PFS) benefit demonstrated by osimertinib compared to placebo in the LAURA trial (hazard ratio [HR]: 0.16 [95% confidence interval, CI: 0.10, 0.24])(1) , and the current lack of effective treatment options for this patient population, imposing a significant psychological burden on patients who feel like they are currently 'doing nothing' when going through active surveillance following chemoradiation. The benefits for patients of remaining progression-free cannot be understated, with the progression to metastatic disease and associated increase in symptom burden being associated with an immense psychological burden, including death anxiety and demoralisation (2). The committee further acknowledged the efficacy of osimertinib in significantly reducing the burden of CNS disease (CNS PFS HR: 0.17 [95% CI: 0.09, 0.32]) (3)and potential for improving overall survival for patients (updated OS HR: 0.67 [95% CI 0.40, 1.14])(4), the committee preferred assumptions led to the cost-effectiveness model estimating a lower proportion of patients alive when treated with osimertinib compared to best supportive care following chemoradiation after 72 months, which was not considered clinically plausible. This response to the draft guidance will focus on: • Implausibility of crossing OS curves (response 2); • Request for crossover adjustment (response 3); • Clinical plausibility of treatment duration estimates (response 4), and • Appropriateness of model structure (response 5).
EAG response	No comment.
2	**The committee's preferred assumptions led to the crossing of OS curves for osimertinib and placebo, which is clinically implausible. In response to the committee request, we have explored scenarios with various combinations of clinically plausible extrapolations, almost all of which result in ICERs below the £30,000 willingness-to-pay threshold.** The latest overall survival (OS) data cut (data cut-off [DCO] date: 29 Nov 2024) was provided as an addendum to the submission and clearly shows separation between the

	osimertinib and placebo arms, despite almost two-thirds of all patients randomised to the placebo arm receiving osimertinib as a subsequent therapy in the trial (as of DCO 29 Nov 2024)(4). This benefit was maintained once patients who had received subsequent osimertinib in the osimertinib arm had been adjusted for (see response 3) and demonstrates that there is an OS benefit from moving osimertinib earlier in the treatment pathway, before patients progress to metastatic disease. Moreover, the growing body of evidence from recent osimertinib monotherapy studies in NSCLC (AURA, ADAURA, FLAURA) have consistently demonstrated that delaying disease progression not only postpones the onset of more advanced disease but frequently leads to improved survival outcomes (5-7). This growing body of trial data from first line, second-line and adjuvant settings reinforces the clinical expectation that moving osimertinib earlier in the treatment pathway will also provide benefits for patients beyond disease control, substantiating its role in optimising long-term outcomes in EGFRm NSCLC. In contrast, the combination of curves selected by the committee result in the osimertinib and placebo OS curves crossing at 72 months which implies that patients initially receiving placebo after chemoradiation would experience better long-term survival outcomes than those treated with osimertinib. This scenario was not discussed in the public committee meeting thus feedback was not obtained on the plausibility of this scenario from clinicians, patient experts, the company or the EAG. Nevertheless, since the appraisal meeting, AZUK have conducted additional interviews with five UK clinical experts who unanimously described the crossing curves as clinically implausible, with one adding that it “defied biology”(8). Whilst the committee’s preferred assumptions led to a crossing of OS curves, further analyses of the combinations of time to progression (TTP), progression-free survival (PFS) and post-progression survival (PPS) extrapolations, considering the resulting OS predictions, were also requested. In this response, we first describe the extrapolations explored, then provide the resulting combinations of extrapolations for consideration by the committee. *TTP and PFS for osimertinib* • The Weibull curve provided a reasonable statistical and visual fit to the Kaplan-Meier (KM) and hazard curves and was considered the most clinically plausible long-term extrapolation of TTP based on clinical expert opinion. During one-to-one interviews with UK clinical experts with experience in treating NSCLC, four out of five clinicians considered the Weibull curve the most clinically plausible extrapolation of TTP in the osimertinib arm (9). One clinician preferred the more optimistic log-normal curve, which was also considered as a plausible alternative by another clinician. Weibull was therefore considered to be well justified in the base case and potentially conservative compared to other plausible distributions. • Whilst the EAG commented that the osimertinib [redacted], this observation is based on a low number of patients at risk (n=9 at 42 months), and the tail of the curve could potentially be overinterpreted. This observation may also be visually exaggerated by the y-axis scale of the hazard plot, as the [redacted]. As a result of this observation, the EAG conducted an exploratory scenario using the exponential distribution, describing it in their report as, “the most pessimistic of the seven standard distributions”. The

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	EAG ultimately retained the Weibull distribution in their base case analysis, and did not claim to have selected the exponential curve based on clinical plausibility or goodness of fit to the data. • The committee preferred base case differed from the company and the EAG, opting for the exponential model because they believed the Weibull distribution overestimates long-term PFS. The figures quoted in the Draft Guidance were from a global advisory board, which did not constitute a formal validation of the modelled curves. The conversation was broad and global in scope, covering numerous topics rather than focusing specifically on long-term outcomes or curve selection. In contrast, the UK clinical validation exercise was conducted specifically to inform the NICE submission. Given its relevance and focus, the UK validation exercise should take precedent when considering clinical validation of the modelled survival curves. • The exponential distribution does not provide a superior fit to the data compared to the Weibull distribution, nor is it supported by clinical opinion. Therefore, we do not consider this distribution to be representative of long-term TTP/PFS. However, in response to the request made by the committee, we have included it in the combination scenarios with other curve selections alongside the retained company base case (Weibull). We have also included scenarios with the gamma distribution, as this is the only distribution to fall between the Weibull and exponential. • The EAG and company agree that using the same distribution to model both TTP and PFS is a reasonable approach, and this assumption been retained in the scenarios tested. *TTP and PFS for placebo* • The generalised gamma distribution was retained to extrapolate TTP and PFS for placebo as there was alignment of this distribution across the Company, EAG and committee. *PPS for osimertinib* • In the Company base case, the Gompertz distribution was selected as it provides a good statistical fit to the osimertinib data from the LAURA, reflects the [redacted] of post-progression death and was considered the most clinically plausible by UK clinical experts (n/N= 3/5)(9). Some of the clinicians consulted commented that the decline in survival may be too rapid, and two clinicians considered the lognormal curve could be a reasonable approximation as it allowed for some long-term survivors. These same two clinicians also selected a more optimistic extrapolation for the placebo arm (see *PPS for placebo*). • The NICE committee and the EAG agree that Gompertz should be used to model PPS for osimertinib, although also said that exponential is a 'useful scenario' given that Gompertz could be considered pessimistic if some long-term survival occurs. • For the scenarios requested by the committee, combinations testing Gompertz and exponential have been included. As two clinicians interviewed by the

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	Company also explicitly preferred lognormal, this has also been included but only when in combination with using Weibull to model PPS for placebo, as this reflects these clinicians' tendency to favour less conservative survival projections for both arms and retains internal consistency with the distributions selected. *PPS for placebo* • In the Company base case, the Gompertz distribution was selected as it provides a good statistical fit to the placebo data from the LAURA, reflects the [redacted] of post-progression death and was considered the most clinically plausible by UK clinical experts (n/N= 3/5)(9). Similar to the comments made about selections for the osimertinib arm, three of the clinicians consulted thought a more optimistic distribution were plausible (Weibull). Two of these three clinicians also selected a more optimistic extrapolation for the osimertinib arm. • The EAGs commentary on why the Gompertz distribution may not be appropriate was focused on a comparison between mean PPS in LAURA to mean OS from FLAURA (osimertinib in untreated locally advanced or metastatic EGFR-positive NSCLC, appraised in TA654). As stated in the committee meeting, this comparison lacks validity as: o All patients in the osimertinib arm in FLAURA received osimertinib, versus only 82% (51/62) of the patients in the LAURA PPS data (N= 62, as per DCO 5th January 2024), with the remaining patients receiving either no active treatment or a less efficacious subsequent treatment (predominantly 2nd generation TKIs or chemotherapy). This is a critical difference, and contrary to what is stated in the draft guidance, this was not adjusted for in the EAGs comparison. o Not only are the treatments received different across these trials, but patient characteristics differ, some of which are considered prognostic (e.g., prior chemoradiation, disease stage), making a comparison of absolute survival outcomes unreliable. o This interpretation was unanimously supported by UK clinicians (N= 5) consulted during this appraisal who clearly stated that this comparison was inappropriate[i](9). The EAGs rationale for disagreeing with the clinical expert's opinion is not stated. o Notably, this comparison did not inform the long-term extrapolation choices for the osimertinib monotherapy arm in the recent FLAURA-2 appraisal (TA1060) highlighting an inconsistency in approach across appraisals. • Whilst we do not agree with the rationale of selecting Weibull based on attempting to align the LAURA PPS for placebo with the FLAURA OS for osimertinib, we recognise that some of the UK clinicians interviewed preferred a distribution with a tail to reflect patients who experience long-term survival. As explained above (in *PPS for osimertinib)*, there was a large degree of overlap between clinicians that favoured a more optimistic distribution for osimertinib in PPS and those that favoured a more optimistic distribution for placebo in PPS. Therefore, we have presented scenarios using Weibull when selecting lognormal for osimertinib. As generalised gamma falls between the Company base case and the EAG and Committee preference, this has also been included in the scenarios.

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	Results • The results of these curve combinations are presented in Appendix A Table 1. All analyses are presented using the committee preferred utility values, subsequent treatment proportions and the removal of a maximum treatment duration of 10 years. We have retained the exponential distribution to model time to treatment discontinuation (TTD), as explained in response number 4. • A systematic selection process towards testing the combinations of curves has been adopted, following the guidance outlined in the NICE TSD DSU 14(10) , whilst responding to the request by the committee to perform "further analyses of PFS and TTP extrapolations, taking into account PPS extrapolations and resulting OS predictions". • Results of clinically plausible selections show that osimertinib represents a cost-effective treatment option at a £30,000/QALY willingness-to-pay threshold in almost all scenarios. In the single outlier scenario where the ICER exceeds £30,000, the model essentially predicts no long-term benefit of using osimertinib earlier in the treatment pathway. Given the unprecedented PFS and CNS PFS benefit demonstrated in the LAURA clinical trial, this result should be considered implausible and has been included for completeness only.
EAG response	The EAG considers that the osimertinib treatment duration estimate for patients initially treated with BSC who have experienced disease progression should inform PPS estimates in the cost effectiveness model. The company model assumes that patients treated with BSC who receive osimertinib post-progression will remain on treatment for longer than patients who are progression-free in the metastatic setting; this assumption was based upon clinical advice to the company and a comparison of median PPS in the LAURA trial (placebo: 41.8 months) with median OS in the FLAURA2 trial (osimertinib monotherapy: 36.7 months) (CS, p137). The EAG considered that this was a reasonable assumption but that the company's modelling of PPS did not account for prolonged osimertinib treatment duration and so revised PPS on this basis (EAG report, Section 6.2.1). The EAG has presented a scenario that uses a shorter osimertinib treatment duration and, accordingly, a more pessimistic distribution to model PPS than preferred by the NICE AC. These assumptions may be more representative of LAURA trial data but suggest that osimertinib treatment duration and survival are similar to patients in the first-line metastatic setting which is not consistent with clinical advice to the company and the NICE AC. The EAG considers that both osimertinib treatment duration and survival for patients who have experienced disease progression in the LAURA trial placebo arm are highly uncertain. *TTP and PFS for osimertinib* The EAG considers that the exponential distribution is a plausible alternative to the Weibull distribution as both distributions have similar statistical fit (EAG report, Table 25) and the exponential distribution was the only distribution to produce a 10-year PFS estimate within the range estimated by clinicians consulted by the company at a global advisory board. The

	company's statement that the EAG, "did not claim to have selected the exponential curve based on clinical plausibility or goodness of fit to the data" is therefore not accurate. The company argues that clinical opinion from a UK advisory board is more relevant than a global advisory board but clinical advice to the NICE AC was that the 5-year and 10-year PFS estimates produced by the Weibull distribution were too high, consistent with the survival estimates from the global advisory board. Given the difference in clinical opinion, the EAG considers that further LAURA trial data are needed to inform how the shape of the hazard changes over time and to help assess the plausibility of different long-term TTP/PFS estimates. *PPS for placebo* The EAG would like to clarify that the mean osimertinib treatment duration estimate in Table 24 of the EAR was adjusted to account for patients who did not receive osimertinib post progression ([redacted] months multiplied by the proportion of patients receiving osimertinib as a subsequent treatment [82%] = [redacted] months). The company have consulted clinicians as to the comparability of the LAURA and FLAURA trials and maintain that any comparison is inappropriate. The EAG highlights that a similar comparison was made by the company to calculate the mean osimertinib treatment duration estimate used in the model. Osimertinib treatment duration in the company model ([redacted] months) was calculated using FLAURA2 trial data (modelled mean treatment duration osimertinib monotherapy arm: [redacted] months). This estimate was increased by [redacted] months based on the following clinical advice to the company (CS, p137): "In the one-to-one interviews conducted in November 2024, four out of five clinicians stated that they would expect placebo patients in the PPS setting in LAURA who receive osimertinib to be on treatment longer than those in the progression-free setting in FLAURA or FLAURA2, driven by the higher median PPS in LAURA (41.8 months) compared with osimertinib monotherapy OS in FLAURA2 (36.7 months)." The rationale provided by clinicians supports the EAG's view that osimertinib treatment duration is prognostic of survival and that PPS for patients in the LAURA trial placebo arm is expected to be higher than survival of patients in the first-line metastatic setting. Furthermore, the company's position that trials in the metastatic setting are not comparable to the LAURA trial and cannot be used to validate survival estimates is contradicted by the data sources and methodology used to derive osimertinib treatment duration. The company has not provided an explanation as to why PPS for patients in the LAURA trial placebo arm would be worse than survival of patients in the first-line metastatic setting, when only 44.4% of patients had metastatic disease upon progression in the LAURA trial and 82% of patients are assumed to remain on osimertinib treatment for longer than patients with metastatic disease. The EAG considers that osimertinib treatment duration and PPS for patients initially treated with BSC is highly uncertain and has presented an analysis using a shorter osimertinib treatment duration of [redacted] months (as observed in the LAURA trial at the January 2024 DCO) and accordingly, a more pessimistic distribution to model PPS (generalised gamma). Results for this scenario and further discussion are presented in Appendix C.

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	PPS for osimertinib The EAG considers it is reasonable to select a more optimistic distribution to model PPS for patients treated with osimertinib if the Weibull distribution is used to model PPS for patients receiving BSC. Using the log-normal distribution to model PPS for patients treated with osimertinib generates a mean PPS estimate of [redacted] months. This is significantly above the implied survival after progression on osimertinib for patients initially treated with BSC when using the Weibull distribution to model PPS ([redacted] months). The EAG's rationale for selecting the exponential distribution in an exploratory scenario was to increase mean PPS in the osimertinib arm (to [redacted] months) such that survival after progression on osimertinib is similar between the LAURA trial treatment arms. Clinical opinion as to whether survival after progression on osimertinib is expected to be similar between treatment arms would help to inform curve selection for PPS. *Results* The EAG does not consider the scenarios presented by the company to be informative as curve selection for LAURA trial placebo arm PPS does not consider the mean osimertinib treatment duration assumed in the model. The updated company base case uses the NICE AC-preferred assumptions for subsequent treatment proportions, which increases the proportion of patients initially treated with BSC receiving osimertinib post-progression in the company model (from [redacted]% to [redacted]%). However, PPS for patients treated with BSC remains unchanged; the EAG does not consider this to be plausible.
3	**Crossover adjustment for subsequent osimertinib in the patients randomised to osimertinib reinforces an overall survival benefit versus placebo in the LAURA trial and further supports the relevance of trial findings for UK clinical practice.** • In the LAURA trial, a small number of patients (N=15 in the first data cut) randomised to osimertinib received subsequent osimertinib treatment after progression. This treatment sequence would not occur in UK clinical practice. Crossover analysis to adjust for this was not explicitly discussed during the public part of the appraisal committee meeting meaning the company, EAG, clinicians and patient experts did not have opportunity to comment on the appropriateness of such an analysis. • Furthermore, the draft guidance states that the "EAG suggested that a crossover adjustment could have been applied to mitigate this issue, but the company did not include one in its submission". This request was not made during the clarification questions and does not feature in the EAG report. • Given the limited incidence of subsequent osimertinib use in the osimertinib arm in the trial, it was reasonable to expect no meaningful impact on overall survival outcomes. However, in response to the request by the committee in the draft guidance, we have conducted a crossover adjustment analysis, [redacted]

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	[redacted] • The crossover adjustment methodologies considered were the rank preserving structural failure time (RPSFT) method, two-stage estimation (TSE), and inverse probability of censoring weighting (IPCW). IPCW and TSE allow adjustment for treatment switching/subsequent therapy using data solely from the osimertinib arm. The IPCW method requires longitudinal data on prognostic factors, however these data were considered insufficient, particularly following disease progression, and therefore the method could not be implemented. For a TSE approach, it is necessary to identify a disease-related timepoint at which treatment switching occurs, referred to as the 'secondary baseline.' The use of progression as a secondary baseline was considered inappropriate given the lag between progression and subsequent therapy receipt; alternatively, defining a secondary baseline at time of subsequent therapy receipt would then lack the necessary patient covariate data required to account for difference between groups from this point. In addition, the sample sizes and event numbers available at the time of either secondary baseline option for estimation of the acceleration factor were too small. To apply the RPSFT method, the estimated acceleration factor would be utilised to adjust the time on subsequent osimertinib for relevant patients on the osimertinib arm. However, due to the inability to apply IPCW and TSE to account for subsequent osimertinib receipt in the osimertinib arm, the RPSFT method was considered a viable alternative. • Full methodological details and detailed results are provided in Appendix B. In summary, [redacted] as illustrated in the Kaplan Meier plots (Figure 1 and Figure 2 in Appendix B). For example, [redacted]
EAG response	The EAG notes that the company's analysis approach (RPSFT method) assumes that the effect of osimertinib is the same whether it's a patient's first exposure (after switching from placebo) or rechallenge (after progression on osimertinib). The EAG considers that it is unlikely that this assumption is valid; however, if the true effect of osimertinib is greater for patients switching from placebo to osimertinib than for patients who receive subsequent treatment with osimertinib, then the company's adjusted treatment effect for osimertinib versus placebo is conservative. The EAG also notes that the company's adjusted OS treatment effects (with and without recensoring) are [redacted]. As the adjusted treatment effects are likely to be conservative and additionally, [redacted].
4	**The company approach to modelling treatment duration for osimertinib is intended to reflect trial evidence and clinical expert consensus , and is considered a pragmatic approach that predicts time on treatment in line with expected UK clinical practice.** • The approach adopted in the company base case was considered to best capture the time on treatment within the LAURA trial whilst extrapolating appropriately and

	aligning with clinical expectations. Whilst osimertinib is a treat-to-progression regimen, during an online clinical advisory board with eight clinicians, it was discussed that an indefinite duration of osimertinib treatment is unlikely to occur in practice(9). Although osimertinib is considered to have a tolerable safety profile, it is not without toxicity, and clinicians referenced expecting 3-5 years of treatment after which patients may be taken off treatment even if progression-free. The exponential model was considered to capture this gradual decline. However, as this curve provides a poor visual fit to the TTD KM data, a piecewise approach was adopted whereby the observed TTD KM was used directly up to a timepoint where there were a small number of patients at risk (month 36). The EAGs claim that this assumption is not supported by the LAURA trial PFS and TTD Kaplan–Meier data does not hold, as the modelling is directly supported by the trial data until 36 months and from an extrapolation derived from the trial data thereafter. • The committee acknowledged that, given the limited availability of long-term data and the clear clinical rationale for not assuming indefinite treatment, the company's piecewise approach may also be plausible for modelling time on treatment. This supports the view that incorporating clinical expert opinion is reasonable and improves the generalisability of the model to anticipated clinical practice. • In addition, to reflect the feedback that patients are unlikely to remain on treatment indefinitely, a maximum modelled treatment period of 10 years was applied. Without this pragmatic assumption, the exponential model used in the company base case predicts that 11% of patients would still be receiving treatment at 10 years, while use of the EAG's preferred Weibull distribution would increase this proportion to 20%. These estimates do not reflect anticipated clinical practice and are therefore considered clinically implausible. • The EAG noted that the maximum modelled treatment period applied in the model only affected treatment costs, and not outcomes. However, the impact on the ICER of adjusting efficacy to reflect this at 10 years is expected to be minimal. • In response to committee and EAG feedback, the scenario results provided in the Appendix were produced adopting an approach without a maximum modelled treatment period, therefore removing the 10-year cap. However, we have maintained the exponential distribution for extrapolating time on treatment beyond the observed trial data. This distribution was selected based on its ability to capture the anticipated gradual decline in treatment duration as noted by clinical experts whilst remaining directly informed by the available trial data. Retaining the exponential distribution ensures that our estimates for time on treatment and associated costs remain more clinically relevant and consistent with the evidence provided by the LAURA trial and expert consultation, although the ICERs provided in the scenarios should be considered conservative and anticipated to overestimate costs given the removal of the maximum treatment duration.
EAG response	The EAG does not agree that the company's approach reflects the trial evidence as there is no separation between the LAURA trial PFS and TTD K-M curves. The separation occurs at the timepoint the exponential distribution is used to extrapolate TTD in the model rather than at a timepoint informed by clinical evidence. The EAG considers the company's argument that some patients may discontinue after 3-5 years of progression-free survival is speculative. The company suggests that discontinuation would occur due to accumulation of toxicity but no evidence is presented to

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	support when this may occur and the resulting impact on treatment discontinuation. Moreover, as there is no evidence of any separation between the PFS and TTD curves in the LAURA trial, modelling of this effect in the extrapolation period would likely require subsequent adjustment to TTP and PFS estimates.
5	**Changing the model structure based on currently available data is not appropriate and would not resolve uncertainty.** • The committee suggest that allowing observed OS data to be directly incorporated into the model, rather than relying on indirectly modelled survival estimates, would reduce uncertainty in modelling assumptions. The draft guidance says that a scenario was requested in which OS is directly modelled using observed OS data (including crossover adjustment), however, this was not raised during the public section of the committee meeting, and there was no discussion on the appropriateness of changing model structure based on the existing evidence base. • Furthermore, the committee concluded that the 3-state semi-Markov model provided by the Company was "reasonable and consistent with models used in other oncology NICE technology appraisals guidance at this line of treatment". The EAG report also stated that the semi-Markov model structure was appropriate. • Changing the model structure to rely on relatively immature OS data would not reliably reduce overall uncertainty. A strength of the semi-Markov structure is that it allows for the OS endpoint to be extrapolated as a function of TTP and PPS, introducing a structural link between mortality and earlier non-fatal events. Furthermore, an STM structure ensures consistency in the long-term model predictions and avoids logical inconsistencies (i.e. PFS and OS crossing), which are common when low maturity data are extrapolated independently in a PSM approach. As provided in the Company Submission (Section B.3.2.2.1), a review of previous NICE technology appraisals shows that a semi-Markov structure is common when OS data is immature. Therefore, we maintain that the semi-Markov structure currently adopted remains the most appropriate approach for addressing these challenges.
EAG response	The EAG considers that using currently available data in a partitioned survival model is unlikely to materially reduce uncertainty. OS data maturity at the November 2024 DCO was 31% therefore survival extrapolation uncertainty is likely to persist. The EAG considers that updated subsequent treatment data from the November 2024 DCO would be informative; however, the company were unable to provide this. The EAG considers that a partitioned survival model would be valuable when more mature OS data becomes available and should not be precluded on that basis that it has not been used in previous appraisals.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- 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 paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as '[redacted]' in turquoise, and all information submitted as '[redacted]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
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Appendices

Appendix A: Curve selection

The Company base case curve selection is in the top row, indicated by the cells shaded in grey.

Table 1 Curve selection scenarios

PF to PD - Osi	PF to PD - Pbo	PD to Dead - Osi	PD to Dead - Pbo	Incr cost	Incr LY	Incr QALY	ICER
Weibull	Gen gamma	Gompertz	Gompertz	[redacted]	[redacted]	[redacted]	£21,629
Weibull	Gen gamma	Gompertz	Gen gamma	[redacted]	[redacted]	[redacted]	£25,083
Weibull	Gen gamma	Exponential	Gompertz	[redacted]	[redacted]	[redacted]	£18,783
Weibull	Gen gamma	Exponential	Gen gamma	[redacted]	[redacted]	[redacted]	£21,045
Weibull	Gen gamma	Log-normal	Weibull	[redacted]	[redacted]	[redacted]	£21,736
Exponential	Gen gamma	Gompertz	Gompertz	[redacted]	[redacted]	[redacted]	£28,778
Exponential	Gen gamma	Gompertz	Gen gamma	[redacted]	[redacted]	[redacted]	£36,095
Exponential	Gen gamma	Exponential	Gompertz	[redacted]	[redacted]	[redacted]	£23,382
Exponential	Gen gamma	Exponential	Gen gamma	[redacted]	[redacted]	[redacted]	£27,417
Exponential	Gen gamma	Log-normal	Weibull	[redacted]	[redacted]	[redacted]	£28,299
Gamma	Gen gamma	Gompertz	Gompertz	[redacted]	[redacted]	[redacted]	£23,693
Gamma	Gen gamma	Gompertz	Gen gamma	[redacted]	[redacted]	[redacted]	£28,077
Gamma	Gen gamma	Exponential	Gompertz	[redacted]	[redacted]	[redacted]	£20,191
Gamma	Gen gamma	Exponential	Gen gamma	[redacted]	[redacted]	[redacted]	£22,930
Gamma	Gen gamma	Log-normal	Weibull	[redacted]	[redacted]	[redacted]	£23,706

ICER: incremental cost-effectiveness ratio; Incr: incremental; LY: life year; PD: progressed disease; PF: progression free; QALY: quality adjusted life year

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Appendix B: Crossover adjustment

Methodology

In the LAURA study, patients were randomised 2:1 to osimertinib or placebo. In both treatment groups, a number of patients received subsequent treatment with osimertinib. Overall survival and data on subsequent treatments from LAURA used for this analysis are from the most recent data cut-off (DCO, dated 29 Nov 2024); Table below summarises the use of osimertinib as a subsequent therapy by randomised treatment group.

Table 2 Use of osimertinib as a subsequent therapy by randomised treatment group (DCO: 29 Nov 2024)

Randomised treatment arm	n (% total subjects randomised)*
Osimertinib	[redacted]
Placebo	[redacted]

*includes patients receiving osimertinib as a first or second subsequent treatment

As noted in the committee draft guidance, this treatment sequence is reflective of the treatment pathway in the NHS for patients in the placebo arm of the LAURA trial. The proportion receiving subsequent osimertinib in the placebo arm was considered reflective of UK clinical practice. However, as indicated by UK clinical experts and the current treatment restrictions for patients who have been previously treated for locally advanced/metastatic disease, osimertinib will not be given following progression in patients who received osimertinib treatment following chemoradiation. The committee expressed an interest in the draft guidance on estimating a treatment effect in the absence of subsequent therapy with subsequent osimertinib in the osimertinib arm.

[redacted]

To estimate the effect of subsequent treatment with osimertinib, the rank-preserving structural failure time (RPSFT) method was used. In this case, the estimated acceleration factor for the impact of receiving subsequent osimertinib was estimated using standard RPSFT approaches utilising data from both the placebo and osimertinib arms, and the resulting acceleration factor was then applied to post-switch times for subsequent osimertinib receipt in the intervention arm. The analysis was performed in R and utilised the rpsftm (1.2.9) package. For this method, the causal effect of treatment is estimated using a counterfactual framework, where counterfactual survival times are those that would have been observed if treatment switching, or in this case subsequent treatment with osimertinib, had not occurred. The counterfactual survival times for osimertinib without subsequent osimertinib are equivalent to the time spent on osimertinib plus the time spent on subsequent osimertinib multiplied by an ‘acceleration factor’. This acceleration factor is the degree to which being on subsequent osimertinib changes survival. The RPSFT method assumes a common treatment effect.
Firstly, to estimate the proportion of time on osimertinib for each patient:

- For patients randomised to placebo who did not receive subsequent therapy with osimertinib, the proportion of time on osimertinib is set to 0;

- A 'treatment group' approach was used whereby subjects were considered to be on treatment until death/censoring for OS.
    - For patients randomised to placebo who did receive subsequent therapy with osimertinib, the proportion of time on osimertinib is calculated as (OS time - time prior to subsequent therapy) / OS time;
    - For patients randomised to osimertinib, the proportion of time on osimertinib is set to 1.

Secondly, the acceleration factor (or psi Ψ) is estimated. The exponential of psi is the amount that we multiply post-switch times by to 'accelerate' them to account for survival having been extended by the receipt of subsequent therapy. For patients randomised to osimertinib, the post-subsequent therapy times are adjusted using the psi parameter, and then the adjusted KM curves are generated.

The analysis is conducted both with and without recensoring. For patients receiving subsequent therapy who are censored for overall survival (i.e., alive at the data cut-off), censoring times must be adjusted. This selective adjustment induces informative censoring, violating the standard assumption of non-informative censoring in survival analysis. To address this, recensoring is applied whereby the acceleration factor is used to modify the administrative censoring time (from randomisation to data cut-off). Patients with events or censoring beyond this recalibrated time are administratively censored at their new accelerated censoring point.

Results

The acceleration factor (psi) is provided in Table . For patients randomised to osimertinib, the post-subsequent therapy times are adjusted using the exp(psi) parameter.

Table 3 Acceleration factor, psi (Ψ)

Method	psi (95% CI)	exp(psi) (95% CI)
Without recensoring	[redacted]	[redacted]
With recensoring	[redacted]	[redacted]

CI: confidence interval

The resulting KM OS curves showing osimertinib with and without adjustment, alongside the placebo arm, are provided in Figure 1 (without recensoring) and Figure 2 (with recensoring).

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Figure 1 LAURA FAS OS with and without adjustment for subsequent osimertinib in the osimertinib arm (no recensoring)

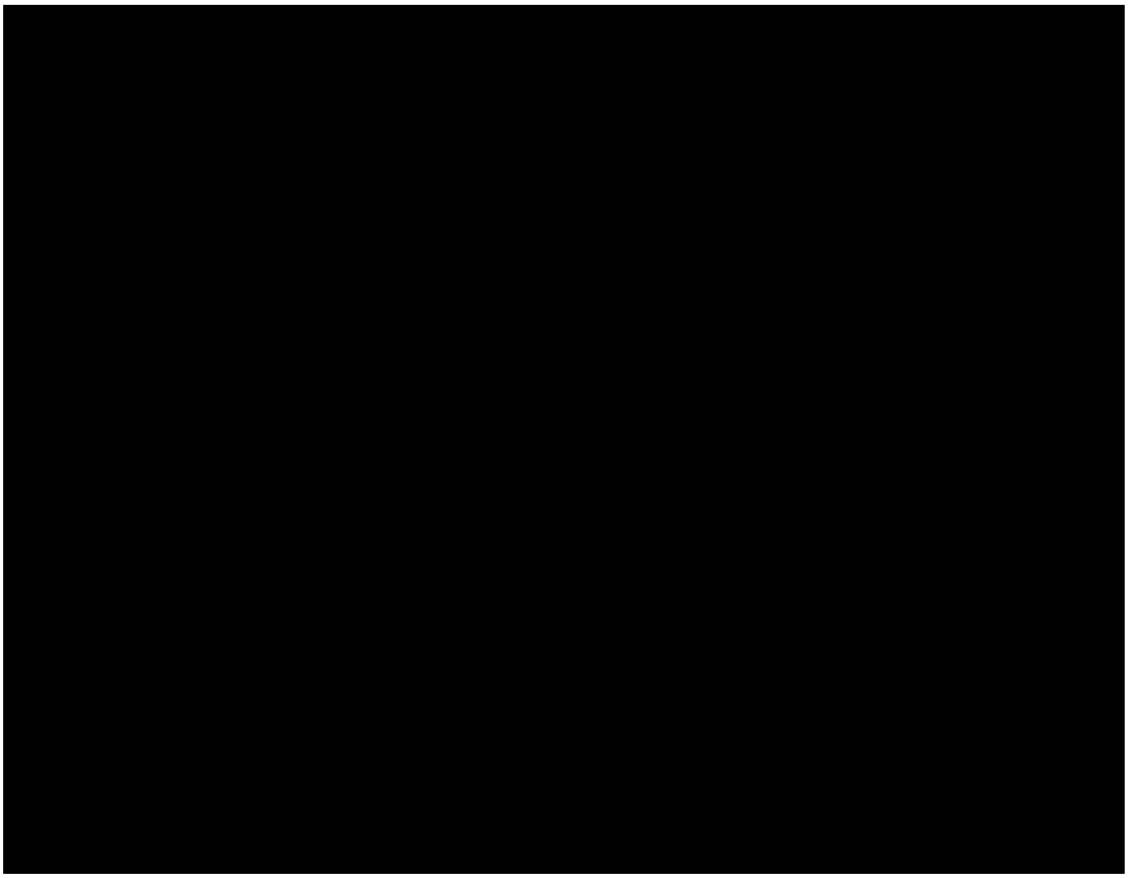

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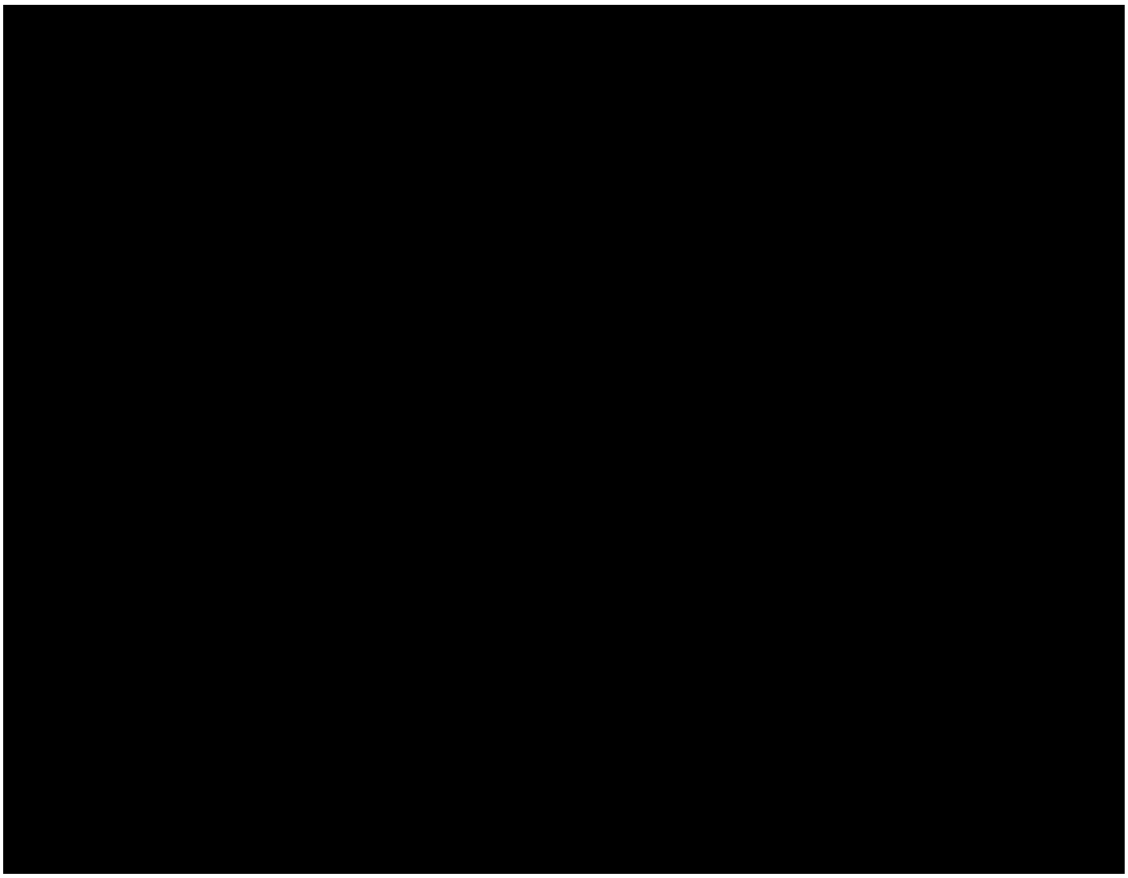
Figure 2 LAURA FAS OS with and without adjustment for subsequent osimertinib in the osimertinib arm (with recensoring)



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Appendix C: EAG analysis

The EAG has presented a scenario with the following changes to the NICE AC-preferred assumptions:

- Osimertinib treatment duration of [redacted] months for patients initially treated with BSC (LAURA trial January 2024 DCO)
- Generalised gamma distribution to generate PPS estimates for patients initially treated with BSC

The EAG considers that patients in the LAURA trial placebo arm may be treated with osimertinib for a similar length of time to patients in the first-line metastatic setting and accordingly, may have similar survival. The EAG highlights that the LAURA trial mean osimertinib treatment duration at the January 2024 DCO was [redacted] months, lower than the modelled mean in the FLAURA2 trial ([redacted] months) but higher than in TA654(11) (21.96 months). The company did not use the LAURA trial estimate in the model as the company considered the data were too immature and considered that treatment duration would be longer compared to patients in the first-line metastatic setting. This assumption was accepted by the EAG.

Updated OS data (November 2024 DCO) presented by the company after the FAC suggests that survival may be overestimated in the company base case for patients in the LAURA trial placebo arm (Gompertz used to model PPS). The EAG highlights that there is a marked decline in the LAURA trial placebo arm K-M estimate at the November 2024 DCO; OS declined from 73% at 3 years to 52% at 4 years (4). Such a sharp decline in the survival function suggests rapid disease progression and accordingly, a much shorter osimertinib treatment duration than assumed by the company. The company was unable to provide any further data from the November 2024 DCO to explain the change in LAURA trial OS K-M data and to verify whether osimertinib treatment duration was consistent with the estimate used in the company model or the estimate from the LAURA trial January 2024 DCO.

Given the uncertainty as to the mean osimertinib treatment duration, the EAG has used the estimate from the January 2024 DCO, consistent with the data used in the company model to estimate PPS.

The generalised gamma distribution was selected as: it produces PPS estimates broadly in line with survival estimates from TA654(11); statistical fit is similar to the Weibull and Gompertz distributions (Table 36 CS) and the 10-]year OS estimate ([redacted]) approximates the midpoint of the estimates suggested by clinicians ([redacted] and [redacted]) consulted by the company in response to draft guidance (8). The 5-year OS estimate ([redacted]) is above the estimates provided by two clinicians ([redacted] and [redacted]).

In this scenario, the adjusted osimertinib treatment duration for patients in the progressed disease health state is similar to TA654 (Table 2). PPS is slightly worse than expected survival in TA654; since patients in the LAURA trial placebo arm have on average less advanced disease upon progression than patients in the first-line metastatic setting, the EAG considers that the PPS estimate may be pessimistic.

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Table 2 Comparison of mean survival in PD state for patients initially treated with BSC and mean survival for patients treated with osimertinib as first-line treatment in metastatic setting

	Mean survival (undiscounted, months)			
	Best supportive care (post-progression)			Osimertinib (TA654(11))
	Updated company base case (Gompertz)	NICE AC preferred (Weibull)	EAG scenario (Generalised gamma)	AC-preferred assumptions
Osimertinib treatment duration	[redacted][a]	[redacted][a]	[redacted][a]	21.96
Mean survival after discontinuing osimertinib (+ mean survival for patients who do not receive osimertinib)	[redacted]	[redacted]	[redacted]	34.19 to 38.26
Total survival	[redacted]	[redacted]	[redacted]	56.15 to 60.22

[a] Adjusted to account for the proportion of patients who did not receive osimertinib after progression
AC=appraisal committee; BSC=best supportive care; EAG=External Assessment Group; PD=progressed disease
Source: company clarification model and TA654(11)

The EAG has plotted the different OS curves implied by the different distributions used to model PPS for patients receiving BSC in Figure 3. The LAURA trial OS K-M data (January 2024 DCO) is plotted up to 39 months as few patients (n=15) remain at risk beyond this timepoint in the placebo arm and the K-M estimate can become unstable. Given the data immaturity, there is no substantial difference in visual fit to the LAURA trial OS K-M data across the distributions used to model PPS but extrapolations vary considerably.

Cost effectiveness results for the updated company base case, NICE AC-preferred assumptions and EAG analysis are presented in Table 3.

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Figure 3 Comparison of OS for different distributions used to model PPS in the LAURA trial placebo arm

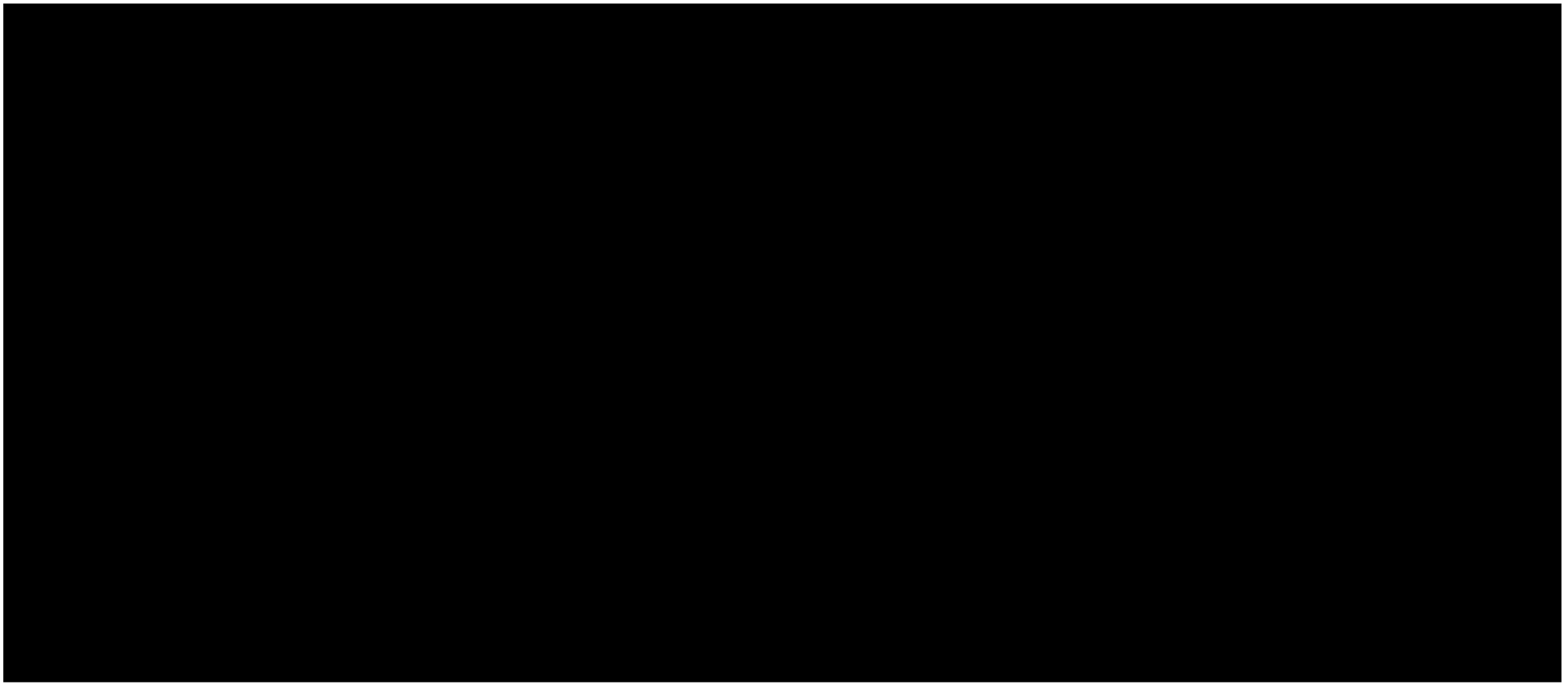

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Table 3 Deterministic cost effectiveness results: osimertinib versus best supportive care (osimertinib PAS and CAA prices)

Scenario/EAG revisions	Osimertinib		BSC		Incremental		ICER (£/QALY)	Change from base case
	Cost	QALYs	Cost	QALYs	Cost	QALYs		
A1. Updated company base case post-ACM1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£21,629**	**-**
R1) Exponential distribution to generate TTP and PFS estimates for patients treated with osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£28,778**	**£7,150**
R2) Osimertinib TTD estimates generated using the same distribution selected for PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£33,620**	**£11,992**
R3) Weibull distribution to generate PPS estimates for patients receiving BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£41,359**	**£19,731**
R4) Generalised gamma distribution to generate PPS estimates for patients receiving BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£25,083**	**£3,454**
R5) Osimertinib treatment duration for patients initially treated with BSC informed by LAURA trial	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£30,921**	**£9,292**
B. NICE AC-preferred assumptions (R1-R3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£103,463**	**£81,835**
C. EAG scenario (R1, R2, R4-R5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£54,575**	**£32,946**

AC=appraisal committee; BSC=best supportive care; CAA=Commercial Access Agreement; EAG=External Assessment Group; HSUVs=health state utility values; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; PD=progressed disease; PF=progression-free; PFS=progression-free survival; PPS=post-progression survival; QALYs=quality adjusted life year; TTD=time to treatment discontinuation; TTP=time to progressio

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NICE National Institute for Health and Care Excellence

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