Single Technology Appraisal

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Contents:

The following documents are made available to stakeholders:

The following papers were shared with the Committee at the second Committee meeting on 13 August 2025 (following the Draft Guidance consultation)

1. **Comments on the Draft Guidance from Johnson & Johnson Innovative**

2. **Consultee and commentator comments on the Draft Guidance** from:
   a. EGFR Positive UK
   b. British Thoracic Oncology Group (BTOG)
   c. NHS England- SACT data

3. **Company response to External Assessment Groups questions on the Draft Guidance response**

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 **External Assessment Group critique of company comments on the Draft Guidance**

The following papers were shared with the Committee at the third Committee meeting on 12 November 2025 (following a request to the company for additional analysis)

5. **Additional Analysis Request for Johnson & Johnson Innovative Medicine**

6. **Response to Additional Analysis Request from Johnson & Johnson Innovative Medicine:**
   a. Response to Additional Analysis Request
   b. Supplementary Appendix

7. **Additional Clarification Questions Following Response to Additional Analysis Request, Including Company Responses**

8. **EAG critique of the company's additional evidence:**

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

NICE National Institute for Health and Care Excellence

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025.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):	Johnson & Johnson Innovative Medicine

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

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.	Nil
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil
Name of commentator person completing form:	Sasha Borges

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.
Executive Summary	**Executive Summary** Johnson & Johnson (J&J) would like to thank the Committee for their time and consideration during the Appraisal Committee meeting (ACM). While we acknowledge the efforts involved in the process, J&J are particularly disappointed with the decision to not recommend amivantamab plus lazertinib (amivantamab-lazertinib) for untreated non-small-cell lung cancer (NSCLC) in adults with epidermal growth factor (EGFR) exon 19 deletions or exon 21 L858R substitution mutations for the following reasons: • **NICE have taken an inequitable approach to this appraisal compared with the parallel osimertinib-chemotherapy appraisal:** The submissions for TA1060 and ID6256 have been made in parallel, and it is therefore reasonable to expect that they are treated equitably and fairly, namely compared to the same current NHS

Please return to: **NICE DOCS**

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

established standard of care, osimertinib monotherapy. Indeed, throughout all interactions and submissions to NICE, osimertinib monotherapy was consistently identified as the only established standard of care in the UK and therefore only relevant comparator. This view was aligned with expert opinion consensus and External Assessment Group (EAG)-nominated clinical feedback. In light of the recommendation for TA1060 just weeks before the ACM for ID6256, NICE decided that a formal comparison with osimertinib-chemotherapy is required for decision making. This introduces inequitable complexity and uncertainty into this appraisal versus the TA1060 appraisal leading to delayed patient access.

- **This appraisal presented a valuable opportunity for patients:** to access a chemotherapy-free treatment with a clinically meaningful and statistically significant overall survival (OS) benefit versus standard of care. This decision results in a delay in making this treatment available to patients.

- **Benefit in all patients versus osimertinib**: The benefits of MARIPOSA extend to all patients (intention-to-treat [ITT] population). The MARIPOSA data set was assessed by numerous regulatory bodies in the US and Europe, including the Medicines and Healthcare products Regulatory Agency (MHRA). The risk-benefit of amivantamab-lazertinib, within the licensed indication, was assessed to be in favour of the combination without restriction to a particular subgroup, including age. Therefore, the Committee's investigation of generalisability of MARIPOSA data based on inconsistencies observed in subgroups not powered to assess clinical effectiveness is superfluous and contrary to the thorough risk-benefit assessment carried out by regulatory authorities.

J&J are committed to working with NICE to ensure National Health Service (NHS) patients have access to the first chemotherapy-free regimen with a clinically and statistically significant OS benefit. To such end, J&J have provided comments and additional analyses for the consultation on the Draft Guidance Document (DGD), aiming to address the Committee's key areas of uncertainty.

Our approach involved carefully evaluating the EAG and Committee's preferences and aligning with these preferences where appropriate. Subsequently, J&J established the foundation for comparative analysis versus osimertinib-chemotherapy (TA1060), again aligning with the Committee's preferences from TA1060, with the aim of enabling consistency in decision-making for treatments within the same indication. J&J's aim was to minimise changes from the Committee's recommendations, intervening only when a clear, justified rationale necessitated deviation – such as eliminating settings that were contradictory or clinically implausible. This methodology highlights J&J's commitment to following the recommendations of the Committee, while ensuring clinical plausibility and coherence.

NICE National Institute for Health and Care Excellence

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

	Key Issues Addressed 1. Osimertinib-chemotherapy is not a relevant comparator since it is not established practice in the UK and was not routinely commissioned at the time of submission or at the ACM; however, while J&J maintains that the need for a comparison with osimertinib-chemotherapy represents an inequitable approach to assessing the value of parallel submissions, osimertinib-chemotherapy has been included in the model as an additional comparator to fulfil the Committee's request. 2. J&J have provided additional analyses which includes the modelling of progression-free survival (PFS) using the December 2024 data cut-off (DCO) to fulfil the request from the EAG and Committee. J&J would like to highlight that PFS by blinded independent central review (BICR) was not available beyond the August 2023 DCO as the primary endpoint, as pre-defined in the clinical study report (CSR) and statistical analysis plan (SAP), was met. As a result, J&J has gone to great lengths to obtain the non-pre-specified investigator-assessed (INV) PFS, which is consistent with the results seen in the PFS final analysis provided in the initial submission. This has now been incorporated into the model, even though it is not the primary endpoint as defined in the trial. The INV PFS has a minimal impact on the incremental cost-effectiveness ratio (ICER) and is, therefore, not a key driver of cost-effectiveness. 3. J&J accepts the Committee's preferred time to treatment discontinuation (TTD) extrapolations for amivantamab, lazertinib and osimertinib monotherapy and has updated the economic model accordingly. 4. For completeness, J&J have investigated the subgroup of participants older than 65 years old through providing further data from the MARIPOSA trial. As part of these analyses, inconsistent and unexplained results were observed for the subgroup of older participants receiving osimertinib, a well-known and frequently used treatment in NHS clinical practice. This clearly demonstrates the risk of overinterpreting subgroup analyses that may lack enough participants or statistical strength (i.e., are insufficiently powered) to reliably detect real differences in clinical effectiveness and further reinforces the generalisability of these results regardless of age and other baseline characteristics. 5. Amivantamab received UK marketing authorisation for a subcutaneous (SC) formulation on 9th July 2025, and the model has been updated accordingly. The unit cost for intravenous (IV) and oral administration for other treatments in the model has been updated in line with the Committee's recommendation. 6. The approach to modelling health state utilities regardless of treatment allocation has been maintained, due to updates to the formulation of amivantamab and the addition of osimertinib-chemotherapy as comparator, addressing initial comments.

Please return to: **NICE DOCS**

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

	This approach is aligned with what has been accepted in the NICE appraisal for osimertinib-chemotherapy (TA1060). **Economic Model Updates** Alongside these responses, a revised Company base case with updated patient access scheme (PAS) prices are provided, thereby offering greater value for money to the NHS. A detailed list of changes made to J&J base case cost-effectiveness analyses are presented in Appendix B and provided in the reference pack.[1] Finally, factual inaccuracies identified within the DGD are detailed in Appendix C.
1	**Section 3.3: The Committee acknowledged that, even when its preferred assumptions were incorporated into the model, substantial uncertainty remained, particularly the impact of including osimertinib-chemotherapy as a comparator. The Committee would like to see an analysis including osimertinib-chemotherapy as a comparator.** J&J has followed the NICE process throughout this appraisal, which specifies that the comparator must reflect established NHS practice in the UK. Throughout the submission, and in all interactions with NICE, osimertinib monotherapy was consistently identified as the only treatment representing current standard of care. This is because osimertinib-chemotherapy was not routinely commissioned at the time of submission or at the time of the first ACM for amivantamab-lazertinib (ID6256) held on 12th June 2025; rather, osimertinib-chemotherapy (TA1060) was recommended by NICE on 8th May 2025 for the 1L treatment of cEGFR-mutated NSCLC, and only entered routine commissioning on 9th July 2025.[2] Given the NICE manual on health technology evaluations states that relevant comparators should be treatments that are established practice in the NHS, J&J regards the request from the Committee to include osimertinib-chemotherapy as a comparator to be misaligned with NICE process for this evaluation.[3] At the very least, this approach introduces inequity between parallel appraisals leading to increased complexity and uncertainty. This request not only undermines the consistency and fairness of the evaluation process but also results in unnecessary delays to patient access to this potentially beneficial treatment. J&J, however, wish to work constructively with NICE to ensure patients in the UK have access to an innovative, chemotherapy-free and targeted therapy which is more effective than current standard of care. Therefore, the economic model has been updated to provide a comparison of amivantamab-lazertinib versus osimertinib-chemotherapy, in line with the Committee request in Section 3.3 of the DGD.

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

	The latest available data from the osimertinib-chemotherapy arm of the FLAURA2 trial were incorporated into the model. The approach to modelling this new comparator is described in full in Appendix B.2, and a summary of the additional model inputs used in the cost-effectiveness analysis for the comparison of amivantamab-lazertinib versus osimertinib-chemotherapy is provided in Appendix B.3. The modelling assumptions used for osimertinib-chemotherapy are aligned with the assumptions preferred and accepted by the Committee in the appraisal of osimertinib-chemotherapy (TA1060) earlier this year.[2] Extrapolation curves for osimertinib-chemotherapy were selected based on the available details within the Committee Papers for appraisal TA1060, in addition to the consideration of visual fit to the data from FLAURA2 and long-term clinical plausibility.[2] The approach of adopting most of the selected settings from the earlier appraisal was primarily aimed at streamlining the process and minimising unnecessary discussion. Given the limited timeframe, J&J has aligned with the majority of the final settings determined by the Committee and NICE. This alignment is the best way to ensure a smooth and efficient decision-making process. The base case results demonstrate that, at amivantamab and lazertinib PAS prices, amivantamab-lazertinib is a cost-effective use of NHS resources when compared to osimertinib-chemotherapy at list price. In all scenario analyses, amivantamab-lazertinib at PAS price remained dominant over osimertinib-chemotherapy at list price, indicating that the cost-effectiveness of amivantamab-lazertinib versus osimertinib-chemotherapy remains robust when altering key modelling assumptions and approaches.
2	**Section 3.4: The Committee would like to see an analysis modelling progression-free survival from the latest data cut.** The primary endpoint of the MARIPOSA trial, PFS assessed by BICR, was met at the 11th August 2023 DCO, where amivantamab-lazertinib demonstrated a 30% reduction on the risk of disease progression by BICR or death compared with osimertinib monotherapy. To address this request from the Committee, J&J have provided longer-term PFS data from the 4th December 2024 DCO, with a median study follow-up of 37.8 months. This longer-term data was only available for PFS (INV) and not for BICR as presented in the initial data cut (August 2023 DCO). J&J would like to highlight the great lengths gone to obtain the INV PFS which has now been incorporated into the model, even though it is not the primary endpoint as defined in the trial. The INV PFS has a minimal impact on the ICER and is, therefore, not a key driver of cost-effectiveness. The PFS (INV) Kaplan-Meier (KM) curve is presented in Figure 1, demonstrating a mPFS (INV) of [redacted] months for patients in the amivantamab-lazertinib arm, compared with [redacted] months for patients in the osimertinib monotherapy arm, thus prolonging mPFS by [redacted] months as compared with standard of care. This is very similar to results at the 11th August 2023 DCO; mPFS (INV) was [redacted] months in the amivantamab-lazertinib arm and

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

	[redacted] months in the osimertinib monotherapy arm. In addition to comparable median PFS, the longer-term data demonstrate that the PFS advantage is sustained over time. This further supports the clinically meaningful benefit that amivantamab-lazertinib could offer to patients. These updated PFS (INV) data have been used to inform PFS in the model (See Appendix B.3 for further details). **Figure 1: KM plot of PFS by INV (4th December 2024 DCO; FAS)**  **Abbreviations**: FAS: full analysis set; INV: investigator; KM: Kaplan-Meier; PFS: progression-free survival. The long-term PFS (INV) extrapolations for amivantamab-lazertinib, osimertinib monotherapy and osimertinib-chemotherapy are presented in further detail in Appendix B.3, along with the associated statistical fits and the smoothed hazard plots.
3	**Section 3.5: The Committee questioned the generalisability of the MARIPOSA results to the UK population based on the median and the mean age from the Systemic Anti-Cancer Therapy Dataset cohort (median age: 70 years; mean age: 68.5 years).** As presented in the original Company Submission, seven UK-based Key Opinion Leaders (KOLs) confirmed during an advisory board held in October 2024 that the results from the MARIPOSA trial are generalisable to the UK population, and that the baseline characteristics of patients within the trial are reflective of UK clinical practice.[4] They further suggested that a median age of 63 years old is appropriate, and that the results of the full

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

	analysis set (FAS) are generalisable to UK clinical practice.[4] Additional discussions with a UK KOL in July 2025 confirmed this conclusion.[5] In Section 3.5 of the DGD, the Committee state that the anticipated median age of patients in NHS practice expected to be eligible to receive amivantamab-lazertinib is 70 years old, based on the systemic anti-cancer therapy (SACT) dataset of the last 4,000 patients who received osimertinib monotherapy for advanced NSCLC. As J&J do not have access to these data, it has not been possible for a thorough analysis or validation to be performed. The Committee noted that this suggests most people in the target population would be over 65 years old, J&J recommend that caution be taken when drawing conclusions from a median age, given that without a range there is lack of transparency about the distribution of the data. However, given the mean age is lower than the median age in the SACT dataset (68.5 and 70 years old, respectively), this suggests a left skewed distribution with a number of patients significantly younger than the median, which is in keeping with the epidemiology of EGFR positive lung cancer.[6-8] This is further supported by real-world evidence (RWE) from the National Cancer Registries and Analysis Service (NCRAS) dataset on the 'MARIPOSA-like' cohort (for an explanation of this cohort see Document B, Section B.1.3.1), in which over 50% of patients were aged below 65 years old.[8] Notably, the age range of patients in the MARIPOSA, FLAURA and FLAURA2 trials had lower limits of between 25 and 35 years old.[9-11] In addition, the advanced NSCLC category is broader than the current appraisal, and it may also encompass the use of osimertinib for T790M mutations (TA653), typically following first-line 1st or 2nd generation tyrosine kinase inhibitor (TKI) treatments. This patient demographic, being in the second-line and beyond, is generally older compared to those treated in the first-line setting. While the utilisation of osimertinib in this setting is currently limited, there has been substantial historical usage, which could potentially complicate and obscure the dataset further. Therefore, without access to these data J&J are unable to comment on how these 4,000 patients were selected and to what extent they represent a patient cohort that is relevant to this appraisal. To address this Committee concern further, an additional OS subgroup analysis was undertaken, including subgroups of patients [redacted] and [redacted] (Table 2, Appendix A.1), in line with the Committee's preferred assumption of median age in NHS practice. This new analysis demonstrated the OS benefit for amivantamab-lazertinib versus osimertinib monotherapy to be consistent across both subgroups ([redacted]: hazard ratio [HR]: [redacted]; [redacted]: HR: [redacted]). There are no significant interactions in either the subgroups of patients aged [redacted] and [redacted] and patients aged <75 years and ≥75 years, and the effects in both groups for the older patients ([redacted] and ≥75 years) are below 1 in each case. As such, this input has not been updated. For further consideration of age within the MARIPOSA trial, please see Issue 4 below and Appendix A.1.

NICE National Institute for Health and Care Excellence

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

4	**Section 3.5: The Committee would like to see exploration of outcomes for the subgroup of patients aged ≥65 years old, including subgroup analyses, KM data for PFS, OS or TTD, and cost-effectiveness modelling to help it to decide on the cost effectiveness of amivantamab-lazertinib in this subgroup.** While subgroup analyses may provide valuable insights into trends in efficacy across subgroups, these results should always be interpreted with caution. The Committee suggested that MARIPOSA subgroup data indicated a correlation between older age and the clinical efficacy of amivantamab-lazertinib. The Committee proposed that this is due to higher rate of adverse events (AEs) driven treatment discontinuation. The results seen in the subgroup analysis of patients aged ≥65 years old are likely due to unexpected and unexplained overperformance of a subgroup in the osimertinib arm. In fact, it is notable that there are many subgroups within the MARIPOSA trial where the combination of amivantamab-lazertinib has shown substantial benefit, including the predefined subgroup ≥75 years, which further supports that the results in patients aged ≥65 years are a statistical and clinical anomaly. **Modelling the population aged ≥65 would reduce rather than enhance generalisability** J&J note that the Committee has recommended modelling the population aged ≥65 to enhance generalisability, based on the assumption of a generally older demographic within the NHS for this indication. However, this approach inadvertently excludes a substantial segment of the population, thereby compromising rather than improving generalisability. Evidence from UK RWE, and clinical studies such as FLAURA, FLAURA2, and MARIPOSA demonstrates that a significant proportion of patients are under 65. Excluding this group does not support broader generalisability, instead, it unnecessarily limits the value of the analysis and, by extension, its relevance.[5, 8-11] Age is a continuum and an imprecise model for patient performance. The fact that further efficacy decrements are not seen when increasing the age cutoff for participants in MARIPOSA reinforces this. A subgroup analysis of the MARIPOSA trial looking at [redacted] as a cutoff age was conducted; demonstrating inconsistent results across different age groups, highlighting that a singular cutoff in the case of continuous subgroup variables yields a greater chance of observing unexpected and random results. ***Osimertinib arm overperformance in patients aged ≥65 years old*** The apparent difference in PFS benefit in the amivantamab-lazertinib arm between the subgroups of patients aged <65 and ≥65 years old is largely driven by the osimertinib arm overperforming for PFS in the subgroup of patients aged ≥65 years old relative to the ITT population, which impacts the overall comparative hazard ratio. Data from the MARIPOSA trial indicate that PFS and OS data for the patients aged ≥65 years old receiving osimertinib monotherapy overperforms versus the overall population, in a way that does not hold clinical face validity (see Table 4, Appendix A.1). This overperformance is the

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

result of statistical chance and therefore caution should be taken when interpreting subgroup analyses that are not statistically powered to infer relative treatment effect.

[redacted]

and the risk/benefit of the combination was assessed as positive regardless of age.[12]

Correlation between age and efficacy not seen in other studies

Experts agree that the best way to validate subgroup-treatment effect interactions is through reproducibility in other trials; the age results in MARIPOSA have not been demonstrated in other trials of amivantamab.[13] Efficacy results measured by PFS were consistent between age subgroups in PAPILLON (amivantamab-chemotherapy in 1L exon 20 insertion mutations) and MARIPOSA-2 (amivantamab-chemotherapy in post-osimertinib cEGFR-mutated NSCLC).[14, 15] [redacted].

Summary

In summary, based on the above, J&J does not consider that the subgroup data for patients aged ≥65 in the MARIPOSA trial provide evidence of a meaningful difference in the real-world efficacy of amivantamab-lazertinib versus osimertinib monotherapy. Nor do these data suggest any lack of generalisability of the MARIPOSA trial results to the expected clinical outcomes within UK practice. Caution should be exercised in focusing solely on the population aged ≥65, as this approach will limit rather than enhance the generalisability of the findings. It is methodologically incorrect to draw firm clinical conclusions on the clinical efficacy of an intervention based on subgroup analyses, and therefore inappropriate for such analyses to inform the Committee's decision-making. For further consideration of age within the MARIPOSA trial, please refer to Appendix A.1.

NICE National Institute for Health and Care Excellence

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

5	**Section 3.7: The Committee preferred to use the EAG's preferred TTD extrapolations for amivantamab, lazertinib and osimertinib monotherapy.** J&J accepts the Committee's preference and has updated the modelling of TTD for amivantamab, lazertinib and osimertinib monotherapy as follows: • Amivantamab: 2-knot normal • Lazertinib: 1-knot hazards • Osimertinib monotherapy: 1-knot normal
6	**Section 3.9: The Committee preferred the use of treatment-specific utilities for the progression-free health state, modelling the amivantamab-lazertinib and osimertinib monotherapy arms separately. The Committee also noted input from the patient expert that some people may prefer to avoid a clinical environment required for infusions and that there would be a trade-off between better outcomes and a worse adverse event profile.** The Committee concluded that patients receiving amivantamab-lazertinib are unlikely to have the same health utility as those on osimertinib monotherapy, due to differences in the clinical settings for IV amivantamab versus oral osimertinib. However, as the licence for amivantamab has been updated to include SC amivantamab as of 9th of July 2025, it is anticipated that all patients will receive amivantamab-lazertinib in clinical practice as a SC injection of amivantamab in combination with oral lazertinib. As a result, the relative impact of administration route for amivantamab versus osimertinib monotherapy is significantly less relevant when considering progression-free utility values, due to the decreased administration time, chair time and AEs associated with SC versus IV amivantamab (see Appendix B.1). This is further supported by efficacy data from the PALOMA trials, in which SC amivantamab has demonstrated a reduction in certain AEs and improvement in overall patient satisfaction compared with IV administration (for further details, see B.2.11 of the Document B of the original Company Submission and Appendix B.4 below). The use of treatment-independent health state utility values (HSUVs) is therefore appropriate given the improved patient experience associated with SC vs IV administration of amivantamab meaning any treatment-specific differences in utilities are due to AEs, which are incorporated into the model separately. In addition, the introduction of SC amivantamab is expected to address concerns raised from the patient expert in Section 3.3 of the DGD, stating that some people may prefer to avoid the clinical environment that is required for IV administration, given that SC amivantamab would result in significantly less time spent by the patient in a clinical setting (SC: 4.8 minutes versus IV: 5 hours; 98.4% reduction in administration time).[16]

Please return to: **NICE DOCS**

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

	In addition to the benefits and improvements that amivantamab SC would offer, J&J recognises that osimertinib-chemotherapy is now also required as a comparator, with the chemotherapy component invariably administered intravenously. However, in TA1060, progression-free (PF) utilities were maintained as similar for both osimertinib monotherapy and osimertinib-chemotherapy. Importantly, patients receiving chemotherapy would be exposed to more AEs, greater clinical burden, and long administration times compared to patients receiving osimertinib monotherapy. Therefore, the earlier arguments for treatment-specific utility values are less pertinent when comparing the three treatments, particularly now that amivantamab is administered subcutaneously. As such, the approach to modelling health state utilities regardless of treatment allocation has been maintained and aligns with what has been accepted in the NICE appraisal for osimertinib-chemotherapy (TA1060). In the base case, the utility values for the PF and progressed disease (PD) states are derived from TA1060, with an assumption of equal utility in the osimertinib-chemotherapy arm (see Appendix B.4 for further details).[17]
7	**Section 3.10: The Committee preferred to use the amivantamab administration costs provided by the CDF clinical lead.** As noted above, amivantamab received UK marketing authorisation for a SC formulation in July 2025, and the model has been updated accordingly. At this stage, there is no clinical rationale for IV amivantamab to be preferred over SC, and since amivantamab is not yet available on the NHS, there is no evidence to suggest that hospitals will start using IV if SC is available. Therefore, costs associated with the SC administration of amivantamab are included, and those associated with the IV formulation have been removed. The administration costs used for the remaining IV and oral treatments in the economic model have been updated to align with the Committee preferred assumptions. Despite this costing update, it is notable that several benefits anticipated with the SC formulation of amivantamab are not captured in the updated economic model. Results from the PALOMA-3 trial demonstrate a reduction in administration time for SC vs IV administrations (SC: 4.8 minutes versus IV: 5 hours; 98.4% reduction in administration time), correspondingly reducing patient chair time, with SC amivantamab (36 minutes) compared with IV (3.4 hours).[16] This is supported by a poster published by Baldwin et al.[18] which states that the SC formulation can be given in a 30-minute outpatient appointment. This is expected to yield significant nursing capacity savings as compared with IV administration, which will help boost efficiency in the NHS in line with a key focus of the NHS 10-year plan.[18] The updated administration unit costs reflected in the model, including for SC and IV administrations, are outlined in Appendix B.5 in Table 13, alongside further detail regarding the uncaptured benefits of using the SC administration.

NICE National Institute for Health and Care Excellence

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

	An alternative unit cost for the SC administration has been explored in the scenario analysis (Appendix B.11).

Please return to: **NICE DOCS**

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

References

1. Johnson & Johnson Data on File. CEM Changes Summary.
2. National Institute for Health and Care Excellence (NICE). Osimertinib with pemetrexed and platinum-based chemotherapy for untreated EGFR mutation-positive advanced non-small-cell lung cancer. Available at: https://www.nice.org.uk/guidance/ta1060 [Accessed: July 2025].
3. National Institute of Health and Care Excellence (NICE). NICE health technology evaluations: the manual (PMG36). 2023. Available at: https://www.nice.org.uk/process/pmg36/resources/nice-health-technology-evaluations-the-manual-pdf-72286779244741/ [Accessed August 2024].
4. Johnson & Johnson Data on File. Advisory Board Report for Amivantamab MARIPOSA HTA Submissions. October 2024.
5. Johnson & Johnson Data on File. Additional Clinical Validation. July 2025.
6. Gomez-Randulfe I, Scanlon LA, Carter M, et al. First-line osimertinib compared to earlier generation TKIs in advanced EGFR-mutant NSCLC: A real-world survival analysis. Lung Cancer 2025;200:108084.
7. Mazzeo L, Corso F, Baili P, et al. Data analytics for real-world data integration in TKI-treated NSCLC patients using electronic health records. ESMO Real World Data and Digital Oncology 2025;7.
8. Johnson & Johnson Data on File. RWE NCRAS IPD Analysis, 2024.
9. Ramalingam Suresh S, Vansteenkiste J, Planchard D, et al. Overall Survival with Osimertinib in Untreated, EGFR-Mutated Advanced NSCLC. New England Journal of Medicine 2020;382:41-50.
10. Planchard D, Jänne PA, Cheng Y, et al. Osimertinib with or without Chemotherapy in EGFR-Mutated Advanced NSCLC. N Engl J Med 2023;389:1935-1948.
11. Cho BC, Lu S, Felip E, et al. Amivantamab plus Lazertinib in Previously Untreated EGFR-Mutated Advanced NSCLC. N Engl J Med 2024;391:1486-1498.
12. European Medicines Agency (EMA). Lazcluze assessment report. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/lazcluze. [Accessed: July 2025].
13. PM R. Subgroup analysis in randomized controlled trials: importance, indications, and interpretation. Lancet 2005; 365:176-86. Rothwell PM. Subgroup analysis in randomized controlled trials: importance, indications, and interpretation. Lancet 2005; 365:176-86.
14. Zhou C TK, Cho BC, et al. Amivantamab plus Chemotherapy in NSCLC with EGFR Exon 20 Insertions. N Engl J Med. Oct 21 2023;doi:10.1056/NEJMoa2306441.
15. Passaro A WJ, Wang Y, et al. Amivantamab plus chemotherapy with and without lazertinib in EGFR-mutant advanced NSCLC after disease progression on osimertinib: primary results from the phase III MARIPOSA-2 study. Ann Oncol. Jan 2024;35(1):77-90. doi:10.1016/j.annonc.2023.10.117.
16. Leighl NB, Akamatsu H, Lim SM, et al. Subcutaneous Versus Intravenous Amivantamab, Both in Combination With Lazertinib, in Refractory Epidermal Growth Factor Receptor-Mutated Non-Small Cell Lung Cancer: Primary Results From the Phase III PALOMA-3 Study. J Clin Oncol 2024;42:Jco2401001.
17. National Institute for Health and Care Excellence (NICE). Osimertinib for untreated EGFR mutation-positive non-small-cell lung cancer. Available at: https://www.nice.org.uk/guidance/ta654 [Accessed: July 2025].
18. Baldwin A, Hughes A, Greystoke A. 99 Patient experiences of atezolizumab subcutaneous formulation compared to intravenous in Newcastle, and the impact on services delivering systemic anti-cancer treatments. Lung Cancer 2025;200.
19. Williamson SF GM, Mander AP, et al. Subgroup analysis in randomized controlled trials frequently categorized continuous subgroup information. J Clin Epidemiol 2022; 150:72-9.
20. Brookes ST WE, Peters TJ, et al. Subgroup analyses in randomized controlled trials: quantifying the risk of false-positive and false-negatives. Health Technol Assess 2001; 5:1-56.
21. European Medicines Agency (EMA). Guideline on the investigation of subgroups in confirmatory clinical trials. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-subgroups-confirmatory-clinical-trials_en.pdf [Accessed: July 2025].
22. Chih-Hsin Yang J. et al. Amivantamab Plus Lazertinib vs Osimertinib in First-line (1L) EGFR-mutant (EGFRm) Advanced NSCLC: Final Overall Survival (OS) from the Phase 3 MARIPOSA Study. Presented at: European Lung Cancer Congress (ELCC); March 26-29, 2025. Paris, France.

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

23. Center for Drug Evaluation and Research. NDA/BLA Multi-disciplinary Review and Evaluation. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2024/219008Orig1s000MultidisciplineR.pdf. [Accessed: July 2025].
24. Soto-Perez-de-Celis E, Li D, Yuan Y, et al. Functional versus chronological age: geriatric assessments to guide decision making in older patients with cancer. Lancet Oncol 2018;19:e305-e316.
25. Borghaei H, Yim YM, Guerin A, et al. Severe adverse events impact overall survival and costs in elderly patients with advanced non-small cell lung cancer on second-line therapy. Lung Cancer 2018;119:112-119.
26. Chrischilles EA, Pendergast JF, Kahn KL, et al. Adverse events among the elderly receiving chemotherapy for advanced non-small-cell lung cancer. J Clin Oncol 2010;28:620-7.
27. Johnson & Johnson Data on File. MARIPOSA Clinical Study Report. DCO: 11 August 2023.
28. Johnson & Johnson Data on File. MARIPOSA Clinical Study Report. DCO: 4 December 2024.
29. Gemeinsamer Bundesausschuss. Osimertinib in combination with pemetrexed and platinum-based chemotherapy for the first-line treatment of adult patients with advanced NSCLC whose tumors harbor EGFR mutations as a deletion in exon 19 or a substitution mutation in exon 21 (L858R). Module 4a - Appendix 4G. Available at: https://www.g-ba.de/downloads/92-975-7842/2024_07_23_Modul4A_Osimertinib_Anhang_4G.pdf. [Accessed: July 2025].
30. Jackisch C, Manevy F, Frank S, et al. White Paper on the Value of Time Savings for Patients and Healthcare Providers of Breast Cancer Therapy: The Fixed-Dose Combination of Pertuzumab and Trastuzumab for Subcutaneous Injection as an Example. Adv Ther 2022;39:833-844.
31. Manevy F, Filkauskas G, Levy P, et al. Potential non-drug cost differences associated with the use of the fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection (PH FDC SC) in the treatment of HER2-positive early breast cancer patients in Western Europe and the United States. Journal of Clinical Oncology;39:544-544.
32. National Health Service (NHS). Fit For the Future: 10 Year Health Plan for England. Available at: https://assets.publishing.service.gov.uk/media/68760ad755c4bd0544dcae33/fit-for-the-future-10-year-health-plan-for-england.pdf [Accessed July 2025].
33. Alexander M, Cheng Y, Lee S-H, et al. Subcutaneous vs Intravenous Amivantamab: Patient Satisfaction and Resource Utilization Results from the PALOMA-3 Study. Presented at: World Conference on Lung Cancer (WCLC); September 7-10, 2024. San Diego, CA, USA.
34. Ouwens MJNM, Philips Z, Jansen JP. Network meta-analysis of parametric survival curves. Research Synthesis Methods 2010;1:258-271.
35. Electronic Medicines Consortium. Rybrevant 1600 mg solution for injection. Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/101168/smpc [Accessed: July 2025].
36. Sun Min Lim, Jiunn-Liang Tan, Josiane Mourão Dias, et al. Subcutaneous amivantamab and lazertinib as first-line treatment in patients with EGFR-mutated, advanced non-small cell lung cancer (NSCLC): Results from the phase 2 PALOMA-2 study. Journal of Clinical Oncology 2024:abstr LBA8612.
37. National Institute for Health and Care Excellence (NICE). Daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma (Managed Access Review of TA573) [ID4057]. Available at: https://www.nice.org.uk/guidance/ta897/documents/committee-papers [Accessed: July 2025].
38. National Health Service (NHS). National Schedule of NHS Costs 2023/24 (2025). Available at: https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/ [Accessed: February 2025].
39. British National Formulary (BNF). Key information on the selection, prescribing, dispensing and administration of medicines, 2024. Available at: https://bnf.nice.org.uk/ [Accessed: December 2024].
40. European Medicines Agency (EMA). Osimertinib assessment report. Available at: https://www.ema.europa.eu/en/documents/product-information/tagrisso-epar-product-information_en.pdf [Accessed: July 2025].

NICE National Institute for Health and Care Excellence

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

Appendices

Appendix A: Clinical effectiveness results

J&J has included updated PFS (INV) data from the 4th December 2024 DCO within the cost-effectiveness model (CEM, Table 1), with the KM curves presented in Figure 2. The most up to date data from the MARIPOSA trial for all other endpoints were provided in the original Company Submission and the Addendum document.

Table 1: PFS (INV) results based on 4th December 2024 and 11th August 2023 DCOs

	DCO: 4th December 2024		DCO: 11th August 2023	
	Amivantamab-Lazertinib (N=429)	Osimertinib (N=429)	Amivantamab-Lazertinib (N=429)	Osimertinib (N=429)
Event, n (%)	[redacted]	[redacted]	189 (44.1)	230 (53.6)
mPFS, months (95% CI)	[redacted]	[redacted]	23.9 (20.2, 22.5)	19.9 (18.6, 20.7)
HR (95% CI)	[redacted]		0.79 (0.65, 0.95)	
p-value	[redacted]		0.014	

Abbreviations: CI: confidence interval; DCO: data cut-off; HR: hazard ratio; INV: investigator; PFS: progression-free survival.
Source: Johnson & Johnson data on file.

Figure 2: KM plot of PFS by INV (4th December 2024 DCO; FAS)

Abbreviations: FAS: full analysis set; INV: investigator; KM: Kaplan-Meier; PFS: progression-free survival.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

Appendix A.1: Subgroup analysis

Limitations of subgroup analyses

While subgroup analyses may provide valuable insights into trends in efficacy across subgroups, these results should always be interpreted with caution. This is especially true for any unanticipated effects.[19] Brookes *et al.* (2001) conducted a study in which trial data were simulated to explore expected rates of false positive and false negative subgroup results.[20] In simulated trials that demonstrated an overall treatment benefit, formal interaction tests identified a subgroup interaction in only 5% of cases. However, when simply analysing the subgroup categories independently, results across two subgroups, where one was significant and the other was not, occurred 41% to 66% of the time, respectively. These findings highlight that most subgroup differences in results are not due to the subgroup itself, but are instead due to limitations with statistical analysis, particularly in cases where a study design lacked statistical powering for subgroups.[20]

Furthermore, guidance on subgroup analyses issued by the EMA highlights that, when examining subgroups, there is an additional risk that randomisation may not be fully maintained and, therefore, findings within individual subgroups are more likely to be influenced by baseline covariate imbalances between treatment groups rather than by the true effect of the treatment.[21] These limitations underscore the importance of careful interpretation when considering subgroup findings, as they should not be the sole basis for decision-making. In the MARIPOSA study, the risk of misinterpreting subgroup analyses is demonstrated when looking solely at the subgroup of participants aged ≥65 years, given such analyses were not part of the hypothesis testing in the trial and should not be used to infer definitive treatment effects.[22]

The Committee suggested that MARIPOSA subgroup data indicated a correlation between age and the clinical efficacy of amivantamab-lazertinib. J&J would like to note that the selection of 65 years as an age marker is not based on a specific biological or medical rationale. Focussing specifically on the subgroup of patients aged ≥65 years old is not methodologically correct and cannot support any decisions on the cost-effectiveness of amivantamab-lazertinib. As noted by a clinical expert during the ACM, there is no biological reason why the efficacy of amivantamab-lazertinib would vary by age group, nor any rationale that a signal for reduced benefit would be seen specifically in patients aged 65 years to 69 years, and not patients aged 70 years and above. Additionally, there is no rationale for the former cohort of patients to experience more AEs than the latter, affecting survival outcomes; this was further confirmed with a UK Thoracic Oncologist.[5]

Arbitrary selection of age subgroups

A subgroup analysis of the MARIPOSA trial looking at [redacted] as a cutoff age was conducted; demonstrating inconsistent results across different age groups (Table 2). With the [redacted] cutoff age the sample size (n=[redacted] for amivantamab-lazertinib; n=[redacted] for osimertinib) [redacted] compared with the ≥75-years subgroup (n=51 for amivantamab-lazertinib; n=53 for osimertinib). Based on this change in age transition point by 5 years, an OS benefit for the combination of amivantamab-lazertinib versus osimertinib in both [redacted] can be seen. There is no biological rationale that a specific signal for reduced benefit would be seen specifically in patients 65 years to 69 years or patients 65 to 74 years.

The results of the additional subgroups (e.g. [redacted]) confirms that age does not preclude any survival benefit for amivantamab-lazertinib in older patients. Specifically, the results in patients ≥75 years and in

patients [redacted] highlight that there is not a clear correlation between older age with OS. There are no significant interactions in either set of age subgroup (<75 years versus ≥75 years, or [redacted]), and the effects in both groups for the older patients (≥70 years and ≥75 years) are below 1 in each case. These results again highlight that a singular cutoff in the case of continuous subgroup variables yields a greater chance of observing unexpected and random results.

Additionally, age alone is a poor marker of frailty and is not analogous to patient fitness or performance, as evidenced by the Eastern Cooperative Oncology Group (ECOG) performance score (PS) subgroups which directly reflect patient performance and are consistent with the overall OS benefit (Figure 3).[22-24]

Table 2: OS subgroup analysis across age subgroups (DCO: 4th December 2024)

Age groups, n	Subgroup Size		HR [95% CI]	Interaction term
	Amivantamab-lazertinib (N=429)	Osimertinib (N=429)		
<65 years	235	237	0.53 [0.40, 0.70]	[redacted]
≥65 years	194	192	1.11 [0.84, 1.48]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	
<75 years	378	376	0.75 [0.60, 0.93]	[redacted]
≥75 years	51	53	0.79 [0.47, 1.33]	

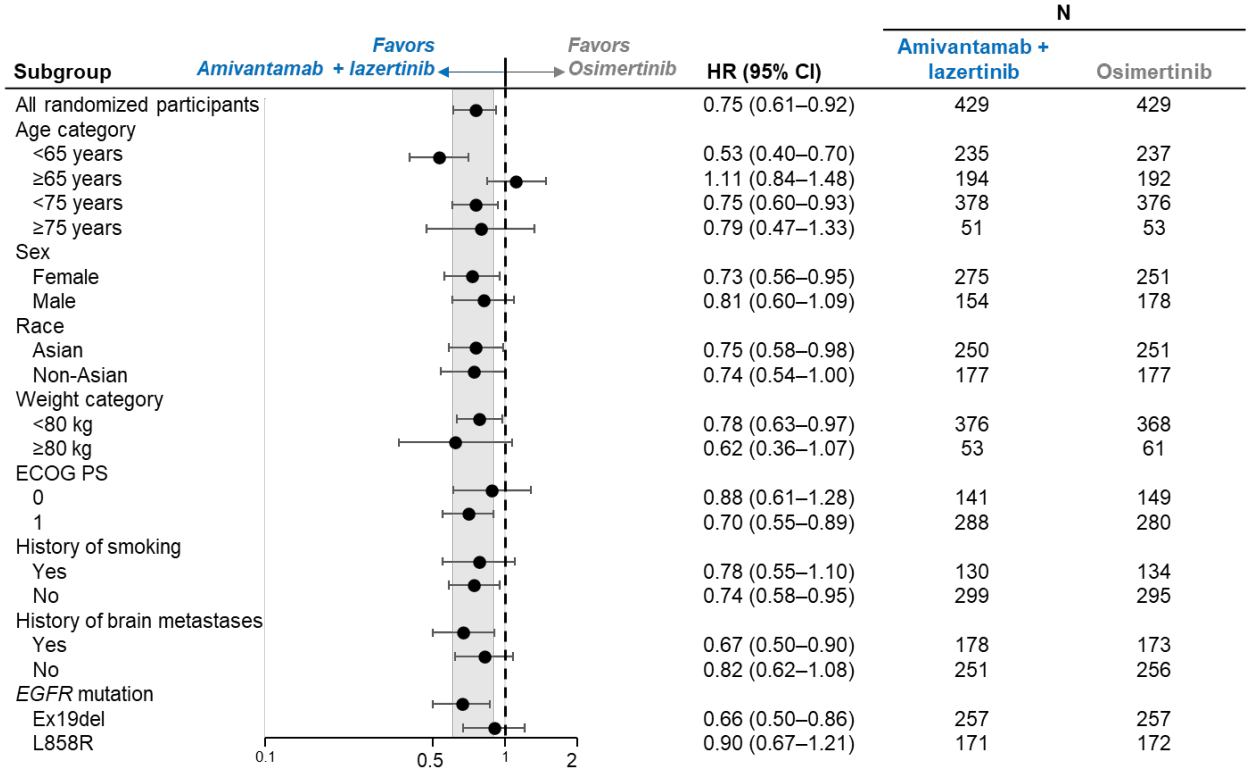
Abbreviations: DCO: data cut-off; HR: hazard ratio; OS: overall survival.
Source: Johnson & Johnson Data on File; Chih-Hsin Yang *et al.* ELCC 2025.[22]

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

Figure 3: Forest plot of OS for subgroups defined by baseline disease characteristics (4th December 2024 DCO; FAS)



Subgroup	HR (95% CI)	N: Amivantamab + lazertinib	N: Osimertinib
All randomized participants	0.75 (0.61–0.92)	429	429
Age category			
<65 years	0.53 (0.40–0.70)	235	237
≥65 years	1.11 (0.84–1.48)	194	192
<75 years	0.75 (0.60–0.93)	378	376
≥75 years	0.79 (0.47–1.33)	51	53
Sex			
Female	0.73 (0.56–0.95)	275	251
Male	0.81 (0.60–1.09)	154	178
Race			
Asian	0.75 (0.58–0.98)	250	251
Non-Asian	0.74 (0.54–1.00)	177	177
Weight category			
<80 kg	0.78 (0.63–0.97)	376	368
≥80 kg	0.62 (0.36–1.07)	53	61
ECOG PS			
0	0.88 (0.61–1.28)	141	149
1	0.70 (0.55–0.89)	288	280
History of smoking			
Yes	0.78 (0.55–1.10)	130	134
No	0.74 (0.58–0.95)	299	295
History of brain metastases			
Yes	0.67 (0.50–0.90)	178	173
No	0.82 (0.62–1.08)	251	256
EGFR mutation			
Ex19del	0.66 (0.50–0.86)	257	257
L858R	0.90 (0.67–1.21)	171	172

Footnotes: Hazard ratio for the analysis of all patients is from a proportional hazards model stratified by mutation type (Exon 19del or Exon 21 L858R), race (Asian or Non-Asian), and history of brain metastasis (present or absent). Hazard ratio for the analysis of subgroups is from an unstratified proportional hazards model. Grey indicated 95% CI for all randomised patients. Subgroup analyses were not part of the hypothesis testing of the trial and should not be used to infer definitive treatment effects.
Abbreviations: CI: confidence interval; DCO: data cut; ECOG: Eastern Cooperative Oncology Group; EGFR: epidermal growth factor receptor; Ex19del: exon 19 deletion; FAS: full analysis set; HR: hazard ratio; L858R: exon 21 L858R substitution mutations; OS: overall survival; PS: performance status.
Source: Chih-Hsin Yang *et al.* ELCC 2025.[22]

Osimertinib overperformance in patients aged ≥65 years old

The Committee suggested that the perceived lack of clinical effectiveness in older patients is linked to older patients stopping treatment faster because of the AE profile of amivantamab-lazertinib. While there was an expected increase in some AEs in the older (≥65 years) subgroup, well described in literature, the apparent difference in PFS benefit in the amivantamab-lazertinib arm between the subgroups of patients aged <65 and ≥65 years old is largely driven by the osimertinib arm overperforming in the subgroup of patients aged ≥65 years old relative to the ITT population, which impacts the overall comparative hazard ratio.[25, 26] Consequently, the outcomes for the osimertinib monotherapy arm in the MARIPOSA trial, particularly within patients aged ≥65 years old, should be taken into consideration when assessing the comparative effectiveness of amivantamab-lazertinib versus osimertinib monotherapy on OS.

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

The mPFS for all patients in the osimertinib monotherapy arm in the MARIPOSA trial was 16.59 months, versus [redacted] months for patients aged ≥65 years old.[12] PFS being [redacted] in the older subgroup than in the overall population does not hold clinical face validity as it does not align with expected clinical reality. Given there is no biological rationale to explain why patients aged ≥65 years old in the osimertinib monotherapy arm in the MARIPOSA trial would have a longer mPFS compared with the overall mPFS for osimertinib monotherapy, this result further exemplifies that caution is needed when interpreting random subgroup analyses that are not statistically powered to draw conclusions from. The [redacted] osimertinib monotherapy [redacted] for participants ≥75 years with only [redacted] months mPFS (versus 16.50 months for all patients) in the MARIPOSA trial additionally underscores this premise.[12] As such, the overperformance of the osimertinib monotherapy arm in PFS is considered a data anomaly that is translating to an apparent [redacted] in OS for patients aged ≥65 years old receiving amivantamab-lazertinib and, therefore, this subgroup analysis should not be used to infer definitive treatment effects.

To further evaluate the clinical efficacy of amivantamab-lazertinib compared with osimertinib monotherapy in participants ≥65 years old, a comparison was undertaken comparing PFS in the subgroup of patients aged ≥65 years old receiving amivantamab-lazertinib versus the full population from the osimertinib monotherapy arm of the MARIPOSA trial. Even in this imbalanced analysis, where older participants in the amivantamab-lazertinib arm are compared to all participants in the osimertinib arm, the combination of amivantamab-lazertinib demonstrates a favourable trend compared with osimertinib (HR: 0.88; 95% CI: 0.70, 1.11).

Table 3: Progression-free survival for amivantamab-lazertinib and osimertinib monotherapy in the ITT population, by age subgroup (DCO: 11th August 2023)

	Stratified Analysis		Unstratified Analysis			
	Amivantamab-lazertinib (N=429)	Osimertinib (N=429)	Amivantamab-lazertinib, <65 years (N=235)	Amivantamab-lazertinib, ≥65 years (N=194)	Osimertinib monotherapy, <65 years (N=237)	Osimertinib monotherapy, ≥65 years (N=192)
Event (n, %)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Censored (n, %)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time to event (months)						
Median (95% CI)	23.72 (19.1, 27.7)	16.6 (14.8, 18.5)	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; DCO: data cut-off; ITT: intention-to-treat; NE: not evaluable.
Source: Cho *et al.* 2024.[11] Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 11th August 2023). Table 12, page 60.[27] Johnson & Johnson Data on File.

Furthermore, a comparison of OS outcomes in older patients indicates an overperformance of osimertinib monotherapy in the MARIPOSA trial (Table 4). While it can generally be assumed that older patients die earlier than younger patients in clinical trials due to their age alone, the mOS for osimertinib monotherapy

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

patients ≥65 years in MARIPOSA ([redacted]) is [redacted] than the mOS in the overall ITT population of the MARIPOSA trial (36.7 months) and the FLAURA2 trial (36.7 months).[13]

These analyses were provided to the EMA and MHRA in the Marketing Authorisation Application. The risk/benefit of the combination was assessed as positive regardless of age as reflected in the Public Assessment Reports and Summaries of Product Characteristics.[12]

Table 4: Median OS for osimertinib across MARIPOSA and FLAURA2 trials

Subgroup for OS	Median OS in the osimertinib arm	
	MARIPOSA	FLAURA2
Total population	36.7 months (DCO: 4th December 2024)	36.7 months
≥65 years old	[redacted] (data on file; DCO: 11th August 2023)	34.7 months

Abbreviations: OS: overall survival.
Source: Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 4th December 2024).[28] GBA Dossier for benefit assessment: osimertinib.[29]

Overall, these data indicate that PFS and OS data for the patients aged ≥65 years old receiving osimertinib monotherapy in the MARIPOSA trial overperforms versus the overall population, in a way that does not hold clinical face validity. This analysis indicates that the lack of apparent benefit from the combination of amivantamab-lazertinib in patients aged ≥65 years is primarily attributable to the unexpected overperformance of osimertinib within this group. Importantly, this overperformance appears to result from statistical chance rather than a true difference in efficacy or safety profile. One clinical expert postulated that this may be due to a group of patients with less aggressive disease or less high-risk features such as co-mutations, brain or liver metastases.[5] Additionally, osimertinib has been widely used and studied world-wide in NSCLC. There is no known signal for older patients to derive superior benefit. Therefore, caution should be taken when interpreting subgroup analyses that are not statistically powered to infer relative treatment effect. This, in turn, impacts the comparative effectiveness estimates derived for amivantamab-lazertinib versus osimertinib monotherapy in this subgroup, where the relative efficacy of amivantamab-lazertinib will be underestimated as compared with expected real-world outcomes.

[redacted]

NICE National Institute for Health and Care Excellence

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025.
Please submit via NICE Docs.

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Please return to: **NICE DOCS**

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

[redacted]			

Abbreviations: AE: adverse event; Ami: amivantamab; FAS: full analysis set; Laz: lazertinib; Osi: osimertinib monotherapy.
Source: Johnson & Johnson Data on File.

Table 6: OS sensitivity analysis excluding early deaths for patients aged ≥65 years old in the MARIPOSA trial

Data cut	HR for patients aged ≥65 years old (95% CI)
First data cut (DCO: 11th August 2023)	[redacted]
Second data cut (DCO: 13th May 2024)	[redacted]
Final OS analysis (DCO: 4th December 2024)	[redacted]

Abbreviations: DCO: clinical cut-off; HR: hazard ratio; OS: overall survival.
Source: Johnson & Johnson Data on File.

Additional supportive data from other amivantamab clinical trials

The age results in MARIPOSA have not been demonstrated in other trials of amivantamab. Experts agree that the best way to validate subgroup-treatment effect interactions is through reproducibility in other trials.[13]

PALOMA-3 studied the combination of SC amivantamab with lazertinib versus IV amivantamab with lazertinib in patients with locally advanced or metastatic NSCLC EGFRm with disease progression on or after osimertinib and platinum-based chemotherapy. [redacted], which confirms no age effect observed. Furthermore, efficacy results measured by PFS were consistent between age subgroups in PAPILLON (amivantamab-chemotherapy in 1L exon 20 insertion mutations) and MARIPOSA-2 (amivantamab-chemotherapy in post-osimertinib cEGFR-mutated NSCLC). [14, 15]

The fact that an age effect has not been seen in any other amivantamab study underscores the fact that the results seen in the MARIPOSA trial, when age cutoff of 65 years is applied, are an anomaly as explained above.

Appendix B: Updated Cost-Effectiveness Results

Appendix B.1: Background and Context

The updates made to the CEM as compared with the model provided by J&J along with the Addendum are outlined within a document in the reference pack, and are summarised below.[1]

The CEM previously submitted and considered by the Committee is referred to as the 'previous model'. The updated model presented alongside this document is referred to as the 'updated model'.

At the Committee's request, J&J has provided an updated CEM including PFS (INV) data from the latest DCO (4th December 2024) and a comparison with osimertinib-chemotherapy. In recognition of the preferred assumptions of the evaluation Committee, the updated cost-effectiveness analysis submitted as part of this response document updates TTD extrapolations to the EAG-preferred assumptions: 2-knot normal, 1-knot hazard and 1-knot hazard models for amivantamab, lazertinib and osimertinib monotherapy, respectively (DGD, Section 3.7).

In addition, the following updates to the modelling approach have been made:

- A comparison versus osimertinib-chemotherapy has been included. Full details of any new modelling inputs or approaches required to develop the economic analyses between amivantamab-lazertinib, and osimertinib-chemotherapy are detailed below.
- The SC formulation of amivantamab received UK marketing authorisation for this indication, with approval granted on 9th July 2025. Given the preference of both clinicians and patients for SC injection rather than IV infusion, administration costs associated with amivantamab within the model have been simplified and updated to reflect SC administration only.
- The model has been updated to use PFS by INV instead of PFS by BICR for amivantamab-lazertinib and osimertinib monotherapy to facilitate a comparison against osimertinib-chemotherapy, which used PFS by INV from TA1060 (See Appendix B.3).[2] The curve choices for amivantamab-lazertinib and osimertinib monotherapy have been reassessed given the difference in PFS endpoint from the previous model.

J&J note the Committee preference to update the baseline mean age in the model (62.3 years old) to align with the SACT dataset (68.5 years old). However, given the baseline characteristics of the MARIPOSA trial were validated as generalisable to UK clinical practice by UK clinicians, and we are unable to validate the relevance of the SACT-derived starting age to this appraisal and that this analysis will not aid the generalisability, this input has not been updated. Furthermore, J&J note the Committee's concerns about the cost-effectiveness of amivantamab-lazertinib in patients aged ≥65 years old – additional OS subgroup analyses demonstrated that there is no clear correlation of age with OS efficacy gains in either treatment arm of the MARIPOSA trial, indicating that age does not impact the benefit with the combination of amivantamab-lazertinib.[23] For this reason, no economic results by age are provided.

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

Additionally, J&J note the Committee preference to use treatment-specific utilities in the comparison of IV amivantamab-lazertinib versus osimertinib monotherapy, given concerns raised from the patient expert in Section 3.3 of the DGD that some patients may prefer to avoid the clinical environment that is required for IV administration. However, as discussed further in response to Issue 6 above, the license update to include a SC formulation of amivantamab for this indication means that any differences in utility based on administration route are significantly less relevant. On top of that, in TA1060, progression-free utility values were similar for both osimertinib monotherapy and osimertinib-chemotherapy. However, patients receiving IV chemotherapy face more AEs, greater clinical burden, and experience long administration times. As a result, treatment-specific utility values are not adequate when comparing the three treatment options, especially now that amivantamab is administered subcutaneously. Therefore, the use of pooled HSUVs is appropriate given that any treatment-specific differences in utilities are due to AEs, which are already incorporated into the model separately. For this reason, the model has not been updated to consider treatment-specific utility values. The HSUVs implemented in the updated base case are discussed further in Appendix B.4.

Cost-effectiveness results for amivantamab-lazertinib versus osimertinib monotherapy and versus osimertinib-chemotherapy from this updated model are detailed in Appendix B.9.

Inclusion of a comparison with osimertinib-chemotherapy

At the time of the initial submission for this appraisal and at the point that the addendum was submitted, osimertinib-chemotherapy had a negative draft guidance, and J&J had no information regarding the potential outcome of the appraisal. Furthermore, during the entire NICE process and at the time of the first ACM, osimertinib-chemotherapy was not under routine commissioning and osimertinib monotherapy was considered established NHS clinical practice in the UK. Therefore, as outlined in Issue 1 above, J&J do not consider osimertinib-chemotherapy to be a relevant comparator for this submission, given how recently it was recommended by NICE, with the osimertinib-chemotherapy and amivantamab-lazertinib submissions being developed in parallel. The approach to comparator selection laid out in the NICE manual on health technology evaluations further suggests that the inclusion of osimertinib-chemotherapy as a comparator is misaligned with NICE process for this evaluation; therefore, J&J were not prepared for this request from the Committee.[3]

Despite this, J&J wish to work with NICE to ensure patients in the UK have access to innovative, chemotherapy-free and targeted therapy which is more effective than current standard of care. Therefore, the economic model has been updated at short notice to provide a comparison of amivantamab-lazertinib versus osimertinib-chemotherapy, in line with the Committee's request.

Prior to incorporation of osimertinib-chemotherapy into the model, J&J considered the settings for TTD, OS and PFS for amivantamab-lazertinib and osimertinib monotherapy and made selections in line with the recommendations from the NICE Committee and the EAG. Alongside this evidence, J&J thoroughly examined data from the FLAURA2 trial utilised in the appraisal of the recently approved osimertinib-chemotherapy (TA1060). Published data along with the Committee's preferences were used to construct modelling assumptions and inform settings which permitted osimertinib-chemotherapy to be included as a comparator in the CEM. These assumptions and settings were validated from a clinical plausibility perspective, and by running various statistical tests. They are discussed in detail in subsequent sections of this document.

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

Amivantamab administration route

As noted above, UK marketing authorisation for SC amivantamab in this indication has been approved in July 2025, with an anticipated UK launch in August 2025. Therefore, all costs associated with the administration of amivantamab within the model have been updated to reflect SC Q2W administration only, given that there is no clinical rationale or evidence for the IV amivantamab being used over the SC amivantamab.

Studies in other oncology areas have demonstrated lower non-drug costs associated with SC formulation than IV, which can be considered here to assess the potential impact of the amivantamab SC formulation. A 2022 white paper on the value of SC treatment in breast cancer captured reductions in costs derived from treatment preparation and administration, including costs for patient chair time and clinician time, as well as non-drug consumables costs, compared with those associated with IV treatment.[30] As less administration time is required with SC treatment compared with IV formulations, the additional time savings for patients may also reduce overall productivity loss, accounting for up to 11% of non-drug cost differences in Western Europe based on a cost-minimisation analysis.[18, 31]

Results from the PALOMA-3 trial also demonstrate substantial reductions in administration time for SC formulations compared to IV, with median administration times of 4.8 minutes (range: 0, 18) versus 5.0 hours (range: 0.2, 9.9), respectively, representing a 98.4% reduction in administration time.[16] By cycle 3, patient satisfaction, measured through the Therapy Administration Satisfaction Questionnaire (TASQ), was higher with SC administration compared to IV for a range of domains including patient convenience, psychological impact, and overall treatment satisfaction. Furthermore, a significantly higher number of patients expressed satisfaction with SC administration, with 85% of patients preferring SC amivantamab compared to 35% with IV administration (reported at the end of treatment; $p<0.001$).[16] These results suggest that the SC formulation of amivantamab is likely to both reduce the pressure on NHS services, releasing capacity in chemotherapy units for other treatments, while improving patient satisfaction.

In addition to reduced chair time, some centres have adjusted their treatment SACT delivery models to maximise the benefits from the capacity release associated with SC formulations, in the form of SC dedicated delivery chairs or days, as well as outpatient setting.[18] In a 2025 report on the service impact of the atezolizumab SC formulation versus its IV formulation in Newcastle, total annual capacity savings were predicted to range from 911.5 to 1,353 hours, including savings related to appointment times, aseptic production and nursing capacity.[18] The positive impact on NHS capacity from using a SC formulation of amivantamab may translate into shorter waiting times for treatment initiation for SC treatment compared with IV.

Overall, transitioning to the SC formulation is likely to enhance NHS capacity and efficiency for several compelling reasons. The NHS 10-year plan aims to address key systemic challenges, many of which can be supported directly or indirectly through increased capacity and improved operational efficiency.[32] Notably, the plan outlines reforms to how tariffs are structured, incentivising providers to deliver the most clinically and cost-effective care. It emphasises a shift towards tariffs based on best clinical practices that maximise both productivity and patient outcomes. The NHS aims for providers to be reimbursed for services at a price that delivers best value, with the aim of increasing the number of new best practice tariffs year on year. Switching from IV to SC formulations is an example of a shift towards best practice; it facilitates more efficient service

delivery by optimising capacity and resource utilisation. Importantly, this transition can result in reduced costs overall without compromising the quality of treatment or patient outcomes.

In summary, the introduction of SC amivantamab is likely to translate to reduced non-drug costs, efficiency gains and a reduction in NHS pressures, compared with the IV formulation. Considering these benefits are not captured within the updated model, J&J assert they should be explicitly considered within the decision-making process, as the overall outcomes presented from the CEM are likely to represent a conservative assessment of the overall cost-effectiveness of amivantamab-lazertinib to the UK NHS. Importantly, patients also express a clear preference for SC versus IV formulations, associated with the treatment time savings that reduce the daily life impact of undergoing cancer treatment, ultimately resulting in further quality-of-life improvements.[30]

The HRG code N10AF (specialist nursing, cancer related, adult, face to face), associated with a 45-minute appointment, has been used to estimate the base case administration cost for SC amivantamab. The PALOMA-3 trial reported that the average administration time for SC amivantamab was 4.8 minutes (range: 0, 18 minutes), and the average chair time was 36 minutes, suggesting that the time reflected in the unit cost used is appropriate and potentially over-estimates the cost of SC administrations in the model, resulting in a conservative approach.[16, 33] The outpatient cost for N10AF was used, informed by the 2025 report on the service impact of the atezolizumab SC formulation versus its IV formulation in Newcastle which suggests that monotherapy SC regimens were administered in outpatient or healthcare centres.[18]

For IV administrations, a day case for delivery as an average of more complex parenteral chemotherapy at first attendance (SB13Z) and subsequent elements of a chemotherapy cycle (SB15Z) is assumed, in line with the preference of the EAG and the NICE Committee in the DGD and the Committee papers for TA1060. A scenario analysis assuming an average chair time of 36 minutes, based on the chair time reported for SC amivantamab administration in the PALOMA-3 trial, was explored.[33] In this alternative scenario, a proportion of the N10AF code was considered, based on 36 minutes out of the total 45 minutes of nurse time. Furthermore, regarding the NHS efficiencies and reforms to tariffs detailed in the NHS 10-year plan (as noted above), in addition to the alignment with TA1060, a scenario of utilising the NHS payment scheme is also incorporated. The updated unit costs used in the model are presented in Appendix B.5. Finally, given the anticipated licensing of SC amivantamab administered Q4W [redacted] a scenario was explored to test the impact of this. Scenario analysis results are presented in Appendix B.11.

Appendix B.2: Approach to modelling osimertinib-chemotherapy

General approach to modelling osimertinib-chemotherapy

The initial basis for comparison with FLAURA2 primarily focused on NICE's final positions for TA1060 and the Committee's preferred assumptions regarding the MARIPOSA indication. Furthermore, serving as main supplementary evidence, the proportional hazards assumption was evaluated for OS and PFS within both the MARIPOSA and FLAURA2 trials. This assessment aimed to determine if an indirect treatment comparison (ITC) based on hazard ratios reported in both trials could be used to derive osimertinib-chemotherapy curves in the model. To this end, log-cumulative hazards over log-time and Schoenfeld residuals over time were

plotted and assessed visually. To aid this analysis, the information and conclusions regarding proportional hazards presented in TA1060 were also considered.

Testing in-trial assumptions of proportional hazards

Figure 4 and Figure 5 show, respectively, log-cumulative hazards and Schoenfeld residuals of OS in MARIPOSA. The log-cumulative hazard curves are not parallel and cross twice, while Schoenfeld residuals show an overall decreasing trend in hazard ratio over time. Consequently, a visual inspection of these plots are suggestive of non-proportional hazards for OS.

Figure 4: Log-cumulative hazards of OS in MARIPOSA

Abbreviations: OS: overall survival.

Figure 5: Schoenfeld residuals for OS in MARIPOSA

Footnotes: P-value of test for null hypothesis of proportional hazards: 0.13.
Abbreviations: OS: overall survival.

The log-cumulative hazard curves of PFS (INV) in Figure 6 also cross early, showing an initial convergence and then slow divergence over time. The Schoenfeld residuals in Figure 7 also show a decreasing hazard ratio over time, although less apparent than in the case of OS. Therefore, these plots, from a visual inspection, are suggestive of non-proportional hazards for PFS (INV).

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

Figure 6: Log-cumulative hazards of PFS (INV) in MARIPOSA

Abbreviations: INV: investigator-assessed; PFS: progression-free survival.

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

Figure 7: Schoenfeld residuals for PFS (INV) in MARIPOSA

Footnotes: P-value of test for null hypothesis of proportional hazards: 0.08.
Abbreviations: INV: investigator-assessed; PFS: progression-free survival.

Schoenfeld residuals and log-cumulative hazards of OS in FLAURA2 were presented in Figure 16 and Figure 17 of the Company Submission, obtained from the draft guidance consultation Committee papers for TA1060, both showing clear violation of the proportional hazards assumption, with curves crossing in the latter figure and hazard ratio initially decreasing and then increasing in the former.[2] The same plots for PFS (INV) were shown in Figures 23 and 24, also indicating non-proportional hazards and hazard ratio increasing over time. Both the submitting company and the EAG concluded that the proportional hazards assumption was not met in FLAURA2.

In conclusion, the proportional hazards assumption cannot be fully supported in either trial, although its violations are more apparent in FLAURA2. As a result, assuming constant hazard ratios to derive osimertinib-chemotherapy OS and PFS in the model would not be appropriate and would produce misleading results if used in extrapolations. For this reason, an ITC based on hazard ratios was not considered to be a viable option to inform the model.

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

Approach to modelling osimertinib-monotherapy based on conclusions of non-proportional hazards

A HR-based ITC relies on the assumption that treatment effect remains constant over time to ensure comparability and consistency of results across the studies included in the analysis. Time-varying effects, as demonstrated in the residual plots, are likely to bias an ITC between two sets of data. For this reason, it was considered invalid to use the HR between amivantamab-lazertinib and osimertinib-chemotherapy beyond the observed data, meaning an HR-based ITC is not appropriate as an approach for informing long-term survival in the model.

An alternative approach to ITC for survival outcomes that does not require the proportional hazards assumption described in the literature uses parametric distributions to model survival with each intervention, and the indirect estimate of treatment effect is based on differences in distribution parameters, such as shape and scale.[34] However, this and similar approaches require survival of all interventions in all trials, including the common comparator, to be modelled using the same type of distribution. This would not be appropriate for the OS of FLAURA2 interventions, for which different distributions were selected by both the company and the EAG in TA1060, all of which were different from the best distributions for amivantamab-lazertinib and osimertinib in MARIPOSA. Distribution choices for PFS (INV) in TA1060 also differed from the best distributions for amivantamab-lazertinib and osimertinib discussed later in this document.

To appropriately capture the evolution of changing hazards in OS, PFS and TTD over time with all interventions, modelling individual hazard curves is therefore necessary. Parametric distributions for OS and PFS (INV and BICR) of osimertinib-chemotherapy were fitted independently to individual patient data (IPD) reconstructed from published KM curves from FLAURA2. To account for potential differences in prognostic factors between MARIPOSA and FLAURA2, it was assumed that any such differences would be reflected in differences in outcomes between the common comparator (osimertinib) arms of both trials; this is similar to the assumptions underlying anchored ITCs. These differences were captured as hazard ratios of osimertinib in MARIPOSA versus osimertinib in FLAURA2, estimated using reconstructed IPD for osimertinib outcomes in the latter trial, which was applied to survival curves of osimertinib-chemotherapy in the model. Comparisons of osimertinib outcomes in the two trials are detailed in sections of this document dedicated to specific survival outcomes.

All model inputs used to incorporate the additional comparison against osimertinib-chemotherapy in the economic analysis are presented below, including clinical parameters and characteristics, utility values, and other model inputs specific to osimertinib-chemotherapy such as drug acquisition costs, healthcare resource use, and subsequent treatments. The modelling assumptions used for osimertinib-chemotherapy are based on the assumptions preferred and accepted by the Committee in the appraisal of osimertinib-chemotherapy (TA1060) earlier this year.[2]

Appendix B.3: Survival Inputs and Assumptions

Updated PFS (INV) data for amivantamab-lazertinib and osimertinib monotherapy from the MARIPOSA trial

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

In the updated model base case, PFS was modelled using PFS (INV) data from the respective arms of the MARIPOSA trial (4th December 2024 DCO). A comparison of the KM curves for PFS (BICR) at the 11th August 2023 DCO and PFS (INV) at the 4th December 2024 DCO is presented in Figure 8. The more mature data reduces uncertainty with respect to PFS extrapolations. The extrapolations have been updated based on the differences in the KM curves between the two endpoints and DCOs.

Figure 8: Kaplan-Meier estimates for PFS (BICR) at the 11th August 2023 DCO and PFS (INV) at the 4th December 2024 DCO

Abbreviations: BICR: Blinded Independent Centralised Review; DCO: data cut-off; INV: investigator; PFS: progression-free survival.

Amivantamab-lazertinib

The PFS (INV) KM curve and independently fitted extrapolations for amivantamab-lazertinib are presented in Figure 8. Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) of the amivantamab-lazertinib PFS distributions are provided in (Table 7). Although the generalised gamma had the 3rd best AIC and 6th best BIC ranking, it is the most visually plausible when also considering the shape of the smoothed hazard curve, which shows a plateau or even a decrease in hazard near the end (Figure 10). As such, taking into account the totality of evidence including statistical fit, visual fit and clinical plausibility, the generalised gamma extrapolation for amivantamab-lazertinib PFS was selected for the base case. Scenarios exploring a

higher (exponential) and lower (gamma) curve were explored to assess the impact of alternative PFS curves. Scenario analysis results are presented in Appendix B.11.

Figure 9: Long-term PFS (INV) projections of amivantamab-lazertinib; parametric extrapolations (DCO: 4th December 2024; FAS)

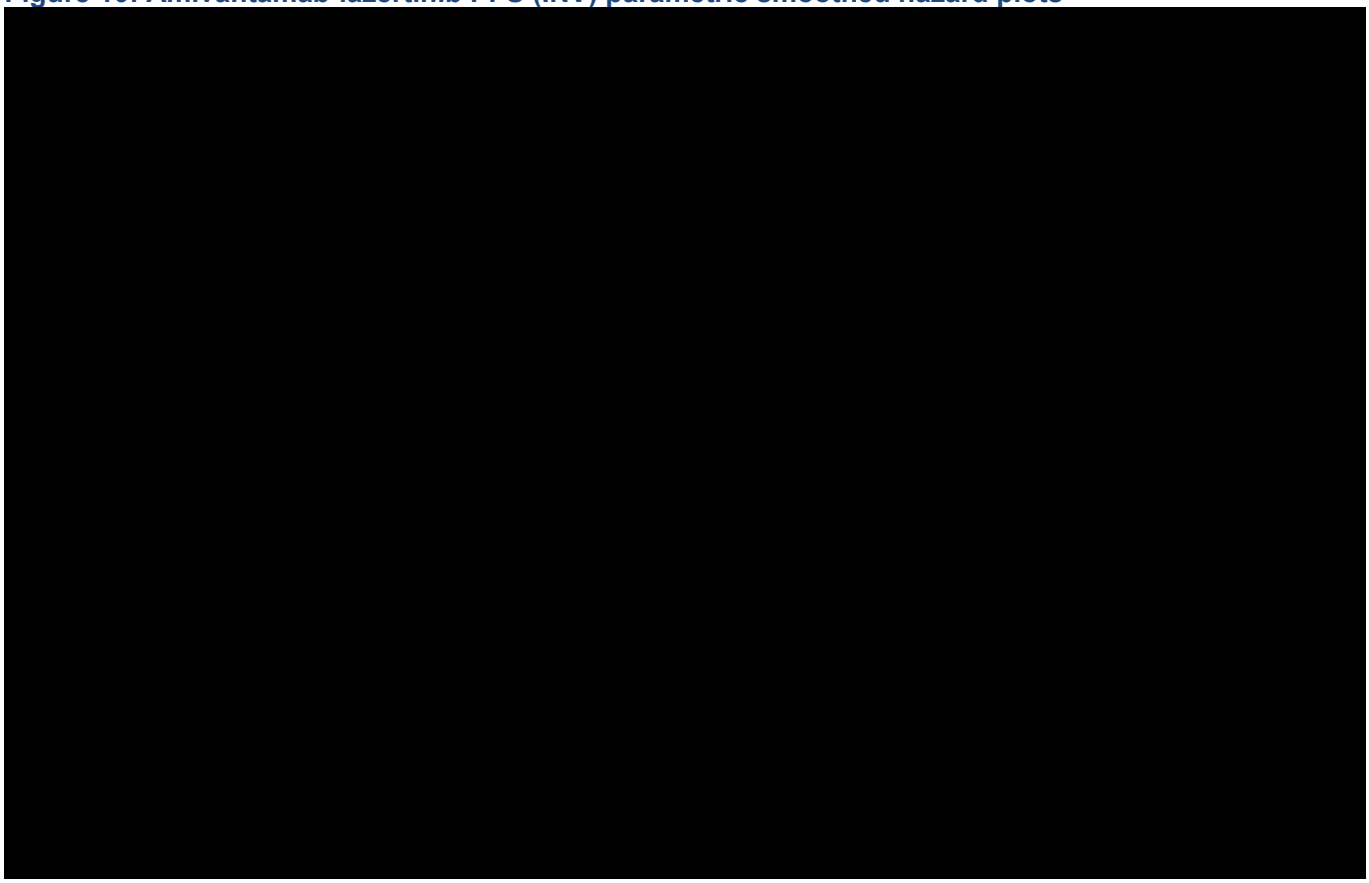
Abbreviations: DCO: data cut-off; FAS: full analysis set; INV: investigator; KM: Kaplan-Meier; PFS: progression-free survival.

Table 7: AIC and BIC of amivantamab-lazertinib PFS (INV) distributions

Parametric curve	AIC	BIC	AIC Rank	BIC Rank
Weibull	2409.28	2417.40	2	3
Exponential	2412.13	2416.20	6	1
Lognormal	2421.93	2430.05	7	7
Loglogistic	2411.29	2419.41	4	4
Gompertz	2411.83	2419.42	5	5
Gamma	2408.76	2416.89	1	2
Generalised gamma	2410.35	2422.53	3	6

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; PFS: progression-free survival.

Figure 10: Amivantamab-lazertinib PFS (INV) parametric smoothed hazard plots



Abbreviations: INV: investigator; PFS: progression-free survival.

Osimertinib monotherapy

The PFS (INV) KM curve and independently fitted extrapolations for osimertinib monotherapy are presented in Figure 11. AIC and BIC of the osimertinib monotherapy PFS distribution are provided in Table 8. As such, considering the totality of evidence including statistical fit, visual fit and clinical plausibility, the generalised gamma extrapolation for osimertinib monotherapy PFS was selected for the base case. Scenarios exploring a higher (exponential) and lower (gamma) curve were explored to assess the impact of alternative PFS curves. Scenario analysis results are presented in Appendix B.11.

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

Figure 11: Long-term PFS (INV) projections of osimertinib monotherapy; parametric extrapolations (DCO: 4th December 2024; FAS)

Abbreviations: DCO: data cut-off; FAS: full analysis set; INV: investigator; PFS: progression-free survival.

Table 8: AIC and BIC of osimertinib monotherapy PFS (INV) distributions

Parametric curve	AIC	BIC	AIC Rank	BIC Rank
Weibull	2735.99	2744.11	2	2
Exponential	2756.24	2760.30	6	6
Lognormal	2758.18	2766.31	7	7
Loglogistic	2738.62	2746.74	4	3
Gompertz	2746.42	2754.54	5	5
Gamma	2734.71	2742.84	1	1
Generalised gamma	2736.64	2748.83	3	4

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; INV: investigator; PFS: progression-free survival.

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

Figure 12: Osimertinib monotherapy PFS (INV) parametric smoothed hazard plots

Abbreviations: INV: investigator; PFS: progression-free survival.

Osimertinib-chemotherapy

The PFS KM curve and independently fitted parametric curves for osimertinib-chemotherapy are presented in Figure 13. The PFS data used, obtained from the FLAURA2 trial (TA1060), was assessed by INV, in line with the updated PFS data available from the MARIPOSA trial (DCO: 4th December 2024).[2] AIC and BIC of each of the osimertinib-chemotherapy PFS distributions are provided in Table 9. In line with the Committee's preferred base case in TA1060, the Weibull extrapolation for osimertinib-chemotherapy PFS was selected for the base case.

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

Figure 13: Long-term PFS projections of osimertinib-chemotherapy (DCO: 4th December 2024; FAS)

Abbreviations: CP: chemotherapy; INV: investigator; OSI: osimertinib; PFS: progression-free survival.

Table 9: AIC and BIC for osimertinib-chemotherapy PFS (FLAURA2) distributions

Distribution	AIC	BIC	AIC Rank	BIC Rank
Exponential	1139.50	1143.10	6	5
Weibull	1130.30	1137.60	3	2
Lognormal	1154.90	1162.20	7	7
Loglogistic	1137.60	1144.90	5	6
Gompertz	1123.40	1130.70	1	1
Gamma	1132.70	1140.00	4	4
Generalised gamma	1126.70	1137.60	2	2

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; PFS: progression-free survival. Note: AIC and BIC values were reproduced from the company submission in TA1060.

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

Figure 14: Osimertinib-chemotherapy PFS (INV) parametric smoothed hazard plot

Abbreviations: INV: investigator; PFS: progression-free survival.

Figure 14 shows PFS (INV) KM curves of osimertinib arms in MARIPOSA and FLAURA2. The estimated HR of osimertinib in MARIPOSA vs. osimertinib in FLAURA2 is 0.93 (95% CI: 0.77 to 1.13), and it was applied to the PFS curve of osimertinib-chemotherapy in the model.

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

Figure 15. Kaplan-Meier estimates of PFS (INV) of osimertinib in MARIPOSA and FLAURA2

Abbreviations: INV: investigator-assessed; PFS: progression-free survival.

The selected base case curves for modelling PFS for amivantamab-lazertinib (generalised gamma), osimertinib monotherapy (generalised gamma) and osimertinib-chemotherapy (Weibull) with the hazard ratio adjustment applied are presented in Figure 16. The selected generalised gamma curve for osimertinib monotherapy PFS falls below the corresponding curve for TTD, to reflect the continued use of osimertinib monotherapy post-progression in clinical practice, as confirmed by UK clinicians and in TA1060. This alignment to UK practice holds for the amivantamab-lazertinib and osimertinib-chemotherapy, whereby the PFS curves fall below the corresponding lazertinib and osimertinib TTD curves, respectively.

NICE National Institute for Health and Care Excellence

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

Figure 16: Long-term PFS projections of amivantamab-lazertinib, osimertinib monotherapy and osimertinib-chemotherapy selected for the base case

Clinical efficacy – OS

The OS KM curve and independently fitted parametric curves for osimertinib-chemotherapy are presented in Figure 17. AIC and BIC of each of the osimertinib-chemotherapy OS distributions is provided in

Table 10. The Gompertz and 2-knot odds extrapolations represent the best BIC and AIC rank, respectively; however, in line with the Committee's preferred base case in TA1060, the 2-knot odds spline model was selected for the long-term projection of osimertinib-chemotherapy OS.[2] An alternative scenario of the 2-knot normal spline model was explored, aligning with the discussion of the Committee within TA1060. Scenario analysis results are presented in Appendix B.11. Since the 2-knot odds and 2-knot normal models were explored in this analysis, the extrapolation curves and statistical fit data have been presented for these spline models only; however, other spline models are available to be explored in the model.

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

Figure 17: Long-term OS projections of osimertinib-chemotherapy

Abbreviations: CP: chemotherapy; KM: Kaplan-Meier; OS: overall survival; OSI: osimertinib.

Table 10: AIC and BIC of osimertinib-chemotherapy OS (FLAURA2) distributions

Distribution	AIC	BIC	AIC Rank	BIC Rank
Exponential	1078.10	1081.80	5	5
Weibull	1077.30	1084.60	6	2
Lognormal	1097.30	1104.60	9	9
Loglogistic	1082.80	1090.10	8	8
Gompertz	1069.70	1077.00	3	1
Gamma	1078.40	1085.60	7	7
Generalised gamma	1074.40	1085.30	4	6
2-knot spline, odds scale	1068.60	1083.10	2	4
2-knot spline, normal scale	1068.30	1082.80	1	3

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; OS: overall survival. Note: AIC and BIC values were reproduced from the company submission in TA1060 (except for 1-knot spline, normal scale, which was not reported).

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

Figure 18: Osimertinib-chemotherapy OS parametric smoothed hazard plots

Abbreviations: OS: overall survival.

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

Figure 19: Osimertinib-chemotherapy OS splines smoothed hazard plots

Abbreviations: OS: overall survival.

Figure 20 shows OS KM curves of osimertinib arms in MARIPOSA and FLAURA2. The estimated HR of osimertinib in MARIPOSA vs. osimertinib in FLAURA2 is 1.06 (95% CI: 0.85 to 1.32), and it was applied to the OS curve of osimertinib-chemotherapy in the model.

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

Figure 20. Kaplan-Meier estimates of OS of osimertinib in MARIPOSA and FLAURA2

Abbreviations: OS: overall survival.

The selected base case curves for modelling OS for amivantamab-lazertinib (Weibull), osimertinib monotherapy (Weibull) and osimertinib-chemotherapy (2-knot spline with odds scale) with the hazard ratio adjustment applied are presented in Figure 21. The Weibull curve was maintained for the base case long-term extrapolations of both amivantamab-lazertinib and osimertinib monotherapy OS data based on the Committee's preference, its strong statistical and visual fit, and close alignment with clinical timepoint estimates (see Section B.3.3.2 of original CS and Section 3 of the addendum). The 2-knot odds spline model was selected for osimertinib-chemotherapy to align with the Committee's preferred base case in the NICE appraisal of osimertinib-chemotherapy (TA1060). Additionally, this selection was made to reflect the most clinically, statistically and visually plausible curve. The economic model includes the option to explore other spline fits.

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

Figure 21: Long-term OS projections of amivantamab-lazertinib, osimertinib monotherapy and osimertinib-chemotherapy selected for the base case

Clinical efficacy – TTD

Osimertinib and chemotherapy TTD in the osimertinib-chemotherapy arm were modelled separately. TTD for the platinum-based chemotherapy component of the osimertinib-chemotherapy arm followed the same TTD as pemetrexed but for a fixed number of treatment cycles (12 weeks).

A similar approach to OS and PFS was used, with TTD of osimertinib and chemotherapy modelled with independent parametric fits to FLAURA2 data and hazard ratio adjustment derived from comparison of TTD in osimertinib arms of MARIPOSA and FLAURA2. However, publicly available data on TTD in FLAURA2 were more limited than for other outcomes; although KM curves were presented in TA1060 (company submission, Figures 28–30), they lacked information about numbers at risk at different time points.[2] This made established algorithms for IPD reconstruction much less effective, and some parametric models fitted to reconstructed IPD did not match curves presented in TA1060 well. Because of this, parametric TTD distributions ultimately included in the CEM were fitted directly to digitised points of parametric curves from TA1060. Consequently, covariance matrices for these fits were not available and their parameters were not included in probabilistic analysis. Reconstructed IPD were only used to obtain the hazard ratio between osimertinib arms in MARIPOSA and FLAURA2.

Osimertinib (in the osimertinib-chemotherapy arm)

The TTD KM curve and independently fitted parametric curves for osimertinib (as part of osimertinib-chemotherapy) are presented in Figure 22. AIC and BIC of the osimertinib TTD distributions are provided in Table 11.

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

Figure 22: Long-term TTD projections of osimertinib in the osimertinib-chemotherapy arm

Abbreviations: CP: chemotherapy; OSI: osimertinib; TTD: time to treatment discontinuation.

Table 11: AIC and BIC of osimertinib (as part of the osimertinib-chemotherapy arm) TTD extrapolations (FLAURA2)

Distribution	AIC	BIC	AIC Rank	BIC Rank
Weibull	1182.80	1190.10	4	3
Exponential	1181.30	1184.90	3	1
Lognormal	1194.50	1201.80	7	7
Loglogistic	1187.70	1194.90	6	6
Gompertz	1180.50	1187.80	1	2
Gamma	1183.00	1190.30	5	4
Generalised gamma	1181.00	1191.90	2	5

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; TTD: time to treatment discontinuation. Note: AIC and BIC values were reproduced from the company submission in TA1060.

For the long-term extrapolation of osimertinib (as part of the osimertinib-chemotherapy arm) the average of the Gompertz and gamma curves, 'Gompertz-gamma', was used to align with the approach taken in TA1060.[2] This novel approach was used in TA1060 in the absence of an extrapolation curve that accurately reflects the long-term expectations for treatment duration of osimertinib in this treatment arm. When incorporating this data into the updated model, the same conclusion was reached, and therefore aligning with the decision made in TA1060 is appropriate. A scenario analysis was conducted exploring the higher gamma TTD curve for osimertinib (osimertinib-chemotherapy). Scenario analysis results are presented in Appendix B.11.

The selection of the TTD for osimertinib within the osimertinib-chemotherapy arm was carefully aligned with the TTD curve established for osimertinib monotherapy, as preferred by the EAG and the Committee. The use of gompertz or generalized gamma extrapolations would result in TTD curves intersecting the osimertinib monotherapy TTD arm at an early point. This lacks clinical validity, as it does not accurately capture the sustained treatment effect of osimertinib-chemotherapy, that was seen in TA1060 which presented an OS benefit. Consequently, these curves do not accurately depict realistic treatment trajectories within the clinical setting.

Chemotherapy (in the osimertinib-chemotherapy arm)

The TTD KM curve and independently fitted parametric curves for chemotherapy are presented in Figure 23. AIC and BIC of each TTD distribution is provided in Table 12.

Figure 23: Long-term TTD projections of chemotherapy in the osimertinib-chemotherapy arm

Abbreviations: CP: chemotherapy; KM: Kaplan-Meier; OSI: osimertinib; TTD: time to treatment discontinuation.

Table 12: AIC and BIC of chemotherapy (as part of the osimertinib-chemotherapy arm) TTD extrapolations (FLAURA2)

Distribution	AIC	BIC	AIC Rank	BIC Rank
Weibull	1589.80	1597.10	5	6
Exponential	1590.70	1594.30	6	5
Lognormal	1571.30	1578.50	1	1
Loglogistic	1575.90	1583.20	3	2
Gompertz	1582.50	1589.70	4	4
Gamma	1591.60	1598.80	7	7
Generalised gamma	1573.10	1584.00	2	3

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; TTD: time to treatment discontinuation. Note: AIC and BIC values were reproduced from the company submission in TA1060.

In line with the approach taken in TA1060, exponential distribution was selected for chemotherapy (as part of osimertinib-chemotherapy) TTD in the base case.[2]

TTD in osimertinib arms of MARIPOSA and FLAURA2

Figure 24 shows TTD KM curves of osimertinib arms in MARIPOSA and FLAURA2. The estimated HR of osimertinib in MARIPOSA versus. osimertinib in FLAURA2 is 1.04 (95% CI: 0.85 to 1.29), and it was applied to the TTD curves of osimertinib and chemotherapy in the model.

Figure 24. Kaplan-Meier estimates of TTD of osimertinib in MARIPOSA and FLAURA2

Abbreviations: TTD: time to treatment discontinuation.

TTD extrapolations for the osimertinib and pemetrexed components of the osimertinib-chemotherapy arm versus amivantamab, lazertinib and osimertinib (as part of the monotherapy arm)

The selected base case curves for modelling TTD for amivantamab (2-knot normal), lazertinib (1-knot hazards), osimertinib (in the osimertinib monotherapy arm; 1-knot normal), osimertinib (in the osimertinib-chemotherapy arm; 'Gompertz-gamma') and chemotherapy (exponential) are presented in Figure 25.

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

Figure 25: Long-term TTD projections of amivantamab, lazertinib, osimertinib (as part of the monotherapy arm), osimertinib (as part of the osimertinib-chemotherapy arm) and pemetrexed (as part of the osimertinib-chemotherapy arm) selected for the base case

Abbreviations: CP: carboplatin-pemetrexed; KM: Kaplan-Meier; pop.: population; TTD: time to treatment discontinuation.

Appendix B.4: Health state utility values

As the licence for amivantamab has been updated to include SC amivantamab as of July 2025, it is anticipated that patients will receive amivantamab-lazertinib in clinical practice as a SC injection of amivantamab in combination with oral lazertinib.[5] As such, the relative impact of administration route for amivantamab versus osimertinib monotherapy is diminished and less relevant for progression-free utility values, due to the decreased administration and chair time associated with SC versus IV amivantamab. This is supported by data from the PALOMA-3 trial, where median administration time was reduced by 98.4% with SC amivantamab (4.8 minutes; range: 0, 18 minutes) compared with the IV dose (up to 5 hours for the first infusion; range: 0.2, 9.9 hours), correspondingly reducing patient chair time (SC amivantamab: 36 minutes; IV amivantamab: 3.4 hours).[16]

The use of treatment-independent HSUVs is therefore appropriate given that any treatment-specific differences in utilities are due to AEs, which are incorporated into the model separately. This is supported by efficacy data from the PALOMA trials, in which SC amivantamab was associated with fewer AEs than IV administration. Data from the PALOMA-3 trial show SC amivantamab was associated with a five-fold reduction in the incidence of infusion-related reactions (IRRs) compared with IV amivantamab (13% versus 66%, respectively) and these events were primarily mild in nature (Grade ≥3: 0.5% versus 4%, respectively).[16] Additionally, SC amivantamab was associated with a reduced incidence of venous thromboembolisms (VTEs) compared with the IV formulation (11% versus 37%, respectively).[16, 35] The generalisability of the PALOMA-3 data to the population of interest to this submission is supported by preliminary results from Cohorts 1 and 6 of PALOMA-2, which demonstrated that SC amivantamab in combination with lazertinib had a similar response rate to historic IV amivantamab in combination with lazertinib in 1L cEGFRm advanced NSCLC, with an improved safety profile.[36]

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

In addition, the introduction of SC amivantamab is expected to address concerns raised from the patient expert in Section 3.3 of the DGD, stating that some people may prefer to avoid the clinical environment that is required for IV administration, given that SC amivantamab would result in significantly less time spent by the patient in a clinical setting.[16] On top of that, in TA1060, progression-free utility values were similar for both osimertinib monotherapy and osimertinib-chemotherapy. However, patients receiving IV chemotherapy face more AEs, greater clinical burden, and experience long administration times compared with those receiving osimertinib monotherapy. As a result, treatment-specific utility values are not adequate when comparing the three treatment options, especially now that amivantamab is administered subcutaneously.

By reducing administration times, chair times and patient experience compared with IV, SC administration should address the majority of the Committee's concerns which led to the use of treatment-specific utilities being suggested. The approach to modelling health state utilities regardless of treatment allocation has therefore been maintained, and is additionally aligned to the approach accepted in the NICE appraisal for osimertinib-chemotherapy (TA1060), which used pooled HSUVs rather than treatment-specific ones when exploring oral alone (osimertinib monotherapy) compared with oral in combination with IV (osimertinib-chemotherapy). While the MARIPOSA trial represents the most appropriate source of health state utilities available given that the utilities are obtained from the same source as the efficacy data, J&J acknowledge the Committee preference for utility values to be aligned with the prior NICE appraisal of osimertinib-chemotherapy (TA1060; PF: 0.794; PD: 0.678).[2, 17] Therefore, J&J have aligned to these values in the updated base case, with an assumption of equal utility in the osimertinib-chemotherapy arm. Given osimertinib-chemotherapy involves IV administration, this assumption of equal utility values in this treatment arm is conservative.

A scenario analysis has also been performed using pooled (i.e., non-treatment specific) PF and PD HSUVs from the MARIPOSA trial; the utility values used in this scenario are [redacted] and [redacted] for the PF and PD states, respectively. An additional scenario using treatment-specific PF HSUVs for amivantamab-lazertinib ([redacted]) and osimertinib monotherapy ([redacted]) was explored. In this scenario, the utility of osimertinib monotherapy is greater than that of amivantamab-lazertinib, and osimertinib-chemotherapy is assumed equal to amivantamab-lazertinib. Scenario results are presented in Appendix B.11.

Appendix B.5: Drug administration costs

The drug administration unit costs used in the model are presented in Table 13. In alignment with TA1060 and the Committee's preference in the Draft Guidance for this current appraisal (ID6256), an average of the SB13Z and SB15Z (NHS Reference Costs, Day Case) has been used to model the IV administration within the osimertinib-chemotherapy arm (£477.00).[2] Given the marketing authorisation for the SC formulation of amivantamab has now been granted, the detailed IV per cycle costs detailed within the first ACM are no longer relevant. Instead, to account for the reduced chair and nurse time associated with SC administration compared with IV administration, the N10AF code is used for modelling the SC administration of amivantamab.[37] Finally, within the first ACM for ID6256 it was noted that if oral treatment is continued beyond the alternative treatment option, it should be costed on a four-weekly cycle; this has been incorporated into the model.

As detailed above, the code used for IV administrations within TA1060 was an average of SB13Z and SB15Z. Given the efficiencies outlined within the NHS 10-Year Plan, a scenario using the NHS payment scheme rather than the day case NHS reference cost has been explored, which was in line with the administration costs suggested in TA1060. In the absence of an NHS payment scheme cost for N10AF,a conservative scenario has been explored which assumes the SB12Z payment scheme cost for the SC administration. This code is inherently incorrect for SC administrations as it does not fully account for the short administration and chair time, nor does it fully reflect the efficiencies gained with SC. Additionally, it is highly inflated compared to the actual care it represents. Therefore, the payment scheme cost associated with it aligns with some of the efficiencies that SC will bring and provides an upper limit to the uncertainty for SC administrations. An additional scenario has been incorporated which explores the actual chair time for administering amivantamab SC; given the N10AF code is for 45 minutes of chair time, this has been adjusted to 36 minutes based on the results from the PALOMA-3 trial.[33] Scenario results are presented in Appendix B.11.

Table 13: Drug administration unit costs*

Mode of administration	Cost (£)	Source
Oral therapy one-off cost	240.44	National Schedule of NHS Costs 2023/24, SB11Z - Deliver Exclusively Oral Chemotherapy; Medical Oncology Service.[38] Applied to the first oral administration only
Simple IV administration	418.00	National Schedule of NHS Costs 2023/24, SB12Z - Deliver Simple Parenteral Chemotherapy at First Attendance; Day case; Medical Oncology Service[38]
Complex IV administration	570.00	National Schedule of NHS Costs 2023/24, SB14Z - Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance; Day case; Medical Oncology Service[38]
More complex IV administration	528.00	National Schedule of NHS Costs 2023/24, SB13Z – Deliver more Complex Parenteral Chemotherapy at First Attendance; Day case; Medical Oncology Service[38]
Subsequent elements of a chemotherapy cycle	426.00	National Schedule of NHS Costs 2023/24, SB15Z – Deliver Subsequent Elements of a Chemotherapy Cycle; Day case; Medical Oncology Service[38]
Average of SB13Z and SB15Z	477.00	Average of SB13Z / SB15Z – Deliver more Complex Parenteral Chemotherapy at First Attendance / Deliver Subsequent Elements of a Chemotherapy Cycle; Day case; Medical Oncology Service[38]
Cost per SC administration	115.00	National Schedule of NHS Costs 2023/24, N10AF - Specialist nursing, cancer related, adult, face to face[38]
Oral administration	240.44	National Schedule of NHS Costs 2023/24, SB11Z – Deliver Exclusively Oral Chemotherapy

Abbreviations: IV: Intravenous; NHS: National Health Service; SC: subcutaneous.
Footnotes: Given the NHS reference costs dashboard is not currently available, the exact values cannot be presented here and instead rounded estimates have been included based on the materials available.

Appendix B.6: Drug acquisition costs

The drug acquisition unit costs used in the model for osimertinib-chemotherapy are presented in Table 14. These costs were sourced from the BNF and eMIT. The weekly drug acquisition cost for osimertinib-

chemotherapy is presented in Table 15. Following from the NICE agreed approach within TA1060, the platinum component of osimertinib-chemotherapy is modelled as 100% carboplatin.[2] Whilst not readily available at the time of this response, a scenario exploring the impact of a four-weekly (Q4W) dose of amivantamab SC was explored. The marketing authorisation for this dosing frequency is expected in approximately [redacted]

Table 14: Drug acquisition unit costs for osimertinib-chemotherapy

Treatment	Administration route	Unit strength (mg)	Units per pack	Price per pack (£)	Cost per unit (£)	Source
Osimertinib*	Oral	80	30	5,770.00	192.33	BNF, Tagrisso[39]
Osimertinib*	Oral	40	30	5,770.00	192.33	BNF, Tagrisso[39]
Pemetrexed	IV	500 mg	1	28.76	28.76	eMIT 2024
Carboplatin	IV	600 mg	1	38.93	38.93	eMIT 2024

Footnote: *The actual net price of osimertinib as part of the osimertinib-chemotherapy combination therapy may differ from the net price of osimertinib provided as monotherapy, given osimertinib is part of a CAA. However, given details on pricing are confidential and unknown to J&J, an equal price of osimertinib is assumed for osimertinib-chemotherapy as for osimertinib monotherapy.
Abbreviations: BNF: British National Formulary; CAA; coverage access agreement; IV: Intravenous.

Table 15: Drug acquisition cost per dose for osimertinib-chemotherapy

Component	Dose (mg)	Treatment duration	Units (vials/caps) per admin	Cost per average dose required (£)
Osimertinib	80	Taken once daily until progression	1	192.34
Pemetrexed	840	Once every 3-week cycle until disease progression	2	57.53
Carboplatin	575	Once every 3-week cycle for 4 cycles	1	38.93

Abbreviations: mg: milligram.

Appendix B.7: Subsequent treatments

The methodology used to model the subsequent treatment costs for osimertinib-chemotherapy is aligned with the methodology used for osimertinib monotherapy. The proportion of patients receiving subsequent treatments at 2L following osimertinib-chemotherapy was obtained from the FLAURA2 trial, and 3L+ was aligned with osimertinib monotherapy and amivantamab-lazertinib, presented in Table 16. All other inputs used to model the subsequent treatments for osimertinib-chemotherapy were aligned with those used for osimertinib monotherapy in the original submission. The methodology and inputs used to model the

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

osimertinib monotherapy subsequent treatments remain unchanged from the original submission and are outlined in Section B.3.5.1 of Document B.

Table 16: Proportion of patients receiving 2L and 3L+ treatments by 1L regimen

1L Regimen	% Receiving 2L Treatment[a]	% Receiving 3L+ Treatment[a]	Sources
Osimertinib-chemotherapy	46.3%	[redacted]	2L: FLAURA2 3L+: MARIPOSA-2

[a] Patients not receiving 2L or 3L+ treatment were assumed to receive BSC.
Abbreviations: 1L: first line; 2L: second line; 3L+: third-line or later; BSC: best supportive care.

Appendix B.8: Adverse events

Grade 3 or higher treatment-emergent adverse events (TEAEs) were included if they occurred in ≥5% of patients in one of the modelled treatment arms, as informed by the FLAURA2 Phase 3 trial.[10, 40] Additionally, Grade ≤2 VTE was included given that this is a clinically relevant consideration for amivantamab treatment. Incidence rates and durations of AEs for 1L treatment were sourced from the FLAURA2 trial for osimertinib-chemotherapy (Table 17).

Table 17: Incidence of AEs included in the CEM

Adverse Event	Osimertinib-chemotherapy (%)
Dermatitis acneiform	1.4%
Alanine aminotransferase increased	1.4%
Hypalbuminaemia	0.0%
Paronychia	0.7%
Infusion related reaction	0.0%
Rash	0.4%
Pulmonary Embolism	0.0%
Grade ≤2 VTE	0.0%
Pneumonia	2.2%
Anaemia	19.9%
Neutropenia	13.4%
Neutrophil count decreased	11.2%
Platelet count decreased	7.6%
Thrombocytopenia	6.9%

Abbreviations: AE: adverse event; CEM: cost-effectiveness model; VTE: venous thromboembolism.
Source: Planchard *et al.* 2023.[10] EMA, Osimertinib EPAR.[40]

NICE National Institute for Health and Care Excellence

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

Appendix B.9: Base case economic results

The base case results from the updated model at amivantamab and lazertinib PAS prices are presented in Table 18.

In line with the results presented at the addendum stage, the base case results continue to demonstrate that, at amivantamab and lazertinib PAS prices, amivantamab-lazertinib is a cost-effective use of NHS resources when compared to both comparators at its list price, dominating both comparators. For completeness, the base case results at list prices are presented in Table 19.

NICE National Institute for Health and Care Excellence

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

Table 18: Deterministic DGD response base case results (at amivantamab and lazertinib PAS prices)

	Total Costs	Total LYs	Total QALYs	Incremental Costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Amivantamab-lazertinib	[redacted]	5.21	[redacted]	-	-	-	-
Osimertinib	[redacted]	3.68	[redacted]	[redacted]	1.54	[redacted]	−£101,178.24
Osimertinib-chemotherapy	[redacted]	4.50	[redacted]	[redacted]	0.72	[redacted]	−£332,735.72

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life years; NHB: net health benefit; PAS: patient access scheme; QALYs: quality-adjusted life years.

Table 19: Deterministic DGD response base case results (at amivantamab and lazertinib list prices)

	Total Costs	Total LYs	Total QALYs	Incremental Costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Amivantamab-lazertinib	[redacted]	5.21	[redacted]	-	-	-	-
Osimertinib	[redacted]	3.68	[redacted]	[redacted]	1.54	[redacted]	£243,515.82
Osimertinib-chemotherapy	[redacted]	4.50	[redacted]	[redacted]	0.72	[redacted]	£452,292.30

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life years; NHB: net health benefit; PAS: patient access scheme; QALYs: quality-adjusted life years.

Please return to: **NICE DOCS**

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

Appendix B.10: Sensitivity analyses

Probabilistic sensitivity analysis

An updated probabilistic sensitivity analysis was conducted using the updated CEM. The incremental net monetary benefit (INMB) convergence plot is presented in Figure 26, which incorporates the PAS discounts for amivantamab and lazertinib. Additionally, the probabilistic cost-effectiveness planes for amivantamab-lazertinib versus osimertinib monotherapy and osimertinib-chemotherapy are presented in Figure 27 and Figure 28, respectively. In line with the results from the previous model, these results indicate that at a £30,000 WTP threshold, amivantamab-lazertinib (at amivantamab and lazertinib PAS prices) retains a [redacted] probability of being cost-effective when compared with osimertinib monotherapy and osimertinib-chemotherapy, given that amivantamab-lazertinib demonstrates a better health effect with lower overall costs. The cost-effectiveness acceptability plane (CEAC) indicates that the probability of amivantamab-lazertinib being cost-effective [redacted] (Figure 29).

Figure 26: INMB convergence plot (updated model; at amivantamab and lazertinib PAS prices)

Abbreviations: CP: carboplatin-pemetrexed; INMB: incremental net monetary benefit; PAS: patient access scheme.

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

Figure 27: Probabilistic cost-effectiveness plane for amivantamab-lazertinib versus osimertinib monotherapy (updated model; at amivantamab and lazertinib PAS prices)

Abbreviations: PAS: patient access scheme; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year.

Figure 28: Probabilistic cost-effectiveness plane for amivantamab-lazertinib versus osimertinib-chemotherapy (updated model; at amivantamab and lazertinib PAS prices)

Abbreviations: PAS: patient access scheme; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year.

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

Figure 29: Cost-effectiveness acceptability curve for amivantamab-lazertinib versus osimertinib monotherapy and osimertinib-chemotherapy (updated model; at amivantamab and lazertinib PAS prices)

Abbreviations: CEAC: cost-effectiveness acceptability curve; CP: carboplatin-pemetrexed; PAS: patient access scheme.

Deterministic sensitivity analysis

Updated tornado diagrams showing the top 10 most influential parameters on the ICER in the updated model are provided in Figure 30 and Figure 31 for amivantamab-lazertinib versus osimertinib monotherapy and osimertinib-chemotherapy, respectively. Overall, the scale and shape of the parametric extrapolations for OS for amivantamab-lazertinib and osimertinib monotherapy are the most influential parameters, followed by the TTD rate for osimertinib monotherapy and amivantamab. For the comparison of amivantamab-lazertinib versus osimertinib-chemotherapy, the most influential parameter is the shape of the parametric extrapolation for OS for amivantamab-lazertinib. The model is otherwise robust to variation in inputs and settings. In alignment with the results presented in the CS and J&J response to Clarification questions, all results generated from the deterministic sensitivity analysis (DSA) provide a negative ICER due to amivantamab-lazertinib (at amivantamab and lazertinib PAS prices) being dominant in all instances.

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

Figure 30: DSA tornado diagram for amivantamab-lazertinib versus osimertinib monotherapy (updated model; at amivantamab and lazertinib PAS prices)

Abbreviations: DSA: deterministic sensitivity analysis; ICER: incremental cost-effectiveness ratio; OS: overall survival; PFS: progression-free survival; TTD: time to treatment discontinuation or death.

Figure 31: DSA tornado diagram for amivantamab-lazertinib versus osimertinib-chemotherapy (updated model; at amivantamab and lazertinib PAS prices)

Abbreviations: CP: carboplatin-pemetrexed; DSA: deterministic sensitivity analysis; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; OS: overall survival; PAS: patient access scheme; PFS: progression-free survival; TTD: time to treatment discontinuation or death.

NICE National Institute for Health and Care Excellence

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

Appendix B.11: Scenario analyses

A number of scenario analyses were explored, in which model assumptions or parameters were altered. The robustness of the model results to changes in the following modelling approaches and assumptions were investigated:

- Using treatment-specific PF HSUVs for amivantamab-lazertinib and osimertinib monotherapy, assuming osimertinib-chemotherapy is equal to amivantamab-lazertinib
- Using pooled HSUVs from the MARIPOSA trial
- Using NHS Payment Scheme Prices to inform IV and SC administration costs
- Using Healthcare Resource Group (HRG) code N10AF for SC administration, proportioned by actual chair time
- Exploring alternative survival extrapolations for PFS, OS and TTD
- Using a Q4W dose for SC amivantamab

Results of the updated deterministic scenario analyses for the comparison of amivantamab-lazertinib against osimertinib monotherapy and osimertinib-chemotherapy are presented in Table 20 and Table 21, respectively.

In all analyses, amivantamab-lazertinib at PAS price remained dominant over osimertinib monotherapy and osimertinib-chemotherapy at list price, indicating that the cost-effectiveness of amivantamab-lazertinib versus osimertinib monotherapy and osimertinib-chemotherapy remains robust when altering key modelling assumptions and approaches.

NICE National Institute for Health and Care Excellence

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

Table 20: Scenario analysis results for amivantamab-lazertinib versus osimertinib monotherapy (updated model; deterministic)

Scenario		At amivantamab and lazertinib PAS prices		
		Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Base case		[redacted]	[redacted]	−£101,178.24
Utility				
1	Treatment-specific PF HSUV (amivantamab-lazertinib: [redacted]; osimertinib monotherapy: [redacted])	[redacted]	[redacted]	−113,783.88
2	Pooled HSUV from the MARIPOSA clinical trial (PF: [redacted]; PD: [redacted])	[redacted]	[redacted]	−96,152.04
Administration costs				
3	NHS Payment Scheme Prices (IV administration: SB13Z/SB15Z [£365]; SC administration: SB12Z [£182])	[redacted]	[redacted]	−97,265.43
4	N10AF SC administration cost proportioned by chair time: 36 minutes	[redacted]	[redacted]	−102,521.44
PFS parametric extrapolations				
5	Higher PFS curve selections (exponential extrapolation for amivantamab-lazertinib and osimertinib monotherapy)	[redacted]	[redacted]	−102,186.25
6	Lower PFS curve selections (gamma extrapolation for amivantamab-lazertinib and osimertinib monotherapy)	[redacted]	[redacted]	−102,350.81
Dosing regimen of SC amivantamab				
7	Q4W dose [redacted]	[redacted]	[redacted]	−109,227.82

Abbreviations: AE: adverse events; HSUV: health state utility value; ICER: incremental cost-effectiveness ratio; incr.: incremental; INV: investigator; OS: overall survival; PAS: patient access scheme; PD: progressed disease; PFS: progression-free survival; QALYs: quality-adjusted life years; RWE: real-world evidence; SC: subcutaneous; TTD: time to treatment discontinuation or death.

NICE National Institute for Health and Care Excellence

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

Table 21: Scenario analysis results for amivantamab-lazertinib versus osimertinib-chemotherapy (updated model; deterministic)

Scenario		At amivantamab and lazertinib PAS prices		
		Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Base case		[redacted]	[redacted]	−332,735.72
Utility				
1	Treatment-specific PF HSUV (amivantamab-lazertinib: [redacted]; osimertinib-chemotherapy: [redacted])	[redacted]	[redacted]	−333,234.75
2	Pooled HSUV from the MARIPOSA clinical trial (PF: [redacted]; PD: [redacted])	[redacted]	[redacted]	−297,164.88
Administration costs				
3	NHS Payment Scheme Prices (IV administration: SB13Z/SB15Z [£365]; SC administration: SB12Z [£182]	[redacted]	[redacted]	−317,098.02
4	N10AF SC administration cost proportioned by chair time: 36 minutes	[redacted]	[redacted]	−335,794.82
TTD parametric extrapolations				
5	Higher osimertinib TTD curve in the osimertinib-chemotherapy arm: gamma	[redacted]	[redacted]	−391,169.18
PFS parametric extrapolations				
6	Higher amivantamab-lazertinib PFS curve: exponential	[redacted]	[redacted]	−330,462.56
7	Lower amivantamab-lazertinib PFS curve: gamma	[redacted]	[redacted]	−342,694.28
OS parametric extrapolations				
8	Alternative osimertinib-chemotherapy OS curve: 2-knot Normal	[redacted]	[redacted]	−292,650.55
Dosing regimen of SC amivantamab				
9	Q4W dose [redacted]	[redacted]	[redacted]	−351,068.35

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

Abbreviations: AE: adverse events; HSUV: health state utility value; ICER: incremental cost-effectiveness ratio; incr.: incremental; INV: investigator; OS: overall survival; PAS: patient access scheme; PD: progressed disease; PFS: progression-free survival; QALYs: quality-adjusted life years; RWE: real-world evidence; SC: subcutaneous; TTD: time to treatment discontinuation or death.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

Appendix C: Factual inaccuracies

Page number	Quote from the DGD	Factual inaccuracy identified and rationale for requested correction	Correction requested
6	*"Second-line treatments include:* *− atezolizumab with bevacizumab, carboplatin and **pemetrexed** (NICE technology appraisal 584)"*	NICE TA584 is for atezolizumab, plus bevacizumab, carboplatin and **paclitaxel**, not pemetrexed.	*"Second-line treatments include:* *− atezolizumab with bevacizumab, carboplatin and **paclitaxel** (NICE technology appraisal 584)"*
15	*Table 1, column 2, row 2: "**SB15Z**"*	J&J maintained the use of HRG code SB12Z for all combination administrations.	*Table 1, column 2, row 2: "**SB12Z**"*

Abbreviations: DGD: draft guidance document; NICE: National Institute for Health and Care Excellence.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 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):	EGFR+ UK

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

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.	In the last 24 months we received a one-off grant of £3,508 from Janssen to cover some of our patient support activities.
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.
Example 1	We are concerned that this recommendation may imply that ……..

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

1	First, EGFR+ UK notes with concern the committee's statement: "Clinical trial evidence shows that amivantamab plus lazertinib increases how long people have before their condition gets worse and how long people live compared with osimertinib alone. But it is uncertain whether amivantamab plus lazertinib works as well for people of different ages." We believe this line of reasoning sets a deeply troubling precedent. Age is a protected characteristic under the Equality Act 2010, and any implication that access to life-extending treatments could be conditional on age-related subgroup analyses is not only ethically problematic but potentially unlawful. Moreover, we strongly caution against requests for post hoc subgroup analyses based on age. Such analyses were not specified as an a priori hypothesis in the clinical trial design and, therefore, lack the statistical power and methodological rigour to draw meaningful conclusions. To base treatment recommendations or restrictions on such exploratory findings would constitute poor scientific practice. Additionally, as a patient-led charity representing a community of over 1,000 individuals affected by EGFR-mutated lung cancer, EGFR+ UK is uniquely positioned to comment on the demographics of this disease. Based on our most recent data, over 45% of our members were diagnosed under the age of 60. This reflects a broader trend: EGFR-positive lung cancer disproportionately affects younger, often otherwise healthy individuals. Given this demographic reality, we find it difficult to understand the rationale for conducting subgroup analyses based on age. Such an approach risks undermining the generalisability of the evidence and may inadvertently marginalise a substantial portion of the affected population. If anything, subgroup analyses that artificially separate younger and older patients threaten to obscure the real-world applicability of the clinical data. We therefore reject the premise that treatment efficacy should be stratified by age in this context. Clinical decisions and policy recommendations must be grounded in robust, inclusive science that upholds the principles of equity and fairness for all patients. Furthermore, it is essential that the analysis of treatment efficacy remains inclusive and reflective of the diverse patient population it is intended to serve. Stratifying by age not only introduces statistical and ethical concerns, but also risks excluding or minimising benefit in one of the groups most frequently affected by this disease. As such, the trial's overall results (demonstrating benefit across the full study population) should be afforded their appropriate evidentiary weight.
2	EGFR+ UK are concerned by the committee's reasoning that one of the justifications for not recommending amivantamab plus lazertinib was the absence of osimertinib plus chemotherapy as a comparator in the economic model. This rationale is both problematic and unfair. At the time of the company's submission, osimertinib combined with chemotherapy was not an available or routinely commissioned first-line treatment option. It is therefore unreasonable to expect its inclusion as a comparator in the modelling. Holding the submission to a retrospective standard undermines the integrity of the appraisal process and places an undue burden on the evidence provider. Furthermore, it is essential to consider the treatment preferences and lived experiences of patients. Through our consultations with individuals living with EGFR-positive lung cancer, we have found that a significant proportion (approximately half) express a strong desire to avoid chemotherapy as a first-line treatment. This aversion is driven by both the well-documented physical and emotional toll of chemotherapy and the uncertainty surrounding future treatment sequencing.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

	Specifically, patients are anxious about whether receiving platinum-based chemotherapy upfront may limit their options upon disease progression. There is widespread concern that first-line chemotherapy may preclude its use in subsequent lines, effectively "using up" a critical treatment option early in the care pathway. From a patient perspective, the ability to preserve multiple effective treatment lines over time is of paramount importance. A non-chemotherapy option such as amivantamab plus lazertinib may offer not only clinical benefits but also strategic value in maintaining long-term treatment flexibility. We therefore urge the committee to give due consideration to the patient voice and to recognise that treatment sequencing is not simply a clinical or economic matter; it is a deeply personal and strategic decision for those living with this disease.
3	The committee notes that there are uncertainties within the model related to quality of life outcomes. While we acknowledge that all models involve some degree of assumption, we strongly believe that these concerns should be weighed against the lived experiences of patients currently receiving amivantamab, either as monotherapy or in combination with lazertinib. From our engagement with EGFR-positive lung cancer patients who have received this treatment, the feedback has been consistently reassuring. The side-effect profile of amivantamab is reported to be both predictable and manageable; a finding supported by emerging real-world evidence and reflected in clinical trial data such as the COCOON study. Moreover, many patients have now experienced amivantamab delivered via subcutaneous injection. This method of administration appears to maintain efficacy while significantly reducing toxicity and hospital time, with minimal disruption to daily life. We have heard consistently positive feedback from patients who are receiving amivantamab subcutaneously, and for them their quality of life appears to be largely preserved. If comparing amivantamab plus lazertinib to the newly approved osimertinib plus chemotherapy in terms of quality of life, there is, from a patient perspective, a stark and unequivocal contrast. Chemotherapy is associated with substantial and often debilitating side effects that can severely limit physical functioning, independence, and overall wellbeing. By contrast, the combination of amivantamab and lazertinib offers a tolerable and comparatively gentle treatment experience. We therefore urge the committee to give appropriate weight to patient-reported outcomes and qualitative evidence. The preservation of quality of life should not be a secondary consideration; it is a central pillar of cancer care. In this respect, the amivantamab/lazertinib combination offers a compelling and meaningful benefit for patients living with EGFR-mutated lung cancer.
4	
5	
6	

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.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

- 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.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 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):	British Thoracic Oncology Group (BTOG)

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

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.	**Direct – financial** (if you have no interests in this category, state 'None') **J&J:** £1150.20 – Fees received as advisory consultant £234.74 – Fees received for educational activity **Astrazeneca:** **£8132.24 –** Fees received for educational activities £1620 – Fees received as advisory consultant **Boeringer Ingleheim** **£3323..64 – Fees received for educational activities** **£1840.00 – Fees received as advisory consultant** **Roche** **£1500 – Fees received as advisory consultant** **£1125 – Fees received for educational activities** **Pfizer:** **£3208 – Fees received as advisory consultant** **£375 – Fees received for educational activities** **Direct – non-financial** (if you have no interests in this category, state 'None') None **Indirect** (if you have no interests in this category, state 'None') None
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.
Example 1	We are concerned that this recommendation may imply that ……..

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

1	I agree utility should be different for osi single vs ami-laz combination,
2	I agree that Osimertinib -chemotherapy should be considered a comparator, understanding that this is only a recently adopted technology in the NHS, it is rapidly becoming an important option in front line EGFR mutant lung cancer. It is important to underline that there is lack of clinical consensus globally on optimal front line therapy in EGFR mutant lung cancer and what patients are more suitable for one regimen over another. Furthermore there is lack of clinical consensus to what treatment should be second line after chemo-osi or laz-ami.
3	Patient choice and co-morbidity will be an important contributing factor not necessarily captured here when deciding whether to opt for single agent Osimertinib when considering more intensive regimens such as Ami-Laz in clinical setting.
4	It is well known that clinical trials often represent young, fitter and less co-morbid populations. The small number of over 75 year olds in this study means that the outcomes in this cohort are less certain and should be interpreted with caution. There is no biological rationale of reduced efficacy in this cohort and as such urge caution in stratifying outcomes based on age alone and should not be used to discriminate.
5	
6	

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.
- Do not use abbreviations.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 25 July 2025. Please submit via NICE Docs.

- 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.

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 recommendations sound and a suitable basis for guidance to the NHS?

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation

Please return to: **NICE DOCS**

Dear all

Here are the numbers I promised you.

	Mean (years)	Median (years)	<65 years (%)	65-74 years (%)	≥75 years (%)
1L Osimertinib monotherapy (n=4600)	68.5	70	32.7%	33.2%	34.1%
1L Osimertinib plus chemotherapy (n=40)	64.0	63	55%	32.5%	12.5%

For 1L osimertinib plus chemotherapy, n=40 currently, so warnings re data numbers and early days in implementation.

EAG Request for ID6256

a) the vial sizes (mg of amivantamab) approved by the MHRA and the relevant SmPCs for these formulations

The vial sizes approved by the MHRA are 1,600mg and 2,240mg. Both SmPCs are attached.

a) the list price for each vial size (we presume the PAS is applied as a fixed % discount to all vial sizes but please advise if this is not correct)

The 1,600mg vial list price is £3,237.00 and the 2,240mg vial list price is £4,316.00. The list prices have been confirmed and approved. The PAS is applied as a fixed percentage discount to all vial sizes.

b) a table showing distribution of doses for induction and subsequent (maintenance cycles) for both the Q2W and the Q4W dosing schedules and information on the source of these distributions e.g. does the Q2W data come from PALOMA-3 and where does the Q4W data come from?

Table 1: Subcutaneous dose distributions

Regimen	Weight	Dose	Distribution (Induction)	Distribution (Subsequent)
Amivantamab-lazertinib, Q2W	< 80kg	1,600mg	[redacted]	[redacted]
		2,240mg		
	≥ 80kg	1,600mg		
		2,240mg		
Amivantamab-lazertinib, Q4W	< 80kg	1,600mg		
		2,400mg		
		3,520mg		
		4,640mg		
	≥ 80kg	1,600mg		
		2,400mg		
		3,520mg		
		4,640mg		

The distribution of SC doses was calculated based on data from MARIPOSA. This was done by mapping IV doses prepared for patients in MARIPOSA to the recommended SC doses and SC dose-reduction guidance (Table 2).

In PALOMA-3 the rates of dose reductions in subcutaneous (SC) and intravenous (IV) arms were similar to each other.[1] This supports the assumption which has been made that the dose distribution of IV could be transferable to SC. Whilst PALOMA-3

provides evidence on similarity between SC and IV, it should not be used to directly inform the distribution of SC doses as the trial was conducted in a different population (3L cEGFR NSCLC post osimertinib, post chemotherapy).
The distribution of doses was also investigated in Cohorts 1 and 6 of the PALOMA-2 trial.[2] These results were in line with the ones derived from MARIPOSA at a similar follow up time. PALOMA-2 is a less mature trial with a shorter follow-up compared to the MARIPOSA primary analysis (the August 2023 data cut) and is therefore a less reliable source of data for the model. Basing the distribution of doses on the MARIPOSA final analysis (the December 2024 data cut) is therefore most appropriate for modelling the SC formulation.

Correspondence between doses used in these calculations is summarised in Table 2 (except for cycle 1 day 1, for which 350 mg IV was assumed to correspond to the full recommended SC dose; and cycle 1 day 2, on which no SC administrations would take place and which was therefore ignored in the calculations). Each SC dose in the table has a corresponding vial, so the dose reductions do not rely on vial sharing.

Table 2. Correspondence Between IV and SC Amivantamab Doses (Excluding Cycle 1 Days 1 and 2)

IV Dose	Corresponding SC Dose			
	Body weight < 80 kg		Body weight ≥ 80 kg	
	Q2W Schedule[3]	Q4W Schedule[2]	Q2W Schedule[3]	Q4W Schedule[2]
350 mg	1,600 mg	1,600 mg	1,600 mg	1,600 mg
700 mg	1,600 mg	2,400 mg	1,600 mg	2,400 mg
1,050 mg	1,600 mg	3,520 mg	1,600 mg	3,520 mg
1,400 mg	2,240 mg	4,640 mg	2,240 mg	4,640 mg

Sources: Amivantamab SmPC for Q2W.[3] PALOMA-2 dosing schedule for Q4W.[2] Note the pending update to the SmPC to account for the Q4W.
Abbreviations: IV = intravenous; Q2W = once every 2 weeks; Q4W = once every 4 weeks; SC = subcutaneous

As can be seen in Table with the higher dose for the Q4W SC formulation, this less frequent dosing offers more opportunity for dose reductions than the Q2W. Therefore, cost-effectiveness modelling based on the Q4W formulation is provided as a scenario, in the outlook of an upcoming Q4W SC formulation (MHRA approval expected [redacted]).

c) information on the proportion of missed doses applied in the model for SC amivantamab and the source of this data i.e. is this based on the IV formulation in MARIPOSA and if so clarify why data relevant to the SC formulation are not applied

The MARIPOSA trial has been used to incorporate the missed doses for SC. This is fully supported by the information from the PALOMA-3 trial where the proportion of missed doses in SC and IV arms were very similar to each other. Based on this analysis, the proportion of missed doses with SC formulation was assumed to be the same as with the IV MARIPOSA.

Data from PALOMA-3 should not be directly incorporated into the model due to the difference in population between that and the MARIPOSA population.

d) information on the proportion of planned doses administered i.e. is this assumed to be 100% for SC formulation and if so what is the justification for this assumption.

Since the SC formulation is available in different vial sizes, the proportion of planned dose administered was replaced with the distribution of doses used to better reflect how different vials contribute to the effective dose of amivantamab used. This is similar to calculations used for lazertinib and osimertinib and it is described in greater detail in answer b).

e) any other information that is necessary for the committee to understand how the model has been adapted to accommodate the SC formulation including any adjustments to AEs, or other model inputs.

An 87.3% reduction is applied to the risk of infusion-related reactions with amivantamab-lazertinib, based on the difference in the incidence of grade 3 or higher infusion-related reactions between SC and IV amivantamab from PALOMA-3 (0.5% vs 3.8%).

References

1. Leighl NB, Akamatsu H, Lim SM, Cheng Y, Minchom AR, Marmarelis ME, Sanborn RE, Chih-Hsin Yang J, Liu B, John T, Massutí B. Subcutaneous versus intravenous amivantamab, both in combination with lazertinib, in refractory epidermal growth factor receptor–mutated non–small cell lung cancer: primary results from the phase III PALOMA-3 study. Journal of Clinical Oncology. 2024 Oct 20;42(30):3593-605.
2. Lim SM, Han JY, Zhang J, Mascarenhas E, Teixeira CA, Girard N, Peled N, Scott S, Gutierrez M, Bulotta A, Tan JL. 58P: Subcutaneous (SC) after intravenous (IV) amivantamab in advanced NSCLC: Initial results from PALOMA-2. Journal of Thoracic Oncology. 2025 Mar 1;20(3):S46-7.
3. Electronic Medicines Consortium. Rybrevant 1600 mg & 2240mg solution for injection. Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/101168/smpc [Accessed: August 2025].

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256].
A Single Technology Appraisal
2nd Addendum: EAG critique of the company's response to draft guidance

Produced by	Sheffield Centre for Health and Related Research (SCHARR), The University of Sheffield
Authors	Sarah Davis, Senior Research Fellow, SCHARR, University of Sheffield, Sheffield, UK Munira Essat, Senior Research Fellow, SCHARR, University of Sheffield, Sheffield, UK Sarah Ren, Research Associate, SCHARR, University of Sheffield, Sheffield, UK Sunhong Kwon, Research Associate, SCHARR, University of Sheffield, Sheffield, UK Emily Pulsford, Research Assistant, SCHARR, University of Sheffield, Sheffield, UK
Correspondence Author	Sarah Davis, Senior Research Fellow, SCHARR, University of Sheffield, Sheffield, UK
Date completed	7th August 2025

Source of funding: This report was commissioned by the NIHR Evidence Synthesis Programme as project number NIHR171848.

Declared competing interests of the authors

None of the other authors have any conflicts of interest to declare.

Rider on responsibility for report addendum

The views expressed in this report addendum are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

This addendum to the EAG report should be referenced as follows:

Davis S., Essat M., Ren S., Kwon S., Pulsford E. Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]. A Single Technology Appraisal – 2nd Addendum: EAG critique of the company's response to draft guidance. Sheffield Centre for Health and Related Research (SCHARR), 2025.

Contributions of authors

Sarah Davis was project lead. Munira Essat critiqued the clinical effectiveness evidence reported within the company's response to the draft guidance and Sarah Ren critiqued the statistical aspects. Sarah Davis critiqued the updated health economic analysis submitted by the company and undertook additional exploratory analyses.

1 Introduction

In June 2025, NICE published draft guidance on amivantamab with lazertinib for untreated epidermal growth factor receptor (EGFR) mutation-positive advanced non-small-cell lung cancer (NSCLC). As part of the draft guidance, the committee concluded that additional analyses and further evidence were needed to inform the final guidance. These included:

- modelling of progression-free survival (PFS) from the latest data cut
- an exploration of outcomes for the over 65 subgroup including Kaplan-Meier (KM) data for progression-free survival, overall survival and time to treatment discontinuation
- an analysis including osimertinib with chemotherapy as a comparator.

The draft guidance document (DGD) also noted the following committee preferences for the cost-effectiveness analysis based on the evidence available at the time of the first committee meeting.[1] These included:

- using data from the Systemic Anti-Cancer Therapy Dataset cohort to inform the baseline model characteristics
- using the EAG's preferred time to treatment discontinuation (TTD) extrapolations
- using the Weibull extrapolation to model overall survival (OS)
- applying treatment-specific utilities for the progression-free health state
- applying the amivantamab administration costs based on advice from the Cancer Drugs Fund (CDF) clinical lead

In its response to the DGD, the company provided some additional evidence and an updated cost-effectiveness analysis.[2] In its response to the DGD, the company also noted that its subcutaneous (SC) formulation of amivantamab received its UK Marketing Authorisation in July 2025.[3] The company's updated cost-effectiveness analysis therefore includes adaptations to reflect the availability of the SC formulation. This addendum to the EAG report provides the EAG's critique of the additional evidence submitted by the company in July 2025 and should be read in conjunction with the main EAG report.

Sections 2.1 to 2.3 discuss the company's response to the three requests for additional analyses. Section 2.4 discusses the clinical effectiveness and safety data for the SC formulation of amivantamab including a summary of data from the PALOMA-3 trial which compared SC amivantamab with intravenous (IV) amivantamab and which was used to support the new marketing authorisation for subcutaneous amivantamab. Sections 3.1 to 3.6 discuss the company's updated cost-effectiveness analysis including the EAG's critique of the updated analysis. Section 3.7 provides a summary of the EAG's addition analyses Section 4 provides a summary of the cost-effectiveness results for the company's updated base case and the EAG's exploratory analyses, including the EAG's preferred base case analysis. Section 5

provides the EAG's conclusions on the company's additional evidence and a discussion of the remaining uncertainties.

2 Summary of the company's response to the committee's requests for additional analyses

2.1 Additional PFS data from the latest data cut-off

2.1.1 Data provided

The primary endpoint analysis in the MARIPOSA trial was PFS assessed by BICR and was met at 11th August 2023 DCO with a median PFS of 23.7 months and 16.6 months for amivantamab with lazertinib (hereafter referred to as 'ami-laz') and osimertinib monotherapy, respectively. In response to the committee's request, the company provided longer-term PFS data from the 4th December 2024 DCO, with a median study follow-up of 37.8 months.[2] As longer time data were not available for BICR-assessed PFS, the updated PFS data were assessed by INV (see Table 1). The median PFS (INV) is [redacted] months in the ami-laz arm and [redacted] months in the osimertinib monotherapy arm. This is similar to INV assessed median PFS at the 11th August 2023 DCO; [redacted] months in the ami-laz arm and [redacted] months in the osimertinib monotherapy arm. The company stated that only PFS by INV could be identified for the 4th December 2024 DCO and therefore included it in the model, despite it not being the primary endpoint defined in the trial.

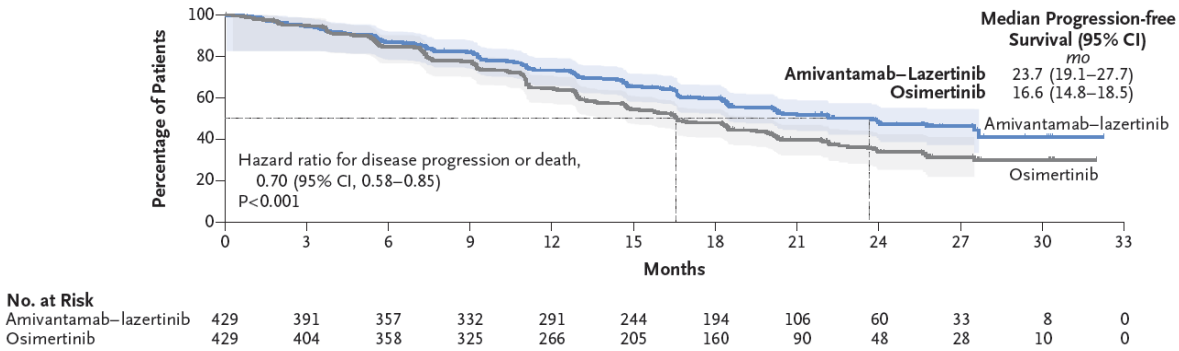
The KM curves for PFS by BICR from DCO 11th August 2023 as previously presented in the EAG report, Section 3.2.2.2 is presented in Figure 5 and by INV from DCO 4th December 2024 is presented in Figure 6.

Table 1. PFS results based on 4th December 2024 and 11th August 2023 DCOs (adapted from Table 1 in DGD response)

	DCO: 4th December 2024 (INV)		DCO: 11th August 2023 (INV)		DCO: 11th August 2023 (BICR)	
	Ami-laz (N=429)	Osimertinib (N=429)	Ami-laz (N=429)	Osimertinib (N=429)	Ami-laz (N=429)	Osimertinib (N=429)
Event, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	192 (44.8)	252 (58.7)
mPFS, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	23.7 (19.1, 27.7)	16.6 (14.8, 18.5)
HR (95% CI)	[redacted]		[redacted]		0.70 (0.58, 0.85)	
p-value	[redacted]		[redacted]		< 0.001	

Abbreviations: BICR: Blinded Independent Central Reviewer Assessment; CI: confidence interval; DCO: data cut-off; HR: hazard ratio; INV: investigator; PFS: progression-free survival.
Source: Johnson & Johnson data on file.

Figure 1. KM plot of PFS assessed by BICR (11th August 2023 DCO; FAS; reproduced from CS, Figure 8)



No. at Risk												
Amivantamab–lazertinib	429	391	357	332	291	244	194	106	60	33	8	0
Osimertinib	429	404	358	325	266	205	160	90	48	28	10	0

Abbreviations: BICR - blinded independent central review; CI - confidence interval; DCO - data cut-off; FAS - full analysis set; KM - Kaplan-Meier; mo - months; PFS - progression-free survival.
Source: Cho *et al.* 2024. Figure 1A.[4]

Figure 2. KM plot of PFS by INV; 4th December 2024 DCO; FAS (reproduced from Figure 1 in DGD response)

Abbreviations: FAS: full analysis set; INV: investigator; KM: Kaplan-Meier; PFS: progression-free survival.

2.1.2 Curves fitted to the updated PFS (INV) data

For the updated PFS (INV), the company has used independent fitting for ami-laz and osimertinib. The generalised gamma was selected as the base case model for both ami-laz and osimertinib, after considering its statistical fit, visual fit and clinical plausibility. Also, the company presented a higher (exponential) and a lower (gamma) curve as scenario analyses. The EAG is unable to comment on the shape of empirical hazard plots as the hazard plots in DGD response Figure 10 for ami-laz PFS (INV) appear to be identical to the hazard plots in DGD response Figure 12 for osimertinib PFS (INV), suggesting a potential labelling issue.[2]

For the ami-laz arm, the gamma model has the lowest AIC, and all other models except log-normal have similar AICs. Log-normal and log-logistic models give high predictions, and the other parametric distributions give similar predictions. For the osimertinib arm, the gamma model has the lowest AIC, followed by the Weibull and generalised gamma models, with a difference of less than three points. Log-normal and log-logistic models give high predictions, followed by the exponential model giving medium high predictions and all the other parametric distributions giving similar low predictions. Based on the current evidence, the EAG prefers to use the gamma model as the base case model for both ami-laz and osimertinib.

The company's response to the DGD states that the incorporation of the PFS (INV) data from the latest DCO has minimal impact on the cost-effectiveness estimates.[2] Although the company does not explicitly provide an explicit scenario analysis to support this statement, the EAG notes that the model presented at ACM1 was not particularly sensitive to the PFS estimates. The EAG's has explored applying its preferred PFS curves in its exploratory analysis.

2.2 Company's response to the request for data on the subgroup aged over 65

The committee indicated that the perceived lack of clinical effectiveness in older patients may be linked to older patients stopping treatment faster because of the AE profile of ami-laz and has requested additional analyses for the patients aged ≥65 years old. The company did not provide a cost-effectiveness modelling for the subgroup of patients aged ≥65 years old. Instead, the company argued that: (1) modelling the population aged ≥65 would reduce rather than enhance generalisability, (2) patients aged ≥65 years old in osimertinib arm overperform, (3) [redacted] and (4) correlation between age and efficacy not seen in other studies.

A further subgroup analysis of the MARIPOSA trial was presented in the Appendix with [redacted] as a cutoff age. Results suggest that interaction term is not statistically significant for the [redacted] cutoff.

Table 2 OS subgroup analysis across age subgroups (DCO: 4th December 2024, reproduced from DGD response Table 2)

Age groups, n	Subgroup Size		HR [95% CI]	Interaction term
	Ami-laz (N=429)	Osimertinib (N=429)		
<65 years	235	237	0.53 [0.40, 0.70]	[redacted]
≥65 years	194	192	1.11 [0.84, 1.48]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	
<75 years	378	376	0.75 [0.60, 0.93]	[redacted]
≥75 years	51	53	0.79 [0.47, 1.33]	

Abbreviations: DCO: data cut-off; HR: hazard ratio; OS: overall survival.
Source: Johnson & Johnson Data on File; Chih-Hsin Yang *et al.* ELCC 2025.[5]

The company suggested that the apparent difference in PFS benefit in the ami-laz arm between the subgroups of patients aged <65 and ≥65 years old is largely driven by the osimertinib arm overperforming in the subgroup of patients aged ≥65 years old relative to the ITT population, which impacts the overall comparative hazard ratio.

The company undertook a subgroup analysis of the MARIPOSA trial looking at patients <65 years and ≥65 years and comparing with the ITT population. The overall median PFS in the osimertinib monotherapy arm in the MARIPOSA trial was 16.59 months, versus [redacted] months for patients aged ≥65 years old and [redacted] in patients aged <65 years old (see Table 3).[6] The median PFS in patients ≥75 years was [redacted] months. The company noted that although median PFS is [redacted] in the ≥65 years old subgroup there is no biological rationale to explain this, and the subgroup analyses were not statistically powered to draw a conclusion from. The company also reported PFS for the subgroup of patients aged ≥65 years old in ami-laz versus ITT osimertinib monotherapy population from the MARIPOSA trial. This showed a favourable trend compared with osimertinib (HR: 0.88; 95% CI: 0.70, 1.11).

Table 3. Progression-free survival for ami-laz and osimertinib monotherapy in the ITT population, by age subgroup; DCO: 11th August 2023. (reproduced from Table 3 in DGD response)

	Stratified Analysis		**Unstratified Analysis**			
	Ami-laz (N=429)	**Osimertinib (N=429)**	**Ami-laz, <65 years (N=235)**	**Ami-laz, ≥65 years (N=194)**	**Osimertinib monotherapy, <65 years (N=237)**	**Osimertinib monotherapy, ≥65 years (N=192)**
Event (n, %)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Censored (n, %)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time to event (months)						

Median (95% CI)	23.72 (19.1, 27.7)	16.6 (14.8, 18.5)	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; DCO: data cut-off; ITT: intention-to-treat; NE: not evaluable.
Source: Cho *et al.* 2024.[7] Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 11th August 2023). Table 12, page 60.[8] Johnson & Johnson Data on File.

The company further added that the overperformance of the osimertinib monotherapy arm in PFS is considered a data anomaly that is translating to an apparent [redacted] in OS for patients aged ≥65 years old receiving ami-laz.

The median OS for osimertinib monotherapy in patients ≥65 years in the MARIPOSA is [redacted] is [redacted] than the median OS in the overall ITT population of the MARIPOSA trial (36.7 months) and the FLAURA2 trial (36.7 months), see Table 4.

Table 4. Median OS for osimertinib across MARIPOSA and FLAURA2 trials (reproduced from Table 4 in DGD response)

Subgroup for OS	**Median OS in the osimertinib arm**	
	MARIPOSA	**FLAURA2**
Total population	36.7 months (DCO: 4th December 2024)	36.7 months
≥65 years old	[redacted] (data on file; DCO: 11th August 2023)	34.7 months

Abbreviations: OS: overall survival.
Source: Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 4th December 2024).[9] GBA Dossier for benefit assessment: osimertinib.[10]

The company noted there was [redacted] The company undertook a sensitivity analysis [redacted] (see Table 5) [redacted] The subgroup data were not statistically powered to infer relative treatment effect and should be interpreted with caution.

Table 5: OS sensitivity analysis excluding early deaths for patients aged ≥65 years old in the MARIPOSA trial (reproduced from Table 6 in DGD response)

Data cut	**HR for patients aged ≥65 years old (95% CI)**
First data cut (DCO: 11th August 2023)	[redacted]
Second data cut (DCO: 13th May 2024)	[redacted]
Final OS analysis (DCO: 4th December 2024)	[redacted]

Abbreviations: DCO: clinical cut-off; HR: hazard ratio; OS: overall survival.
Source: Johnson & Johnson Data on File.

The EAG acknowledges the efforts undertaken by the company and agrees that the current evidence may be insufficient to demonstrate a meaningful difference in the efficiency of ami-laz versus osimertinib for patients aged ⩾65 years old. The EAG considers it possible that the [redacted].

2.3 Company's comparison of amivantamab with lazertinib against osimertinib with chemotherapy

In its original company's submission (CS), the company argued that osimertinib with chemotherapy (referred to hereafter as osi-chemo) was not a relevant comparator for ami-laz because osi-chemo was still under appraisal by NICE and was therefore not yet part of the current standard of care in the NHS. In its response to the DGD, the company maintained this position but also provided an economic analysis that included osi-chemo as a comparator to fulfil the committee's request.[2] This section describes the methods used by the company to implement an indirect comparison of clinical effectiveness within the economic analysis (i.e. estimates of OS, PFS and TTD). Other aspects of the economic analysis that were required to incorporate the additional comparator within the economic model, such as resource use for administration of the osimertinib plus chemotherapy arm, are discussed in Section 3.

2.3.1 Suitability of MARIPOSA and FLAURA2 for indirect comparison

As no trials were available comparing ami-laz directly against the comparator of osi-cheo, the company made an indirect comparison by combining data from the MARIPOSA trial,[7] which compared ami-laz against osimertinib, and the FLAURA2 trial, which compared osi-chemo against osimertinib.[11] The chemotherapy regimen used in FLAURA2 was pemetrexed (500 mg/m^2) with either cisplatin (75 mg/m^2) or carboplatin (AUC5). The platinum component was offered for 4 cycles of 3 weeks and pemetrexed was continued until disease progression or until another discontinuation criteria was met (patient decision, investigator decision, adverse events [AEs], non-compliance, incorrect initiation or pregnancy). The osimertinib arms of both trials were consistent with the licensed dose (80 mg once daily).

2.2.1.1 Inclusion and Exclusion Criteria

The inclusion and exclusion criteria of the MARIPOSA and FLAURA2 trials were generally similar. Both trials included patients with untreated, locally advanced or metastatic NSCLC with EGFR exon 19 deletion or L858R substation mutations, who were asymptomatic and had stable central nervous system (CNS) metastases with an Eastern Cooperative Oncology Group (ECOG) or World Health Organization (WHO) performance score (PS) of 0 or 1. (Further details are provided in Table 1).

Table 6. Inclusion and Exclusion Criteria for MARIPOSA and FLAURA2 Trials

MARIPOSA[7]	FLAURA2[11]
Key inclusion criteria	
• Adult patients (≥18 years of age). • Newly diagnosed, histologically- or cytologically-confirmed locally advanced or metastatic NSCLC that is treatment-naïve and not amenable to curative therapy, including surgical resection or chemoradiation. • The tumour must have documented EGFR Exon19del or Exon 21 L858R substitution, as detected by a Food and Drug Administration (FDA)-approved or other validated test in an accredited local laboratory, in accordance with SoC. A copy of the test report (documenting the EGFR mutation) must be included in the participant records and must also be submitted to the sponsor. • ECOG PS of 0 or 1. • Adequate organ and bone marrow function, without history of red blood cell transfusion, platelet transfusion, or granulocyte colony-stimulating factor within 7 days prior to the date of the test. • At least one measurable lesion, according to RECIST v1.1, that has not been previously irradiated.	• Adult patients (≥18 years of age; patients from Japan at least 20 years of age). • Newly diagnosed locally advanced (clinical stage IIIB, IIIC) or metastatic NSCLC (clinical stage IVA or IVB) or recurrent NSCLC, not amenable to curative surgery or radiotherapy. • Patients must have untreated advanced NSCLC not amenable to curative surgery or radiotherapy. Prior adjuvant and neo-adjuvant therapies (chemotherapy, radiotherapy, immunotherapy, biologic therapy, investigational agents), or definitive radiation/chemoradiation with or without regimens including immunotherapy, biologic therapy, investigational agents, are permitted as long as treatment was completed at least 12 months prior to the development of recurrent disease. • Pathologically confirmed non-squamous NSCLC. NSCLC of mixed histology is allowed. • The tumour harbours 1 of the 2 common EGFR mutations known to be associated with EGFR-TKI sensitivity (Ex19del or L858R), either alone or in combination with other EGFR mutations, which may include T790M, assessed by a CLIA-certified (US sites) or an accredited (outside of the US) local laboratory or by central prospective tissue testing. • WHO PS of 0 to 1 at screening with no clinically significant deterioration in the previous 2 weeks. • At least 1 measurable lesion, not previously irradiated that can be accurately measured at baseline and as long as it has not been biopsied within 14 days of the baseline tumour assessment scans.
Key exclusion criteria	
• Have received any prior systemic treatment at any time for locally advanced or metastatic disease (adjuvant or neoadjuvant therapy for Stage I or II disease is allowed, if administered more than 12 months prior to the development of locally advanced or metastatic disease). • Symptomatic brain metastases. A participant with asymptomatic or previously treated and stable brain	• Spinal cord compression and unstable brain metastases. Patients with stable brain metastases who have completed definitive therapy, are not on steroids, and have a stable neurological status for at least 2 weeks after completion of the definitive therapy and steroids can be enrolled. Patients with asymptomatic brain metastases can be eligible for inclusion if in the opinion of the Investigator immediate definitive treatment is not indicated. • Past medical history of ILD, drug-induced ILD, radiation pneumonitis that required steroid treatment, or any evidence of clinically active ILD.

metastases may participate in this study. Participants who have received definitive radiation or surgical treatment for symptomatic or unstable brain metastases and have been clinically stable and asymptomatic for at least 2 weeks before randomization are eligible, provided they have been either off corticosteroid treatment or are receiving low-dose corticosteroid treatment (≤10 mg/day prednisone or equivalent) for at least 2 weeks prior to randomization. • Have received prior EGFR TKI treatment. • Active or past medical history of leptomeningeal disease. • A history of spinal cord compression that has not been treated definitively with surgery or radiation. • Uncontrolled tumour-related pain. • Active or past medical history of interstitial lung disease (ILD)/pneumonitis, including drug-induced ILD, or radiation ILD/pneumonitis. • Uncontrolled inter-current illness. • Concurrent or prior malignancy other than the disease under study. • Have active cardiovascular disease. • Positive hepatitis B, C, or other clinically active infectious liver disease at screening. • Received an investigational drug within 12 months before randomisation or is currently enrolled in an investigational study.	• Any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension and active bleeding diatheses, which in the Investigator's opinion makes it undesirable for the patient to participate in the trial or which would jeopardize compliance with the protocol, or active infection including hepatitis B, hepatitis C and human immunodeficiency virus (HIV). Screening for chronic conditions is not required. Active infection will include any patients receiving treatment for infection. • Inadequate bone marrow reserve or organ function. • Any concurrent and/or other active malignancy that has required treatment within 2 years of first dose of IP. • Any unresolved toxicities from prior systemic therapy (eg, adjuvant chemotherapy) greater than CTCAE Grade 1 at the time of starting study treatment, with the exception of alopecia and Grade 2 prior platinum-therapy related neuropathy. • Refractory nausea and vomiting, chronic gastrointestinal diseases, inability to swallow the formulated product, or previous significant bowel resection that would preclude adequate absorption of osimertinib. • Prior treatment with any systemic anti-cancer therapy for advanced NSCLC not amenable to curative surgery or radiation including chemotherapy, biologic therapy, immunotherapy, or any investigational drug. • Prior adjuvant and neo-adjuvant therapies (chemotherapy, radiotherapy, immunotherapy, biologic therapy, investigational agents), or definitive radiation/chemoradiation with or without regimens including immunotherapy, biologic therapies, investigational agents are permitted as long as treatment was completed at least 12 months prior to the development of recurrent disease. • Have active cardiovascular disease. • Prior treatment with an EGFR-TKI. • Major surgery within 4 weeks of the first dose of investigational product. Procedures such as placement of vascular access, biopsy via mediastinoscopy or biopsy via video assisted thoracoscopic surgery (VATS) are permitted. • Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of the first dose of IP. • Current use of (or unable to stop use prior to receiving the first dose of study treatment) medications or herbal supplements known to be

	strong inducers of cytochrome P450 (CYP) 3A4 (at least 3 weeks prior).

Abbreviations: CTCAE - Common Terminology Criteria for Adverse Events; ECOG PS - Eastern Cooperative Oncology Group performance status; EGFR - epidermal growth factor receptor; NSCLC - non-small cell lung cancer; RECIST v1.1 - Response Evaluation Criteria in Solid Tumors version 1.1; SoC – Standard of Care; TKI - Tyrosine Kinase Inhibitor; WHO PS - World Health Organization performance status

2.2.1.2 Baseline patient characteristics

The baseline patient characteristics of the MARIPOSA trial and The FLAURA2 trial are provided in Table 7. Although baseline characteristics were broadly similar between MARIPOSA and FLAURA2 for the available data, there were in differences in the types of baseline characteristics reported in the two trials, making direct comparisons difficult. The FLAURA2 cohort were younger (median age range 26-85 vs 25-88 years), had a slightly higher proportion of Asian patients (64% vs 59%), fewer patients with ECOG PS 1 (63% vs 66%), and had more patients with a history of smoking (34% vs 31%) compared with MARIPOSA. Furthermore, it should be noted that the MARIPOSA included planned subgroup analyses showing benefit across TP53-mutant, baseline ctDNA-positive, and liver metastasis cohorts. However, in FLAURA2 these subgroup analyses are not available. In addition, BMI (body mass index) data were also not reported in the FLAURA2 study, which made it difficult to compare with MARIPOSA data.

Table 7. Patient Characteristics of MARIPOSA and FLAURA2 Trials (adapted from CS, page 50, Table 7, 8 and 9

Characteristic	**Ami-laz (N=429)**	**Osimertinib (N=429)**	**Lazertinib (N=216)**	**Osi-chemo (N=279)**	**Osimertinib (N=278)**
	MARIPOSA			**FLAURA2**	
Age, years					
Median (range)	64 (25, 88)	63 (28, 88)	63 (31, 87)	61 (26–83)	62 (30–85)
Female Sex, n (%)	275 (64)	251 (59)	136 (63)	173 (62)	169 (61)
Race, n (%)[a]					
Asian	250 (58)	251 (59)	128 (59)	179 (64)	176 (63)
White	164 (38)	165 (38)	79 (37)	74 (27)	83 (30)
American Indian or Alaska Native	7 (2)	7 (2)	4 (2)	11 (4)	6 (2)
Black	4 (1)	3 (1)	4 (2)	2 (1)	3 (1)
Other	4 (1)	3 (1)	1 (< 1)	13 (5)	10 (4)

Characteristic	Ami-laz (N=429)	Osimertinib (N=429)	Lazertinib (N=216)	Osi-chemo (N=279)	Osimertinib (N=278)
	MARIPOSA			FLAURA2	
Body Weight, kg					
Mean (SD)	[redacted]	[redacted]	[redacted]	NR	NR
Median (range)	62.5 (32, 118)	62 (35, 109)	60.5 (41, 118)	NR	NR
Body mass index, kg/m^2					
Mean (SD)	[redacted]	[redacted]	[redacted]	NR	NR
Median (range)	[redacted]	[redacted]	[redacted]	NR	NR
History of smoking, n (%)					
No	299 (70)	295 (69)	143 (66)	188 (67)	181 (65)
Yes	130 (30)	134 (31)	73 (34)	91 (33)	97 (35)
EGFR mutation, n (%)[b]					
Exon 19 deletion	258 (60)	257 (60)	131 (61)	169 (61)	168 (60)
Exon 21 L858R substitution	172 (40)	172 (40)	85 (39)	106 (38)	107 (38)
Both exon 19 deletion and L858R mutation				3 (1)	1 (<1)
Unknown				1 (<1)	2 (1)
History of brain metastasis, n (%)	178 (41)	172 (40)	86 (40)		
CNS metastases, n (%)				116 (42)	110 (40)
ECOG/WHO PS, n (%)					
0	141 (33)[e]	149 (35)[e]	76 (35)[e]	104 (37)[f]	102 (37)[f]
1	288 (67)[e]	280 (65)[e]	140 (65)[e]	174 (62)[f]	176 (63)[f]

Characteristic	Ami-laz (N=429)	Osimertinib (N=429)	Lazertinib (N=216)	Osi-chemo (N=279)	Osimertinib (N=278)
	MARIPOSA			**FLAURA2**	
2	0	0	0	1 (<1)[f]	0[f]
Initial diagnosis NSCLC subtype, n (%)					
Adenocarcinoma	417 (97)	415 (97)	212 (98)	275 (99)	275 (99)
Large cell carcinoma	3 (1)	0	0	0	0
Squamous cell carcinoma	6 (1)	5 (1)	2 (1)	2 (1)	0
Other [d]	2 (< 1)	9 (2)	2 (1)	2 (1)	3 (1)
Not reported	1 (< 1)	0	0	0	0
Location of metastasis at screening, n (%)[e]					
N	[redacted]	[redacted]	[redacted]		
Bone	[redacted]	[redacted]	[redacted]	132 (47)	142 (51)
Liver	[redacted]	[redacted]	[redacted]	43 (15)	66 (24)
Brain	[redacted]	[redacted]	[redacted]		
Lymph Node	[redacted]	[redacted]	[redacted]		
Adrenal Gland	[redacted]	[redacted]	[redacted]		
Lung	[redacted]	[redacted]	[redacted]		
Other	[redacted]	[redacted]	[redacted]		

[a] Race or ethnic group was reported by the patients.
[b] One patient in the ami-laz group had both EGFR mutation types.
[c] ECOG performance-status scores range from 0 to 5, with higher scores indicating greater disability.
[d] Other histologic types included adenocarcinoma and squamous-cell carcinoma, lepidic adenocarcinoma, non–small- cell carcinoma, pleomorphic carcinoma, and unknown.
[e] Patients can be counted in more than one category.
[f]WHO performance-status scores a range from 0 to 5, with higher scores indicating greater disability.
Abbreviations: CNS - central nervous system; ECOG - Eastern Cooperative Oncology Group; EGFR - epidermal growth factor receptor; FAS - full analysis set; NSCLC - non-small cell lung cancer; PS - performance status; SD - standard deviation; WHO - World Health Organization

2.2.1.3 Consistency in outcomes

Both trials reported PFS assessed by blinded independent central review (BICR) using the Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 guidelines to define disease progression. Both trials also reported investigator assessed (INV) PFS. In MARIPOSA the BICR PFS outcome was the primary outcome with INV PFS reported as a secondary outcome, whereas in FLAURA2, the INV PFS

was the primary outcome whereas the BICR PFS was reported as a sensitivity analysis. OS was reported in both trials as a key secondary outcome. TTD was reported by both companies as part of their company submissions. In both cases, the companies reported TTD for individual components of the treatment combinations (i.e. the osimertinib component and the pemetrexed component of the osi-chemo regimen were reported separately, as were the amivantamab and lazertinib components of the ami-laz regimen). TTD was not reported for the platinum component of the osi-chemo regimen as this was offered for a fixed number of cycles.

2.2.1.4 *Conclusion regarding the comparability of the MARIPOSA and FLAURA2 trials*

The EAG did not identify any factors in the inclusion/exclusion criteria of the two trials or the base line characteristics that would indicate that it would be inappropriate to conduct an indirect treatment comparison using these two trials.

2.3.2 Statistical approach used for the indirect treatment comparison

To compare ami-laz versus osi-chemo, the company explored the use of a hazard ratio (HR) based indirect treatment comparison (ITC) approach, given that osimertinib is the common comparator in both MARIPOSA and FLAURA2 trials. After checking the log-cumulative hazard plots and the Schoenfeld residual tests, the company found that the proportional hazards (PH) assumption did not hold for either PFS (INV) or OS in MARIPOSA. Also, the company stated that in TA1060 (NICE appraisal of osimertinib with pemetrexed and platinum-based chemotherapy for untreated EGFR mutation-positive advanced non-small-cell lung cancer),[12] both the submitting company and the EAG agreed that the PH assumption was not met in FLAURA2. As a result, the company concluded that a HR-based ITC approach is not appropriate. The EAG agrees that it may not be appropriate to derive the adjusted survival curves for osi-chemo by applying a constant HR to the survival curves of ami-laz due to the violations of PH assumptions.

Instead, the company assumed that the potential differences between the MARIPOSA and FLUARA2 trials would be reflected by the differences in the outcomes of the common comparator (osimertinib). Thus, they calculated the HR of osimertinib in MARIPOSA versus osimertinib in FLARURA2 and applied the estimated HR to the curves for osi-chemo from FLAURA2. The estimated HR of osimertinib in MARIPOSA versus osimertinib FLAURA2 were [redacted] for PFS, OS and TTD respectively. The EAG notes that the adjustment goes one way for PFS and the other way for OS suggesting that patients receiving osimertinib monotherapy in the MARIPOSA trial do not have consistently worse or better outcomes than those receiving the same treatment in the FLAURA2 trial.

Applying the HR of osimertinib in MARIPOSA versus osimertinib in FLARURA2 to estimate the expected outcomes for osi-chemo in the MARIPOSA trial population would also require the PH

assumption to hold between two trials. However, the company did not assess the PH assumption between the osimertinib arm in MARIPOSA and the osimertinib arm in FLARUA2. The EAG notices that the KM curves for osimertinib from the two trials cross for PFS, OS and TTD, indicating that the PH assumption is unlikely to hold. Also, applying the HR to adjust the survival curves of osi-chemo from FLAURA2 implies that MARIPOSA patients respond either better or worse to the same extent as FLAURA2 patients when treated with osi-chemo compared to osimertinib alone. Therefore, the EAG does not believe that these adjustments can be interpreted as being an adjustment to account for differences between the study populations that make patients in one trial respond better or worse on average than patients in the other trial.

The EAG gathered the reported HRs for PFS and OS from MARIPOSA and FLAURA2 at the latest data cut off (DCO) reported in each case. In the MARIPOSA trial for the comparison of ami-laz with osimertinib, the PFS (BICR) HR was 0.70 (95% CI: 0.58-0.85, p<0.001) at the primary data cut off (11th August 2023). The PFS (INV) HR was [redacted]) at the 4th December 2024 DCO. The OS HR was 0.75 (95% CI: 0.61-0.92; p=0.048) at the 4th December 2024 DCO. In the FLAURA2 trial for the comparison of osi-chemo with the osimertinib monotherapy, the PFS (BICR) HR was 0.62 (95% CI: 0.48-0.80), and the PFS (INV) HR was 0.62 (95% CI: 0.49-0.79, p<0.0001) at the primary endpoint data cut off (03 April 2023 DCO). The OS HR was 0.75 (95% CI: 0.57-0.97) at the 8th January 2024 DCO.

Given the similarities in baseline characteristics between the MARIPOSA and FLAURA2 studies, and the small differences in estimated HRs in the two trials for both PFS and OS, the EAG prefers a naïve indirect comparison between the ami-laz arm of MARIPOSA and the osi-chemo arm of FLAURA2. While the EAG acknowledges that this naïve comparison does not account for potential population differences between the two studies, it has the advantage of not relying on the PH assumption. Nonetheless, an ITC approach that accounts for the time-varying treatment effects and the population heterogeneity would be more appropriate.

2.3.3 Curve choices for the osimertinib with chemotherapy comparator

Overall, the EAG agreed with the company's stated preference to align the curve choices for osi-chemo to those described in the committee's preferences in TA1060. However, the EAG noted that the company appeared to have misunderstood the committee's preferences for the TTD curve for the osimertinib component of the osi-chemo arm.

2.2.3.1 Data used

For extrapolating PFS (INV) and OS for osi-chemo, the company reconstructed pseudo individual patient data (IPD) after digitalising published KM curves in TA1060. For TTD, the company stated that

some fitted parametric models from reconstructed IPD did not match the curves presented in TA1060. Thus, they digitised the parametric curves presented in TA1060 and fitted models to the digitised points directly. TTD for the osimertinib and pemetrexed components of osi-chemo were modelled separately. TTD for carboplatin/cisplatin was not modelled given the fixed number of cycles received.

2.2.3.2 PFS (INV) for osi-chemo

Standard parametric models were fitted to PFS. In line with the committee's preferred base case in TA1060, the Weibull model was selected as the preferred base case model. After assessing the statistical and visual fit, clinical plausibility, and hazard plots, the EAG supports the use of the Weibull model in the base case. Although the AIC of the Weibull model was seven points higher than that of the best-fitting alternative models, the EAG considered its long-term predictions to be more clinically plausible.

Figure 3: Long-term PFS predictions of osi-chemo (DCO: 4th December 2024; FAS, reproduced from DGD response Figure 13)

Abbreviations: CP: chemotherapy; INV: investigator; OSI: osimertinib; PFS: progression-free survival.

2.2.3.3. OS for osi-chemo

Both standard parametric models and the spline models were fitted to OS. In line with the Committee's preferred base case in TA1060, the 2-knot odds spline model was selected as the preferred base case model.[12] After assessing the statistical and visual fit, clinical plausibility, and hazard plots, the EAG supports the use of the 2-knot odds spline model in the base case. The standard parametric models do not appear to provide a good visual fit to the KM curve. The 2-knot odds and 2-knot normal spline models provide a good fit to the KM data and to the hazard plots.

Figure 4: Long-term OS predictions of osi-chemo (reproduced from Figure 17 in DGD response)

Abbreviations: CP: chemotherapy; KM: Kaplan-Meier; OS: overall survival; OSI: osimertinib.

2.2.3.4 TTD for osi-chemo

For the osimertinib component of osi-chemo, the company selected the average of the Gompertz and gamma curves for extrapolation in the company's base case analysis, to align with the approach taken in TA1060. However, the EAG noted that the company appeared to have misunderstood the committee's preferences for the TTD curve. The company appears to have interpreted the committee's preferences as being the average of the Gompertz and the gamma curves, whereas the EAG believes the committee's preference was for the Gompertz curve. In TA1060, both the company and the EAG preferred Gompertz, the model with the lowest AIC in their base case and considered all curves except the Gompertz and generalised gamma to be implausible.[12] The EAG has therefore implemented the Gompertz curve in its preferred analyses. The EAG notes that standard parametric models do not appear to capture the turning point observed in KM curve at around 2 years and spline models may be able to fit the KM data better and provide more plausible long-term extrapolations.

For the pemetrexed component of osi-chemo, the company used exponential distribution for extrapolation in its base case analysis. The exponential model was selected by the company in TA1060 as it gave plausible long-term predictions.[12] The EAG agrees with the use of exponential model but also notes that the exponential model does not provide a good fit to the data and a more flexible model would be more appropriate. The AIC of the exponential model is 18-point higher than the lowest AIC from the fitted parametric models.

Figure 5: Long-term TTD projections of osimertinib component in the osi-chemo arm (reproduced from Figure 22 in DGD response)

Abbreviations: CP: chemotherapy; OSI: osimertinib; TTD: time to treatment discontinuation.

Figure 6: Long-term TTD prediction of chemotherapy in the osi-chemo arm (reproduced from Figure 23 in DGD response)

Abbreviations: CP: chemotherapy; KM: Kaplan-Meier; OSI: osimertinib; TTD: time to treatment discontinuation.

2.4 Clinical effectiveness evidence for the subcutaneous formulation of amivantamab

In its response to the DGD, the company also noted that its SC formulation of amivantamab received its UK Marketing Authorisation in July 2025.[2] The SmPCs for the two new subcutaneous formulations (1600 mg and 2240mg) state, "*The efficacy of Rybrevant subcutaneous formulation in patients with EGFR-mutated locally advanced or metastatic NSCLC is based on achieving non-inferior PK [pharmokinetic] exposure to intravenous amivantamab in the non-inferiority study PALOMA-3 […]. The study demonstrated non-inferior efficacy of subcutaneous to intravenous amivantamab given in combination with lazertinib in patients with EGFR-mutated locally advanced or metastatic NSCLC whose disease has progressed on or after treatment with osimertinib and platinum-based chemotherapy*".[3] The company has assumed in its cost-effectiveness analysis that SC amivantamab is received by all patients and that the data from the effectiveness and safety data from the MARIPOSA study can be assumed to translate directly to the SC formulation. The only adaption made to reflect the fact that SC amivantamab is being used instead of IV amivantamab is a reduction to the rate of infusion related reactions (IRRs) and calculations required to estimate the drug acquisition cost for equivalent doses of SC amivantamab. These are described further in Section 3.5 below.

The company has only presented data from PALOMA-3 in its response to the DGD when discussing the impact of the SC formulation on administration costs, AEs and health related quality of life (HRQoL).[2] The EAG is not in a position to critique the clinical equivalence of SC and IV amivantamab based on non-inferior pharmacokinetic exposure. However, it notes that the balance of costs and benefits for ami-laz versus comparator treatments (i.e. osimertinib monotherapy or osi-chemo) will be dependent on estimates of PFS, OS and TTD, which could be reasonably expected to differ between the SC and IV formulations of amivantamab. As such, the EAG briefly presents some key information regarding the PALOMA-3 trial to allow the committee to make a judgment regarding the degree of uncertainty that is introduced by the company's assumption that the OS, PFS and TTD estimates from MARIPOSA are generalisable to clinical practice if SC amivantamab is used instead of IV amivantamab.

2.4.1 PALOMA-3 trial

PALOMA-3 was a study assessing the non-inferiority of pharmacokinetics, efficacy and safety of SC amivantamab versus IV amivantamab, both in combination with oral lazertinib, in patients with cEGFRm NSCLC whose disease has progressed on or after osimertinib and platinum-based chemotherapy irrespective of the order.13 The dose of SC amivantamab was 1,600 mg for patients weighing under 80 kg and 2,240 mg for patients weighing 80 kg and over, to be given weekly over the first 4 weeks and then every 2 weeks thereafter. The dose of IV amivantamab was the same as used in MARIPOSA and the dose of lazertinib given in both arms matched the dose in MARIPOSA. A protocol amendment was made to include prophylactic anticoagulation for the first 4 months of treatment following the increased risk of VTE reported in the MARIPOSA study.

The clinical efficacy data reported are based on the primary analysis and were collected prior to the January 3, 2024, data cutoff date (see Table 8). In total, 418 patients underwent random assignment (SC group, n= 206; IV group, n= 212). The main results from the PALOMA-3 study are reported by Leighl *et al*.[13]

2.4.1.1. Treatment exposure

Median duration of amivantamab administration on Cycle-1-Day-1 was 4.8 minutes (range, 0-18) in the SC group and 5.0 hours (range, 0.2-9.9) for the first infusion in the IV group. Corresponding values on Cycle-3-Day-1 were 4.8 minutes (range, 0-12) and 2.3 hours (range, 0.5-4.4), respectively. At the data cutoff, 92 patients (45%) in the SC group and 96 patients (46%) patients in the IV group were still undergoing treatment. The median time to discontinuation of amivantamab was 6.7 months in the SC group and 5.6 months in the IV group. The HR for time to treatment discontinuation of amivantamab favoured the SC formulation but the difference was not statistically significant (0.86: 95%CI 0.66 to 1.12).

2.4.1.2 Objective Response Rate

Objective response (complete or partial) was 30% (95% CI, 24 to 37) in the SC group and 33% (95% CI, 26 to 39) in the IV group (relative risk, 0.92; 95% CI, 0.70 to 1.23). Median time to response was 1.5 months in both groups (range, 1.2-6.9 for SC; 1.2-9.9 for IV). Among confirmed responders, median response duration (DoR) was 11.2 months (95% CI, 6.1 to not estimable [NE]) in the SC group and 8.3 months (95% CI, 5.4 to NE) in the IV group. A DoR of ≥6 months was observed in 29% of patients in the SC group and 14% in the IV group.

The proportion of patients with stable disease was 45% in the SC group and 38% in the IV group. Disease control rate was 75% (95% CI, 69 to 81) in the SC group and 71% (95% CI, 64 to 77) in the IV group.

2.4.1.3 Progression-free survival

Median PFS of SC versus IV amivantamab, was 6.1 months (95% CI, 4.3 to 8.1) and 4.3 months (95% CI, 4.1 to 5.7), respectively, but did not reach statistical significance (HR for disease progression or death, 0.84; 95% CI, 0.64 to 1.10; $P = 0.20$).

2.4.1.5 Overall Survival

Death occurred in 43 patients in the SC and 62 patients in the IV group, with progressive disease accounting for 35/43 (81%) deaths and 50/62 (81%) deaths, respectively. The proportion of patients alive at 6 and 12 months was 85% (95% CI, 79 to 89) and 65% (95% CI, 52 to 74), respectively, in the

SC group, and 75% (95% CI, 68 to 80) and 51% (95% CI, 37 to 64) in the IV group. OS was significantly longer in the SC group compared with the IV group (HR for death, 0.62; 95% CI, 0.42 to 0.92; nominal $P = 0.02$).

Table 8. Key Efficacy End Points in PALOMA-3 (reproduced from Leighl et al)

End Point	Subcutaneous Group (n = 206)	Intravenous Group (n = 212)	Treatment Effect (95% CI)	*P*
Objective response[a]				
Patients, % (95% CI)	30 (24 to 37)	33 (26 to 39)	Relative risk for noninferiority, 0.92 (0.70 to 1.23)[b]	0.001
Progression-free survival				
Median, month (95% CI)	6.1 (4.3 to 8.1)	4.3 (4.1 to 5.7)	HR, 0.84 (0.64 to 1.10)	0.20
Patients, % (95% CI)				
At 6 months	50 (43 to 58)	42 (35 to 50)		
At 12 months	37 (28 to 46)	20 (8 to 35)		
Overall survival				
Median, months (95% CI)	12.9 (12.9 to NE)	NE (10.2 to NE)	HR, 0.62 (0.42 to 0.92)[c]	0.02[c]
Patients, % (95% CI)				
At 6 months	85 (79 to 89)	75 (68 to 80)		
At 12 months	65 (52 to 74)	51 (37 to 64)		

Abbreviations: CI - confidence Interval; HR - hazard ratio; NE - not estimable

[a]The objective response (complete or partial response as best response) was assessed by the investigator among all responders.

[b]Odds ratio (95% CI), 0.87 (0.58 to 1.32); $P = .52$. *P* value is calculated via a logistic regression model stratified by brain metastases at baseline (yes *v* no), *EGFR* mutation (L858R *v* Ex19del), race (Asian *v* non-Asian), and last therapy (osimertinib [or another third-generation EGFR-TKI] *v* chemotherapy).

[c]For overall survival, 95% CIs were not adjusted for multiplicity and should not be used in place of hypothesis testing; *P* value is nominal.

2.4.1.6 Adverse events

Table 9 presented AE data from the PALOMA-3 study as reported by Leighl *et al.*[13] It can be seen that fewer patients in the SC group experienced infusion-related reactions (IRRs) (13% for SC vs 66% for IV), with low rates for Grade ≥3 IRRs (0.5% vs 4%). The rate of venous thromboembolism (VTE) was lower for SC versus the IV group (9% vs 14%). The rates of AEs leading to interruption or

discontinuation of any study drug appear to be similar (62% for SC versus 60% for IV for interruption and 13% for SC and 14% for IV for discontinuation). However, the incidence of AEs leading to reduction of any study agent appear marginally higher for the SC formulation (31% versus 25%). The data presented in Table 10 showing AEs associated with dose interruptions, reductions and discontinuations suggest that the additional dose reductions for the SC formulation were driven by higher incidences of rash, paronychia and dermatitis acneiform.

Table 9. Overview of AEs (adapted from Table 3 and Table A3 from Leighl *et al.*)

AE[a]	**Subcutaneous Group (n = 206), No. (%)**		**Intravenous Group (n = 210), No. (%)**	
Any event	204 (99)		209 (99)	
Grade ≥3	107 (52)		118 (56)	
Any serious event	59 (29)		64 (30)	
Any event resulting in death	7 (3)		10 (5)	
Any event leading to:				
Interruption of any study agent[b]	127 (62)		127 (60)	
Reduction of any study agent	63 (31)		52 (25)	
Discontinuation of any study agent	26 (13)		29 (14)	
AEs reported in ≥15% of patients in either group[c]	**All**	**Grade ≥3**	**All**	**Grade ≥3**
Paronychia	111 (54)	8 (4)	108 (51)	3 (1)
Hypoalbuminemia	96 (47)	9 (4)	77 (37)	8 (4)
Rash	95 (46)	8 (4)	91 (43)	8 (4)
Dermatitis acneiform	64 (31)	18 (9)	69 (33)	12 (6)
Nausea	60 (29)	1 (0.5)	52 (25)	3 (1)
Stomatitis	57 (28)	1 (0.5)	69 (33)	5 (2)
Peripheral edema	52 (25)	6 (3)	58 (28)	1 (0.5)
Increased alanine aminotransferase	46 (22)	6 (3)	56 (27)	8 (4)
Decreased appetite	45 (22)	1 (0.5)	52 (25)	3 (1)
Fatigue	44 (21)	3 (1)	43 (20)	5 (2)
Vomiting	44 (21)	2 (1)	41 (20)	1 (0.5)
Diarrhea	43 (21)	3 (1)	39 (19)	2 (1)
Constipation	42 (20)	0	42 (20)	1 (0.5)

Headache	42 (20)	1 (0.5)	36 (17)	1 (0.5)
Increased aspartate aminotransferase	42 (20)	2 (1)	45 (21)	3 (1)
Anemia	39 (19)	4 (2)	40 (19)	5 (2)
Pruritus	33 (16)	0	25 (12)	0
Hypocalcemia	33 (16)	0	27 (13)	0
Myalgia	32 (16)	0	13 (6)	0
Asthenia	31 (15)	4 (2)	23 (11)	2 (1)
Thrombocytopenia	29 (14)	4 (2)	33 (16)	2 (1)
IRR	27 (13)	1 (0.5)	138 (66)	8 (4)
Venous thromboembolism	19 (9)	2 (1)[d]	30 (14)	7 (3)[e]
Pulmonary embolism	6 (3)	NR	9 (4)	NR
Deep vein thrombosis	5 (2)	NR	11 (5)	NR
Other VTE	12 (6)	NR	14 (7)	NR

Abbreviations: AE, adverse event; IRR, infusion-related reaction.
[a]The safety population included all patients who had undergone random assignment and received at least one dose of any trial treatment.
[b]Excluding infusion-/administration-related reactions.
[c]Events in this category are listed according to decreasing incidence in the subcutaneous group.
[d] all grade 3; [e] 6 grade 3 and 1 grade 4

Table 10. AEs Leading to Treatment Interruptions, Reductions, and Discontinuations (reproduced from Leighl *et al.* Table A7)

Event	**Subcutaneous Group (n = 206), No. (%)**	**Intravenous Group (n = 210), No. (%)**
Any event leading to interruptions of any study agent	127 (62)	127 (61)
Grade ≥3 events leading to interruptions of any study agent	73 (35)	76 (36)
Most common events leading to interruptions of any study agent[a]		
Paronychia	27 (13)	10 (5)
Dermatitis acneiform	26 (13)	15 (7)
Rash	25 (12)	17 (8)
Increased alanine aminotransferase	10 (5)	8 (4)
COVID-19	9 (4)	12 (6)
Peripheral edema	8 (4)	7 (3)
Hypoalbuminemia	7 (3)	6 (3)
Pyrexia	7 (3)	4 (2)
Increased aspartate aminotransferase	6 (3)	6 (3)
Vomiting	5 (2)	6 (3)
Nausea	4 (2)	10 (5)
Stomatitis	4 (2)	10 (5)
Fatigue	4 (2)	9 (4)
Asthenia	4 (2)	6 (3)
Pneumonia	3 (2)	7 (3)

Hypotension	0	6 (3)
Any event leading to dose reductions of any study agent	63 (31)	52 (25)
Grade ≥3 events leading to dose reductions of any study agent	6 (3)	8 (4)
Most common events leading to dose reductions of any study agent[b]		
Rash	16 (8)	8 (4)
Paronychia	14 (7)	8 (4)
Dermatitis acneiform	12 (6)	9 (4)
Increased alanine aminotransferase	5 (2)	4 (2)
Stomatitis	4 (2)	2 (1)
Diarrhea	4 (2)	0
Fatigue	3 (1)	5 (2)
Hypoalbuminemia	2 (1)	4 (2)
Any event leading to discontinuations of any study agent	26 (13)	29 (14)
Grade ≥3 events leading to discontinuations of any study agent	20 (10)	21 (10)
Most common events leading to discontinuations of any study agent[b]		
Pneumonitis	7 (3)	6 (3)
Dermatitis acneiform	4 (2)	1 (0.5)
Infusion-related reaction	0	4 (2)

NOTE. The safety population included all patients who were randomly assigned and received at least one dose of any trial treatment. Events are listed according to decreasing incidence in the subcutaneous group.
Abbreviation: AE, adverse event.
[a]Listed are AEs that were reported in at least 3% of patients in either group.
[b]Listed are AEs that were reported in at least 2% of patients in either group.

2.4.1.7 Applicability of PALOMA-3 study

The EAG notes that the PALOMA-3 study was conducted in a third-line population which means it is not directly applicable to the first-line population being considered in this appraisal. The company states that it chose not to use dosing information from PALOMA-3 to directly inform the model because it did not believe it to be applicable for this reason. However, it also stated that the pharmacokinetic results are not expected to be affected by line of therapy or combinations with agents that do not affect the pharmacokinetic profile of amivantamab. The company also noted that there is also an ongoing PALOMA-2 study in which cohorts 1 and 6 include patients with NSCLC with untreated cEGFR mutations ('MARIPOSA' population) receiving first-line SC amivantamab in combination with lazertinib. However, it notes that PALOMA-2 is a less mature trial with shorter follow-up compared with the MARIPOSA study. It therefore preferred to use data from MARIPOSA to estimate dose reductions for the economic model instead of data from either PALOMA-2 or PALOMA-3. However, given that the AE data from PALOMA-3 indicate the potential for a higher incidence of dose reductions for the SC formulation, the EAG considers that the usage of data for MARIPOSA to estimate dose adjustments for the SC formulation introduces some uncertainty.

2.4.2 Uncertainties related to expected clinical outcomes for the subcutaneous formulation

The EAG notes that there is some uncertainty regarding whether the PFS, OS and TTD estimates from the MARIPOSA trial accurately predict outcomes for amivantamab in clinical practice if the SC formulation is used in preference to the IV formulation. It is possible that a less invasive and less time intensive treatment formulation may lead to patients staying on the amivantamab component of ami-laz for longer, which may increase treatment costs. However, a greater duration of treatment may also have an impact on PFS and OS. The potential for this is supported by a trend for longer TTD for SC amivantamab in the PALOMA-3 study, although this difference was not statistically significant. This was accompanied by a non-statistically significant trend for improved PFS and a statistically significant improvement in OS. Although these data may suggest that using the MARIPOSA data in the cost-effectiveness model is unfavourable to ami-laz, given the potential for improved OS and PFS with the SC formulation, it is unclear what the balance of costs and benefits would be given the potential for increased cost due to greater persistence with the amivantamab component of treatment for the SC formulation. The EAG therefore considers this to be an area of unresolved uncertainty that may lead to either better or worse cost-effectiveness than predicted by the company's modelling if ami-laz is recommended for use in clinical practice and the SC formulation is preferred.

3 Updated economic analysis provided by the company

3.1 Introduction

This section summarises the economic analyses presented by the company in their additional evidence document and the results of the additional analyses conducted by the EAG in response to the additional evidence.

3.2 Compliance with the committee's preferences for modelling expressed in the DGD

The company's updated cost-effectiveness complied with the preferences expressed by the committee for the TTD and OS extrapolations applied in the ami-laz and osimertinib monotherapy arms. Due to the company's assumption that all amivantamab will be given as a SC formulation, the committee's advice on the administration costs for amivantamab were no longer considered relevant as these applied to the IV formulation. However, the company did update the administration costs applied to other intravenous treatments and these are discussed in Section 3.6. The company did not comply with the committee's preference for treatment-specific utilities for the progression-free health state as it argued that treatment-independent utilities were appropriate when taking into account the availability of the SC formulation of amivantamab. This is further discussed in Section 3.3. The company also added osi-chemo to the economic analysis as requested. The methods used by the company to make the indirect comparison of clinical outcomes have been previously discussed in Section 2.3 and other aspects of the model adaptation to incorporate the osi-chemo arm are discussed further in Section 3.5. The company also incorporated the PFS INV data from the latest DCO into its update cost-effectiveness analysis. These data have been previously described in Section 2.1 and are not discussed in this Section, although the EAG has presented analyses using its preferred PFS curves in Section 4. The committee also expressed a preference to update the baseline age for the modelled cohort (62.3 years based on MARIPOSA) to reflect data from the Systemic Anti-Cancer Therapy Dataset (SACT) cohort (68.5 years). The company did not comply with this request and therefore the EAG has explored the impact of making this change in its exploratory analysis. The company also did not provide any cost-effectiveness analyses by age subgroups. This issue has been previously discussed in Section 2.2.

3.3 Utilities

The utilities applied in the company and EAG base cases prior to the first committee meeting (ACM1) and the utilities explored in the company's updated economic analysis provided in response to the DGD are summarised in Table 11. The company's updated base case applies utilities for the progression-free (PF) and progressed-disease (PD) health states from TA1060.[12] The company's updated base case applies the same utility values to patients in the PF state regardless of the first line treatment received with the exception of adjustments for AEs. The company's response to the DGD states, " *in TA1060, progression-free utility values were similar for both osimertinib monotherapy and osimertinib-chemotherapy*."[2] However, the EAG believes this to be factually inaccurate as the final guidance for TA1060 states that the committee preferred the EAG's approach to modelling AEs for chemotherapy

which involved applying a disutility across the whole PFS duration.[12] Whilst this disutility is attributed to capturing differences in AEs between the osi-chemo arm and the osimertinib arm, it still results in a difference in utility between the two arms that has been applied for the whole PFS period. Therefore, it contradicts the company's statement that the PF utility values were similar across arms. The EAG notes that in TA1060, the disutilities attributable to Grade ≥3 AEs were set to zero when applying the disutility to the PF state for osi-chemo.[12] If the EAG had access to the disutility applied to the PF state in the osi-chemo arm in TA1060, it would replicate this approach. However, all of the data from TA1060 which detail the size of the disutility applied to the PF state for osi-chemo are redacted meaning that a true replication of the approach taken in TA1060 is not possible.

The company also provides two scenario analyses for utility values. The first applies the treatment-dependent utilities for PFS, which were based on a regression analysis of the utility values collected in MAIPOSA with a treatment interaction term applied. These were the values preferred by the EAG for the PF state in their analyses prior to ACM1. However, in this scenario analysis, the company did not update the utility value applied in the PD state and the value from TA1060 was maintained. No explanation is given as to why this was considered preferable to using the pooled analysis of post-progression utility values from the MARIPOSA trial and the EAG is unclear as to whether this was a deliberate choice by the company or an oversight in the implementation of the scenario analysis. In this scenario analysis, the company applies the PF utilities from the ami-laz arm to the osi-chemo arm. In the company's second scenario analysis, the pooled utility values from pre- and post-progression patients from MARIPOSA were applied in the PF and PD states.

In the absence of data being available on the disutility applied to the osi-chemo arm in TA1060, the EAG prefers to make the same assumption made in the company's first scenario analysis and assumes similar PF utilities for osi-chemo and ami-laz, with the aim of reflecting its belief that both of these regimens would have worse utility compared to osimertinib alone. The statistically significant covariate for treatment arm in the regression of PF utilities from MARIPOSA was identified despite the inclusion of a covariate for grade ≥3 AEs. Therefore, the EAG's interpretation of this data was that this reflected either a disutility related to the requirement for patients to attend regularly for IV infusions, or a disutility related to lower Grade AEs. Therefore, the EAG was comfortable applying this utility difference between the osimertinib and ami-laz arms in addition to the utility decrements included to capture Grade ≥3 AEs. The EAG has maintained this approach for the osi-chemo arm but is unable to confirm if the [redacted] utility decrement applied to ami-laz (relative to osimertinib monotherapy) is similar to the decrement applied to osi-chemo in the TA1060.

The EAG acknowledges that in TA1060, the disutilties for Grade ≥3 AEs were set to zero when applying the disutility in the PF state to osi-chemo. However, it also notes that the QALY decrements associated with AEs included within the model (Grade ≥3 occurring in >5% and Grade ≤2 VTEs) are small relative

to the QALY decrement applied to the ami-laz arm when using the treatment-dependent utility values due to the time limited nature of the AEs. Therefore, any potential double counting of QALY losses due to applying both in the osi-chemo arm is likely to be have minimal impact on the ICER.

Table 11 Summary of the utilities applied by the company and EAG prior to ACM1 and those explored in the company's updated economic analysis

	Source	PFS – ami-laz	PFS - osimertinib	PFS – osi-chemo	PD – all treatments
Company base case pre ACM1	MARIPOSA - Pooled across arms	[redacted]	[redacted]	[redacted]	[redacted]
EAG's preference prior to ACM1	MARIPOSA - Treatment specific for PFs - pooled for PD	[redacted]	[redacted]	[redacted]	[redacted]
Company's updated model - base case	Values from TA1060 [a]	0.794	0.794	0.794	0.678
Company's updated model – scenario 1	- Treatment specific from MARIPOSA for PF - TA1060 for PD	[redacted]	[redacted]	[redacted]	*0.678* [b]
Company's updated model – scenario 2	MARIPOSA - Pooled across arms	[redacted]	[redacted]	[redacted]	[redacted]

[a] These were based on values applied in TA654

[b] This value has been extracted from the model – no explanation is provided as to why the value from TA1060 is more appliable than the pooled value from MARIPOSA for the PD state.

To assist the committee in deciding on the most appropriate utility data, the EAG presents information on the AE data in both the MARIPOSA and FLAURA2 studies below in Table 12, which focuses on all AEs of any grade, and Table 13, which focuses on Grade ≥3 AEs which were captured separately in the model.[7, 11] It can be seen that serious adverse events (SAEs) were higher in the ami-laz arm of MARIPOSA than in osi-chemo arm of FLAURA2 ([redacted] vs 38%) and Grade ≥3 AEs were also higher ([redacted] vs 64%). The profile of AEs appears to differ between the two treatment regimens with ami-laz being associated with higher rates of Grade ≥3 AEs for rash, paronychia, IRRs and VTE, whereas osi-chemo is associated with higher rates of Grade ≥3 anaemia, neutropenia and thrombocytopenia.

However, caution should be applied when interpreting the difference in the AE data from the two trials, as the data would be influenced by various trial-level factors such as follow-up intensity and data cut-off timing.

The EAG was also interested in whether the AEs in the osimertinib monotherapy arm were similar across the two studies as the company's use of unadjusted AEs from the osi-chemo arm in the model implicitly assumes that the rates of AEs were similar for the osimertinib monotherapy arms across the studies. The EAG noted that although the types of AE in the osimertinib monotherapy arm in both trials were broadly similar (rash, diarrhoea, dry skin, pneumonitis), the rates of Grade ≥3 events, SAE and treatment discontinuations differed markedly (see Table 12 and Table 13). In FLAURA2, the osimertinib monotherapy arm had lower rate of Grade ≥3 events (27%) compared with osimertinib arm in MARIPOSA ([redacted]).[7, 11] Similarly, serious AE (SAE) were higher in MARIPOSA osimertinib arm compared with the osimertinib arm in FLAURA2 [redacted] vs 19%), and the rate of treatment discontinuations was also higher ([redacted] vs 11%). These data may indicate that the population in the MARIPOSA study were more prone to having a SAE or Grade ≥3 AEs recorded and means that the higher rate of SAEs and Grade ≥3 AEs for the ami-laz arm in MARIPOSA compared with the osi-chemo arm in FLUARA2 should be interpreted with caution.

Overall, the EAG considers that the differences in Grade ≥3 AEs and SAEs between the osimertinib in the two trials make it difficult to compare AEs across the two trial populations. However, it considers that for both treatment regimens there is potentially a distinct HRQoL impact from both AEs and from the process of care involved in attending hospital regularly for treatment for either amivantamab treatment in patients receiving ami-laz or for maintenance pemetrexed in patients receiving osi-chemo. Although the EAG acknowledges that the duration of time spent in hospital may be lower for the SC formulation of amivantamab, it still considers that there will be an impact on HRQoL from attending hospital every 2 weeks and from Grade <3 AEs, such as rash and paronychia, which it notes were still common when the SC formulation was used in PALOMA-3.[13] It therefore still prefers to apply the treatment-independent utilities from MARIPOSA to the PF health-state in its base case analysis. As the company made no particular argument for why the utility from TA1060 for PD should be preferred over the value for PD from MARIPOSA, other than consistency with TA1060, the EAG maintains the value from MARIPOSA for PD in its base case as it prefers to use a consistent source of values for both health states. Given that the disutility applied in the PF state to osi-chemo in TA1060 is redacted and the EAG is therefore unable to align its approach with that taken in TA1060, it considers it reasonable to apply the same disutility to osi-chemo to reflect the need for regular IV infusions of maintenance pemetrexed and any Grade < 3 AEs.

Table 12. Overall summary of TEAEs for FLAURA2 and MARIPOSA

Event, n (%)	FLAURA2 Osimertinib + Chemo (N=276)	FLAURA2 Osimertinib monotherapy (N=275)	MARIPOSA Osimertinib (N=428) 4th December 2024 DCO	MARIPOSA Ami-laz (N=421) 4th December 2024 DCO
Patients with ≥ 1 AE	276 (100%)	268 (97%)	[redacted]	[redacted]
AEs leading to death[b]	18 (7)	8 (3)	[redacted]	[redacted]
SAEs	104 (38)	53 (19)	[redacted]	[redacted]
AEs leading to discontinuation of any study agent	30 (11)	17 (6)	[redacted]	[redacted]
AEs leading to dose reduction of any study agent	27 (10)	8 (3)	[redacted]	[redacted]
AEs leading to dose interruption of any study agent[c]	120 (43)	52 (19)	[redacted]	[redacted]
Grade ≥ 3 AEs	176 (64)	75 (27)	[redacted]	[redacted]
AEs reported in ≥ 15% of the patients in either group (MARIPOSA DCO: 11th August 2023				
Rash	77 (28)	57 (21)	131 (31)	260 (62)
Dermatitis acneiform	NR	NR	55 (13)	122 (29)
Dry skin	50 (18)	66 (24)	60 (14)	67 (16)
Pruritus	NR	NR	73 (17)	99 (24)
Peripheral oedema	42 (15)	12 (4)	24 (6)	150 (36)
Stomatitis	68 (25)	50 (18)	90 (21)	122 (29)
Constipation	81 (29)	28 (10)	55 (13)	123 (29)
Nausea	119 (43)	28 (10)	58 (14)	90 (21)
Diarrhoea	120 (43)	112 (41)	190 (44)	123 (29)
Vomiting	73 (26)	17 (6)	NR	NR
Paronychia	65 (24)	73 (27)	121 (28)	288 (68)
COVID-19	57 (21)	39 (14)	103 (24)	111 (26)
Hypoalbuminaemia	NR	NR	26 (6)	204 (48)
Decreased appetite	85 (31)	26 (9)	76 (18)	103 (24)
Hypocalcaemia	NR	NR	35 (8)	88 (21)
Anaemia	128 (46)	22 (8)	91 (21)	96 (23)
Leukopenia	NR	NR	66 (15)	26 (6)
Thrombocytopenia	51 (18)	12 (4)	84 (20)	66 (16)
Neutropenia	68 (25)	9 (3)	NR	NR
Neutrophil count decreased	62 (22)	16 (6)	NR	NR
Platelet count decreased	51 (18)	19 (7)	NR	NR
Blood creatinine increase	46 (17)	12 (4)	NR	NR
White-cell count decrease	44 (16)	18 (7)	NR	NR

Event, n (%)	FLAURA2 Osimertinib + Chemo (N=276)	FLAURA2 Osimertinib monotherapy (N=275)	MARIPOSA Osimertinib (N=428) 4th December 2024 DCO	MARIPOSA Ami-laz (N=421) 4th December 2024 DCO
Fatigue	76 (28)	26 (9)	42 (10)	70 (17)
Alanine aminotransferase increased	56 (20)	21 (8)	57 (13)	152 (36)
Aspartate aminotransferase increased	48 (17)	13 (5)	58 (14)	121 (29)
Infusion related reaction	NR	NR	0	265 (63)
Cough	NR	NR	88 (21)	88 (21)
Dyspnoea	NR	NR	68 (16)	68 (16)
TEAE VTEs by anticoagulation status (11th August 2023 DCO; SAS)				
Patients with 1 or more VTEs			[redacted]	[redacted]
Grade ≤ 2 VTE			[redacted]	[redacted]
Grade ≥ 3 VTE			[redacted]	[redacted]

[a]DCO 4th December 2024

Table 13 Number of patients with Grade ≥ 3 TEAEs with frequency of > 5% in either relevant treatment group

	MARIPOSA 11th August 2023 (DCO; SAS)		MARIPOSA 13th May 2024 (DCO; SAS)		FLAURA2	
Event, n (%)	Ami-laz (N=421)	Osimertinib (N=428)	Ami-laz (N=421)	Osimertinib (N=428)	Osimertinib + Platinum Pemetrexed (n = 276)	Osimertinib Monotherapy (n = 275)
Patients with 1 or more Grade ≥ 3 AEs	316 (75)	183 (43)	[redacted]	[redacted]	176 (64)	75 (27)
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]	9 (3)	4 (1)
Rash	65 (15)	3 (1)	[redacted]	[redacted]	1 (<1)	0
Dermatitis acneiform	35 (8)	0	[redacted]	[redacted]	4 (1)	2 (1)
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]	24 (9)	21 (8)
Paronychia	46 (11)	2 (< 1)	[redacted]	[redacted]	2 (1)	1 (<1)
Pneumonia	NR	NR	[redacted]	[redacted]	6 (2)	5 (2)
Respiratory, thoracic and	[redacted]	[redacted]	[redacted]	[redacted]	15 (5)	19 (7)

	MARIPOSA 11th August 2023 (DCO; SAS)		MARIPOSA 13th May 2024 (DCO; SAS)		FLAURA2	
Event, n (%)	Ami-laz (N=421)	Osimertinib (N=428)	Ami-laz (N=421)	Osimertinib (N=428)	Osimertinib + Platinum Pemetrexed (n = 276)	Osimertinib Monotherapy (n = 275)
mediastinal disorders						
Pulmonary embolism	35 (8)	10 (2)	[redacted]	[redacted]	6 (2)	3 (1)
Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]	[redacted]	14 (5)	8 (3)
Hypoalbuminaemia	22 (5)	0	[redacted]	[redacted]	NR	NR
Investigations	[redacted]	[redacted]	[redacted]	[redacted]	62 (22)	16 (6)
Neutrophil count decreased[a]	NR	NR	[redacted]	[redacted]	31 (11)	2 (1)
Platelet count decreased[a]	NR	NR	[redacted]	[redacted]	21 (8)	0
Alanine aminotransferase increased	21 (5)	8 (2)	[redacted]	[redacted]	4 (1)	1 (<1)
Injury, poisoning and procedural complications	[redacted]	[redacted]	[redacted]	[redacted]	6 (2)	1 (<1)
IRR	27 (6)	0	[redacted]	[redacted]	NR	NR
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]	97 (35)	6 (2)
Anaemia[a]	NR	NR	[redacted]	[redacted]	55 (20)	1 (<1)
Neutropenia[a]	NR	NR	[redacted]	[redacted]	37 (13)	2 (1)
Thrombocytopenia[a]	NR	NR	[redacted]	[redacted]	19 (7)	3 (1)
Cardiac disorders	NR	NR	[redacted]	[redacted]	12 (4)	5 (2)
Gastrointestinal disorders	NR	NR	[redacted]	[redacted]	20 (7)	4 (1)
General disorders and administration site conditions	NR	NR	[redacted]	[redacted]	10 (4)	2 (1)

	MARIPOSA 11th August 2023 (DCO; SAS)		MARIPOSA 13th May 2024 (DCO; SAS)		FLAURA2	
Event, n (%)	Ami-laz (N=421)	Osimertinib (N=428)	Ami-laz (N=421)	Osimertinib (N=428)	Osimertinib + Platinum Pemetrexed (n = 276)	Osimertinib Monotherapy (n = 275)
Nervous system disorders	NR	NR	[redacted]	[redacted]	8 (3)	6 (2)
Vascular disorders	NR	NR	[redacted]	[redacted]	4 (1)	7 (3)

[a] Data extracted by EAG from the

3.4 Adaptations to the model to incorporate subcutaneous amivantamab

3.4.1 Clinical effectiveness and safety data for subcutaneous amivantamab

As described previously in Section 2.4, the company's economic analysis assumes that all OS, PFS and TTD data from the IV formation of amivantamab in combination with lazertinib in the MARIPOSA trial can be used to predict outcomes for the SC formulation of amivantamab in combination with lazertinib. The only adjustment to made to the clinical outcomes was to reduce the incidence of IRRs by 87% to reflect the fact that Grade ≥ 3 AEs occurred in only 1 in 206 patients receiving SC amivantamab compared to 8 in 210 patients receiving IV amivantamab in PALOMA-3 ([1/206]/[8/210]=0.123, i.e. 87% reduction). The EAG considers this reasonable given the findings of the PALOMA-3 study.[13]

3.4.2 Drug acquisition costs for subcutaneous amivantamab with lazertinib

Although not provided in its original response to the DGD, following a request from the EAG, the company later provided a written description of it approach to calculating drug acquisition costs for SC amivantamab. In this document the company explained that the distribution of doses reived by patients was calculated to using the IV doses prepared for patients in MARIPOSA and mapping this to the equivalent SC dose using the dose-reduction guidance for the SC formulation. Although the company states that the incidence of dose reductions was similar for the two formulations in PALOMA-3, the EAG considered that there were slightly higher dose reductions for the SC formulation (31% versus 25%).[13] However, given that there is no lower SC dose available than 1,600 mg, the EAG infers that dose adjustments below this level would simply involve wastage of the remainder of the vial of solution for injection. Therefore only dose reductions from 2240 mg to 1,600 mg would have any impact on costs and the EAG considers this to be a minor issue. The company assumes an equivalent rate of missed doses between IV and SC formulations and this seems reasonable given the findings of the PALOMA-3 study (see Section 2.4.1.6).

The company also included a scenario analysis in which the dosing frequency of amivantamab was reduced from every 2 weeks to every 4 weeks after [redacted] (the company's document stated [redacted] but the model parameter was set to [redacted]). The EAG did not check any of the model coding required to implement this scenario analysis as the 4-weekly formulation of SC amivantamab is not yet licensed and therefore the EAG does not consider it relevant to the decision problem.

The 1,600mg vial list price is £3,237.00 and the 2,240mg vial list price is £4,316.00. The PAS ([redacted]%) is applied as a fixed percentage discount to all vial sizes. A summary of the drug acquisition costs for SC amivantamab, given according to its license is provided in Table 14.

The method used to calculate drug costs for lazertinib is unchanged but an updated PAS has also been applied for lazertinib giving a weekly cost of £[redacted]. This gives a total drug acquisition cost for the ami-laz treatment combination (after the induction period) of £[redacted]

Table 14 Drug acquisition cost for subcutaneous amivantamab

Weight	Dose	Cost per unit including PAS	Dose distribution (induction)[a]	Dose distribution (subsequent)[a]	% missed doses	Drug cost per week (induction)	Drug cost per week (subsequent)
< 80kg	1,600mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	2,240mg						
≥ 80kg	1,600mg					[redacted]	[redacted]
	2,240mg						

[a] The SmPC dosing regimen is an induction period of weekly dosing for 4 weeks followed by doses every 2 weeks starting on week 5.

[b] EAG identified an error in the model whereby this was being calculated based on the cost per dose in the induction period – correcting the error results in a very similar cost of £[redacted]

3.4.3 Unit cost for administration of subcutaneous amivantamab

The company has applied the reference cost code of N10AF which relates to a specialist cancer nurse having a face-to-face appointment with an adult in a community health service. The company's response to the DGD describes this as being an outpatient HRG code,[2] however, the EAG believes that this HRG code is used for community nursing services such as district nursing and palliative care and therefore cannot be used as an outpatient cost. The company cites a poster by Baldwin *et al.* which it claims shows that the SC formulation can be given in a 30-minute outpatient appointment. However, the EAG notes that the poster by Baldwin *et al.*[14] describes subcutaneous atezolizumab being delivered in outpatient or healthcare centres when used as monotherapy but being delivered in hospital day units when offered as part of a combination regimen. The EAG is cautious about making the assumption that a new subcutaneous formulation of a drug will be used in a community setting. It believes that amivantamab will be administered in a hospital setting initially whilst clinicians build experience of the AE profile for the subcutaneous formulation. The DGD acknowledged that some centres are administering chemotherapy as outpatient procedures rather than day case procedures.[1] The EAG considers it reasonable to expect that the subcutaneous formulation would be more likely to be given as an outpatient appointment instead of a day case. Therefore, to reflect the anticipated lower resource use required for a subcutaneous administration versus IV administration, the EAG has applied in its base case the outpatient cost for administration of a simple IV parenteral chemotherapy based on the figure used in the original EAG report (£133.39, Table 60 of EAG report).

3.5 Adaptations to the model to incorporate osi-chemo comparator

3.5.1 Estimates of clinical outcomes for osi-chemo in the economic analysis

The approach used by the company to estimate OS, PFS and TTD for osi-chemo has been previously described in Section 2.3. The main EAG conclusion on this matter was that the EAG preferred not to apply the HR for osimertinib in MARIPOSA versus osimertinib in FLAURA2 to adjust for differences in OS, PFS and TTD between the trial populations. The EAG has therefore presented a naïve ITC in its base case. Whilst it acknowledges that this approach is associated with significant limitations it has the advantage of not relying on the PH assumption which the EAG believes is not valid in this case.

The company applied the incidence of Grade ≥ 3 AEs from the osi-chemo arm of FLAURA2 in the model without any adjustment. As discussed in Section 3.3, this may have been unfavourable to ami-laz as the incidence of SAEs and Grade ≥ 3 AEs appears to have been higher in the osimertinib monotherapy arm of MARIPOSA compared to the osimertinib arm of FLAURA2. However, the EAG considers than any bias is likely to be small as the QALY loss associated with Grade ≥ 3 AEs in the economic model is small in both arms.

3.5.2 Estimates of drug acquisition and administration costs for osi-chemo

The company presented drug acquisition costs for the osi-chemo regimen in Appendix B.6 of their response to the DGD.[2] The company has assumed that 100% of the platinum component of the chemotherapy regimen is carboplatin in line with what was accepted in TA1060.[12] These drug acquisition costs are summarised below in Table 15. For drug administration costs, the company assumed a fixed cost across all cycles for the chemotherapy component of osi-chemo rather than having a different cost for the cycles where pemetrexed was given alone. The company applied the average cost of SB13Z and SB15Z as this was the approach taken in TA1060 (£477 = average of £528 [SB13Z] and £426 [SB15Z]).[12] The EAG notes that this differed from the treatment administration costs applied for platinum-based chemotherapy when given second-line or third-line in the model. This is issue of administration costs for subsequent therapies is further discussed in Section 3.6 below, but the EAG was satisfied that the company's approach for first line osi-chemo aligned with the approach in TA1060 and that the company had used NHS reference costs for day case administration as requested.

Table 15 Drug acquisition cost per dose for osimertinib-chemotherapy

Component	Dose (mg)	Treatment duration	Units (vials/caps) per admin	Cost per average dose required (£)	% dose missed[a]	Cost per week (12 week induction)	Cost per week (maintenance)
Osimertinib	80	Taken once daily until progression	1	192.34	2.2%	1,316.38	1,316.38

Pemetrexed	840	Once every 3-week cycle until disease progression	2	57.53	0%	19.18	19.18
Carboplatin	575	Once every 3-week cycle for 4 cycles	1	38.93	0%	12.97	0

Abbreviations: mg: milligram.
[a] assumes 100% of planned dose is given for pemetrexed and carboplatin

3.5.2 Subsequent treatment therapies for patients having first-line osi-chemo

The EAG noticed that the costs for subsequent treatment were higher for osi-chemo than for either ami-laz or osimertinib monotherapy. This was despite the proportion receiving best supportive care (BSC) instead further treatment at second-line being higher for osimertinib chemotherapy. The EAG identified that this was because the company's updated model was using TTD for the pemetrexed component of the osi-chemo treatment regimen to determine the start of subsequent treatment rather than using the TTD for the osimertinib component. This was inconsistent with the approach taken for ami-laz whereby it was the discontinuation of the lazertinib component that was used to determine the start of second-line treatment. It also appears to contradict statements from TA1060 wherein the committee accepted that the pemetrexed component of the osi-chemo treatment regimen tended to be stopped first and the osimertinib component may be continued post-progression.[1] The EAG believes it is more correct for the start of the subsequent treatment to be tied to the end of the osimertinib component of the osi-chemo treatment regimen and has therefore implemented a model adaptation to achieve this in its exploratory analyses, and it has incorporated this change in its base case.

The EAG is also concerned that the company has not adjusted the subsequent treatment costs to account for the fact patients who have had osimertinib combined with platinum-based chemotherapy as first-line treatment are unlikely to be retreated with platinum-based chemotherapy in later lines. The company's updated model is assuming that 100% of second-line treatment is platinum-based chemotherapy, and 25% of third-line treatment is platinum-based chemotherapy. Platinum-based chemotherapy at both second-line and third-line is assumed to consistent of carboplatin with pemetrexed. These assumptions are applied equally regardless of first-line therapy meaning that these assumptions also apply to patients receiving osi-chemo as their first line treatment. Clinical advice to the EAG was that these patients would not be offered a platinum-based chemotherapy treatment regimen if they had progressed after first-line treatment with osi-chemo. The EAG's clinical advisor stated that these patients would be offered docetaxel, and this would be combined with nintedanib if they were fit enough to receive nintedanib. They also stated that there are no standard third-line treatments for these patients.

The EAG has conducted an exploratory analysis to assess the impact on the ICER of assuming that 100% of second-line treatment in patient having first line osi-chemo will be docetaxel with nintedanib.

Although the company's model had the functionality to specify different second-line treatment distributions for each first-line treatment, the EAG identified an error whereby the distribution for the osimertinib arm was being applied in the osi-chemo arm. It therefore corrected this error order before implementing its preferred distribution of second-line treatments for osi-chemo.

The only subsequent line treatment regimen available in the model that would not have already been used in patients having first line osi-chemo and second-line docetaxel with nintedanib would be the ABCP regimen (atezolizumab, bevacizumab, carboplatin and paclitaxel). However, this was not identified as a potential treatment option open to this patient group by the EAG's clinical advisor. Therefore, the EAG has assumed that 100% of patients would receive BSC third-line in its base case analysis. As this potentially underestimate the costs of subsequent treatments in the osi-chemo, the EAG has explored a alternative scenario in which it assumed that all of the patients receiving third-line treatment (after first line osi-chemo and second line docetaxel with nintedanib) would receive ABCP. However, it should be noted that only [redacted]% of patient are assumed to receive third-line treatment.

3.6 Unit costs for administration of oral and IV chemotherapies in first and subsequent line treatment

The company's updated analyses used NHS reference costs for day case administration for all IV and oral systemic anticancer treatments. The administration costs for SC amivantamab has been previously discussed in Section 3.4.3. The unit costs for administration are summarised in Table 16. The noticed some inconsistencies in the approach taken. Firstly, the unit cost for oral administration was applied monthly for first line oral treatments but was applied as a one off cost in the first cycle for oral treatments given as subsequent line therapies. The EAG considered the latter to be an oversight on behalf of the company as it had updated the first line therapies to use monthly rather than one off unit costs for oral administration. It therefore applied monthly costs in its EAG base case analysis. It also noted that different administration costs were applied in the induction and maintenance phases for platinum-based chemotherapies being offered as subsequent line therapies, whereas the company used a single averaged unit cost for first line therapies. For consistency, the EAG amended the model in its base case to use the single average unit cost for subsequent line platinum-based chemotherapy.

Table 16 Summary of administration costs applied in the company's updated analysis

Mode of administration	Cost (£)	Source	Treatment regimens
Oral therapy	240.44	National Schedule of NHS Costs 2023/24, SB11Z - Deliver Exclusively Oral Chemotherapy; Medical Oncology Service.[15]	• First line osimertinib monotherapy (monthly) • Lazertinib in patients who have discontinued amivantamab (monthly)

			• Osimertinib in patients who have discontinued the chemotherapy component of osi+chemo (monthly) • Osimertinib as a subsequent line therapy (one-off)[a] • Nintedanib as a subsequent line therapy (one-off)[a]
Simple IV administration	418.00	National Schedule of NHS Costs 2023/24, SB12Z - Deliver Simple Parenteral Chemotherapy at First Attendance; Day case; Medical Oncology Service[15]	• Docetaxel as a subsequent line therapy • Pemetrexed as a subsequent line therapy after discontinuing carboplatin [b]
Complex IV administration	570.00	National Schedule of NHS Costs 2023/24, SB14Z - Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance; Day case; Medical Oncology Service[15]	• Pemetrexed combined with carboplatin as a subsequent line therapy [b] • Atezolizumab, bevacizumab, carboplatin, paclitaxel as a subsequent line therapy
More complex IV administration	528.00	National Schedule of NHS Costs 2023/24, SB13Z – Deliver more Complex Parenteral Chemotherapy at First Attendance; Day case; Medical Oncology Service[15]	Not applied as single unit cost – only applied as average of SB13Z and SB15Z (see below)
Subsequent elements of a chemotherapy cycle	426.00	National Schedule of NHS Costs 2023/24, SB15Z – Deliver Subsequent Elements of a Chemotherapy Cycle; Day case; Medical Oncology Service[15]	
Average of SB13Z and SB15Z	477.00	Average of SB13Z / SB15Z – Deliver more Complex Parenteral Chemotherapy at First Attendance / Deliver Subsequent Elements of a Chemotherapy Cycle; Day case; Medical Oncology Service[15]	• Pemetrexed with carboplatin as a first line therapy
Cost per SC administration	115.00	National Schedule of NHS Costs 2023/24, N10AF - Specialist nursing, cancer related, adult, face to face[15]	• Amivantamab
[a] the EAG amended this to apply monthly in their exploratory analyses to make the administration costs for subsequent line oral therapies consistent with the administration costs for first-line oral therapies [b] the EAG amended this in its exploratory analyses to make the approach used for subsequent line platinum-based chemotherapy equivalent to the approach used for first-line platinum-based chemotherapy in combination with osimertinib.			

3.7 Additional analyses conducted by the EAG

EA1: Correction of model errors

a) The EAG identified that the formula calculating the drug cost per week for patients weighing under 80 kg and having 1,600 mg SC amivantamab during the maintenance phase (after the four week induction) was referring to the cost per dose for the induction phase. It corrected this as it appeared to be an error rather than a company preference. The correction involved amending cell Q61 to refer to cell L46 instead of cell K46 in the Sheet named 'Detailed Cost Inputs_1L Tx'.
b) The EAG also identified that the calculation of subsequent treatment costs for second-line and third-line treatments for the osi-chemo arm was referring to the distribution of treatments for the osimertinib monotherapy arm. This was corrected in cells F15 and G15 of the Sheet named 'Detailed Cost Inputs_SubTx'. This had no impact in the company's model as the distributions were all set equal across arms, but this correction was necessary to facilitate the EAG's exploratory analyses which modified second-line and third-line treatments for patients having first-line osi-chemo.
c) The EAG also corrected the selection of TTD curve for the osimertinib component of the osi-chemo arm to reflect the committee's preference in TA1060 as the company has misinterpreted the documents and applied the average the gamma and Gompertz curves instead of the Gompertz curve. This was implemented using the existing functionality on the Sheet named 'Clinical Inputs'.

EA2: Update to latest eMIT drug costs

For generic drugs included in the model, the EAG updated the prices to reflect those in the latest price tracker provided to the EAG by NICE (see Table 17). For all other drugs, the EAG used the same price as the company in this main critique document, but analyses incorporating the PAS discounts for comparator drugs can be found in the confidential appendix.

Table 17: The source for the prices used in the confidential appendix where the price differs from that used in the company's model

Treatment	Price in company's analysis	Source for price in company's model	Price used in the confidential appendix	Source for price used in the confidential appendix
Dexamethasone IV 10mg (pack of 1)	30.80	eMIT 24/01/2025	25.17	eMIT 4/08/25
Paracetamol oral 500mg (pack of 100)	0.79	eMIT 24/01/2025	0.66	eMIT 4/08/25
Carboplatin IV 450mg (pack of 1)	23.18	eMIT 24/01/2025	22.92	eMIT 4/08/25
Carboplatin IV 600mg (pack of 1)	38.93	eMIT 24/01/2025	19.75	eMIT 4/08/25
Docetaxel IV 80mg (pack of 1)	9.73	eMIT 24/01/2025	9.48	eMIT 4/08/25
Paclitaxel IV 300mg (pack of 1)	31.89	eMIT 24/01/2025	18.75	eMIT 4/08/25

CAA – Commercial access arrangement; MPSC – Medicines Procurement and Supply Chain; PAS – Patient Access Scheme

EA3: Use of alternative starting age to reflect real-world evidence

The EAG set the baseline age to 68.5 to reflect the mean age in the Systemic Anti-Cancer Therapy Dataset cohort as quoted in the DGD.[1] This was implemented in cell J38 of the sheet named 'Settings'.

EA4: Amended unit costs for subsequent treatments to bring them in line with costs applied to first-line treatments

The EAG amended the costing of oral subsequent treatments to use a monthly unit cost instead of a one-off unit cost at the start of treatment to bring it in line with the unit costs applied for oral treatments given as first-line interventions. This affected the osimertinib when used as a subsequent treatment and nintedanib. It was implemented in cells M191, N191, M194 and N194 of the Sheet called 'Detailed Cost Inputs_SubTx'.

The EAG also preferred to apply the same administration cost for platinum-based chemotherapy to both first and subsequent line use of platinum-based chemotherapy for consistency. As the unit cost applied to first-line platinum-based chemotherapy had been amended by the company to match the unit cost

applied in TA1060, the EAG updated the unit cost applied to subsequent line therapies. This was done by amending cells M188 and N188 of the Sheet called 'Detailed Cost Inputs_SubTx' to refer to the average of costs for SB13Z and SB15Z.

EA5: Use of alternative utilities values as preferred by the EAG prior to ACM1

The EAG maintained its preference for using the treatment-dependent utilities from MARIPOSA for the PF health state and the pooled post-progression utilities from MARIPOSA for the PD state. The EAG implemented this by selected the 'Treatment specific' option in Cell J32 of the sheet named 'Settings'. However, this only modified the utility values for the progression free state. Therefore the EAG also modified the formula in cell H13 of the sheet named 'Utility Inputs' to provide a value of [redacted] instead of 0.678 when the EAG switch was activated and the 'Treatment specific' option was selected.

EA6: Use of alternative distribution for PFS for ami-laz and osimertinib monotherapy

The EAG preferred to use the gamma distribution over the generalised gamma distribution to extrapolate PFS for both the ami-laz and osimiertinib monotherapy arms of the MARIPOSA study. The EAG included this change within its updated base case analysis.

EA7: Use of alternative administration cost for subcutaneous amivantamab

The EAG amended the unit cost applied for SC amivantamab to reflect the outpatient HRG cost for administration of a simple parenteral chemotherapy (SB12Z:£133.39). This replaced the company's preferred cost of £115, which the EAG interpreted as being relevant only if the treatment was administered in the community rather than in an outpatient setting. The amendment was made in cell G13 of the Sheet named 'Detailed Cost Inputs_Unit Cost'.

EA8: Use osimertinib TTD to determine start of subsequent line therapies for the osi-chemo arm

The EAG identified that subsequent treatment costs were using the TTD for pemetrexed instead of the TTD for osimertinib to determine the start of subsequent treatments for the osi-chemo arm. The EAG corrected this by updating formulae in column AB of the Sheet named 'Engine Osi + CP' to refer to column J instead of column K.

EA9: Alternative distribution of subsequent treatments for osi-chemo arm

The EAG set the distribution of second-line treatment for patients having first-line osi-chemo to reflect advice from its clinical expert that docetaxel with nintedanib (where patients were fit enough to receive nintedanib) would be the only second-line treatment option available. This was implemented by setting cells J81:J84=(0,0,100%,0) in the sheet named 'Detailed Cost Inputs_SubTx'.

As the clinical advisor stated that there were no standard third-line treatments available in these patients, the EAG assumed that 100% would receive BSC third-line in its base case. This was implemented by setting cell J74 to 0% and cell K74 to 100% in the sheet named 'Detailed Cost Inputs_SubTx'.

EA10: Remove adjustment to PFS, OS and TTD to reflect differences in the osimertinib arms between MARIPOSA and FLAURA2

The EAG removed the adjustment to PFS, OS and TTD which was applied to the osi-chemo arm to reflect differences in the performance of the osimertinib arms between MARIPOSA and FLAURA2. This was achieved by setting the HRs in cells H41, H76, and H109 of the sheet named 'Clinical Inputs' to 1.

ASA1: Use of alternative distributions for OS

The EAG changed the distributions for OS: to a one-knot hazard model for ami-laz and to a gamma model for osimertinib.

This scenario aimed to assess whether the cost-effectiveness estimates were sensitive to alternative survival curve choices that provided a good statistical fit but different long-term predictions. The EAG's alternative distributions provide a lower 10-year survival prediction for ami-laz (9.8% one-knot hazard model versus 13.4% for Weibull) and a higher prediction for osimertinib (5.4% for gamma versus 2.8% for Weibull) than the company's preferred Weibull distributions. The EAG considers that these alternative distributions provide 10-year OS predictions that are better matched to the clinical expert estimates presented by the company (means of 11.7% and 5% for ami-laz and osimertinib respectively).

ASA2: Use of alternative curve for TTD in the osimertinib component of osi-chemo

For the osimertinib component of osi-chemo, we agree with the choice made in TA1060 to use the Gompertz model for extrapolating TTD. However, the EAG notes that the Gompertz TTD curve of the osimertinib component in osi-chemo crosses the predicted TTD curve for osimertinib monotherapy in MARIPOSA at around 5 years. To address this, the EAG presents a scenario in which the TTD for the osimertinib component of osi-chemo is capped by the predicted TTD curve for osimertinib monotherapy in MARIPOSA.

ASA3: Alternative third-line treatments for patients having osi-chemo first-line

As there was uncertainty regarding the appropriate third-lien treatments for patients having first-line osi-chemo, the EAG conducted an exploratory analysis to see the impact of higher subsequent treatment costs. This was achieved by setting all third-line treatment use to be ABCP (set cells K107:K1104=(0,0,0,100%) in the sheet named 'Detailed Cost Inputs_SubTx'. This also required modification of cells E492 to E495 in the 'Parameters' sheet as these were defaulting to using the values

from the osimertinib arm instead of the distribution specified in the sheet named 'Detailed Cost Inputs_SubTx'.

4 Cost-effectiveness results

The results for the company's updated base case as presented in its response to the DGD provided in Table 18. It can be seen that ami-laz dominates both osimertinib monotherapy and osi-chemo in both the deterministic and probabilistic analysis and the results are reasonably consistent suggesting that the deterministic analysis provides a reasonable approximation of the expected costs and QALY. However, it should be noted that the probabilistic results presented in Table 17 are based on the results saved in the probabilistic results sheet of the submitted model and the EAG was unable to validate these results as it was unable to run the probabilistic analysis using the submitted model without the code running into an error. It should also be noted that this analysis does not include the PAS prices for comparator drugs. Please see the confidential appendix for these results.

Table 18: Company's updated base case with PAS prices for amivantamab and lazertinib and list prices for comparator drugs

Option	Absolute outcomes by treatment arm			Incremental outcomes for ami-laz versus comparator			ICER (£/QALY)
	LYGs*	QALYs	Costs (£)	LYGs	QALYs	Costs (£)	
Company's updated base case using list price for comparators - deterministic							
Ami-laz	5.21	[redacted]	[redacted]				
Osimertinib	3.68	[redacted]	[redacted]	1.54	[redacted]	[redacted]	Ami-laz dominates
Osi-chemo	4.50	[redacted]	[redacted]	0.72	[redacted]	[redacted]	Ami-laz dominates
Company's updated base case using list price for comparators – probabilistic							
Ami-laz	5.25	[redacted]	[redacted]				
Osi	3.70	[redacted]	[redacted]	1.55	[redacted]	[redacted]	Ami-laz dominates
Osi-chemo	4.65	[redacted]	[redacted]	0.59	[redacted]	[redacted]	Ami-laz dominates

The results for the EAG's exploratory analyses (EAs) and additional sensitivity analyses (ASAs) are provided in Table 19. It can be seen that ami-laz dominates both osimertinib monotherapy and osi-chemo in all of the analysis presented. However, it should be noted that this analysis does not include the PAS prices for comparator drugs. Please see the confidential appendix for these results.

The analyses presented demonstrate that the following changes have a substantial impact on the cost-effectiveness estimates for ami-laz versus osi-chemo:

- The correction to use the Gompertz curve to extrapolate TTD for the osimertinib component of osi-chemo (EA1).

- The removal of the adjustment to account for difference in performances for the osimertinib arms in MARIPOSA and FLAURA2 (EA10)
- The EAG's preferred utility values using treatment-dependent utilities from MARIPOSA for the PF state and pooled utilities from MARIPOSA for the progressed-disease state (EA5).
- The correction to assume that second-line treatments in the osi-chemo arm start after osimertinib is discontinued instead of after pemetrexed is discontinued (EA8).
- The changes to reflect the expected subsequent treatments for the osi-chemo arm (EA9).

For the comparison against osimertinib monotherapy, the most significant factor is the choice of utility values (EA5) with the application of an alternative administration cost of SC amivantamab having a smaller impact and the other analyses having minimal impact (EA8, EA9 and EA10 do not apply to this comparison).

Table 19: EAG exploratory analysis results (deterministic analyses)

Option	Absolute outcomes by treatment arm			Incremental outcomes for ami-laz versus comparator			ICER (£/QALY)
	LYGs*	QALYs	Costs (£)	LYGs	QALYs	Costs (£)	
Company's updated base case							
Ami-laz	5.21	[redacted]	[redacted]				
Osimertinib	3.68	[redacted]	[redacted]	1.54	[redacted]	[redacted]	Ami-laz dominates
Osi-chemo	4.50	[redacted]	[redacted]	0.72	[redacted]	[redacted]	Ami-laz dominates
EA1: Corrections							
Ami-laz	5.21	[redacted]	[redacted]				
Osimertinib	3.68	[redacted]	[redacted]	1.54	[redacted]	[redacted]	Ami-laz dominates
Osi-chemo	4.50	[redacted]	[redacted]	0.72	[redacted]	[redacted]	Ami-laz dominates
EA2: EA1 + updated to prices for generic drugs							
Ami-laz	5.21	[redacted]	[redacted]				
Osimertinib	3.68	[redacted]	[redacted]	1.54	[redacted]	[redacted]	Ami-laz dominates
Osi-chemo	4.50	[redacted]	[redacted]	0.72	[redacted]	[redacted]	Ami-laz dominates
EA3: EA2 + baseline age							

Option	Absolute outcomes by treatment arm			Incremental outcomes for ami-laz versus comparator			ICER (£/QALY)
	LYGs*	QALYs	Costs (£)	LYGs	QALYs	Costs (£)	
Ami-laz	5.21	[redacted]	[redacted]				
Osimertinib	3.68	[redacted]	[redacted]	1.54	[redacted]	[redacted]	Ami-laz dominates
Osi-chemo	4.48	[redacted]	[redacted]	0.73	[redacted]	[redacted]	Ami-laz dominates
EA4: EA2 + admin cost for subsequent line therapies to match first-line therapies							
Ami-laz	5.21	[redacted]	[redacted]				
Osimertinib	3.68	[redacted]	[redacted]	1.54	[redacted]	[redacted]	Ami-laz dominates
Osi-chemo	4.50	[redacted]	[redacted]	0.72	[redacted]	[redacted]	Ami-laz dominates
EA5: EA2 + EAG's preferred utility values							
Ami-laz	5.21	[redacted]	[redacted]				
Osimertinib	3.68	[redacted]	[redacted]	1.54	[redacted]	[redacted]	Ami-laz dominates
Osi-chemo	4.50	[redacted]	[redacted]	0.72	[redacted]	[redacted]	Ami-laz dominates
EA6: EA2+ Gamma for PFS for ami-laz and osimertinib monotherapy							
Ami-laz	5.21	[redacted]	[redacted]				
Osimertinib	3.68	[redacted]	[redacted]	1.54	[redacted]	[redacted]	Ami-laz dominates
Osi-chemo	4.50	[redacted]	[redacted]	0.72	[redacted]	[redacted]	Ami-laz dominates
EAG 7: EA2+ Outpatient cost for SC amivantamab							
Ami-laz	5.21	[redacted]	[redacted]				
Osimertinib	3.68	[redacted]	[redacted]	1.54	[redacted]	[redacted]	Ami-laz dominates
Osi-chemo	4.50	[redacted]	[redacted]	0.72	[redacted]	[redacted]	Ami-laz dominates
EA8: EA2+ Use TTD of osimertinib component of osi-chemo as start of second-line treatment							
Ami-laz	5.21	[redacted]	[redacted]				
Osimertinib	3.68	[redacted]	[redacted]	1.54	[redacted]	[redacted]	Ami-laz dominates
Osi-chemo	4.50	[redacted]	[redacted]	0.72	[redacted]	[redacted]	Ami-laz dominates

Option	Absolute outcomes by treatment arm			Incremental outcomes for ami-laz versus comparator			ICER (£/QALY)
	LYGs*	QALYs	Costs (£)	LYGs	QALYs	Costs (£)	
EA9: EA2+ Adjust subsequent treatments for patients having osi-chemo							
Ami-laz	5.21	[redacted]	[redacted]				
Osimertinib	3.68	[redacted]	[redacted]	1.54	[redacted]	[redacted]	Ami-laz dominates
Osi-chemo	4.50	[redacted]	[redacted]	0.72	[redacted]	[redacted]	Ami-laz dominates
EA10: EA2+ Remove the adjustment to osi-chemo to account for differences in outcomes for the osimertinib arms of MARIPOSA and FLAURA2							
Ami-laz	5.21	[redacted]	[redacted]				
Osimertinib	3.68	[redacted]	[redacted]	1.54	[redacted]	[redacted]	Ami-laz dominates
Osi-chemo	4.72	[redacted]	[redacted]	0.50	[redacted]	[redacted]	Ami-laz dominates
EAG base case = EA 1 to EA 10 combined							
Ami-laz	5.21	[redacted]	[redacted]				
Osimertinib	3.68	[redacted]	[redacted]	1.54	[redacted]	[redacted]	Ami-laz dominates
Osi-chemo	4.70	[redacted]	[redacted]	0.52	[redacted]	[redacted]	Ami-laz dominates
ASA1: EAG base case + use of 1-knot hazard for OS for ami-laz and use of gamma for OS osimertinib monotherapy							
Ami-laz	4.79	[redacted]	[redacted]				
Osimertinib	3.96	[redacted]	[redacted]	0.83	[redacted]	[redacted]	Ami-laz dominates
Osi-chemo	4.70	[redacted]	[redacted]	0.09	[redacted]	[redacted]	Ami-laz dominates
ASA2: EAG base case + capping TTD for osimertinib component of omi-chemo so it does not fall below osimertinib monotherapy TTD							
Ami-laz	5.21	[redacted]	[redacted]				
Osimertinib	3.68	[redacted]	[redacted]	1.54	[redacted]	[redacted]	Ami-laz dominates
Osi-chemo	4.70	[redacted]	[redacted]	0.52	[redacted]	[redacted]	Ami-laz dominates
ASA3: Assume all third-line treatment is ABCP in patients having osi-chemo first-line							
Ami-laz	5.21	[redacted]	[redacted]				

Option	Absolute outcomes by treatment arm			Incremental outcomes for ami-laz versus comparator			ICER (£/QALY)
	LYGs*	QALYs	Costs (£)	LYGs	QALYs	Costs (£)	
Osimertinib	3.68	[redacted]	[redacted]	1.54	[redacted]	[redacted]	Ami-laz dominates
Osi-chemo	4.70	[redacted]	[redacted]	0.52	[redacted]	[redacted]	Ami-laz dominates

*Undiscounted

Abbreviations: ASA, additional scenario analysis; EA - exploratory analysis; ICER - incremental cost-effectiveness ratio LYG - life year gained; TTD – time to discontinuation; QALY - quality-adjusted life year;

5 Conclusions

The EAG's additional sensitivity analyses demonstrate that plausible alternative OS curves for the ami-laz and osimertinib monotherapy arms have the potential to have a substantial impact on the estimates of incremental QALYs gained both in the comparison against osimertinib and in the comparison against osi-chemo. The EAG refers the committee to the confidential appendix for the range of ICERs this scenario analysis generates when applying the confidential PAS discounts for comparator treatments. The cost-effectiveness estimates are also moderately sensitive to the choice of utility values with the use of treatment-dependent utility values have opposite impacts on the incremental QALY for the comparisons against osimertinib monotherapy and osi-chemo. The EAG also identified several issues with the comparison against osi-chemo, which it addressed in its exploratory analyses. The extrapolation of the TTD discontinuation from the osimertinib component of the osi-chemo treatment regimen had an important impact on the cost-effective estimates as did the EAG's preference for an unadjusted ITC.

Overall, the EAG considers that there are several areas of uncertainty that are not captured within its exploratory analyses. These include unresolved uncertainty related to the indirect comparison between ami-laz and osi-chemo. The EAG was not satisfied that the company's adjustment was appropriate given that it relied on assuming that the proportional hazard assumption held between the osimertinib arms of the MARIPOSA and FLAURA2 trials. The EAG was also not convinced that the adjustment was reflecting differences in the trial populations as the adjustments for PFS and OS went in the opposite direction. However, the EAG's alternative approach of using an unadjusted ITC is also subject to significant limitations. The EAG would have preferred the company to have explored a more sophisticated method to conduct an adjusted ITC such an approach that accounts for the time-varying treatment effects and the population heterogeneity.

There was also considerable uncertainty introduced in the economic analysis through the assumption that OS, PFS and TTD would be identical for the subcutaneous formulation of amivantamab and the IV formulation. Whilst it could be argued that using the MARIPOSA data in the cost-effectiveness model is unfavourable to ami-laz, given the potential for improved OS and PFS with the SC formulation, it is

unclear what the balance of costs and benefits would be, given the potential for increased cost if there is greater treatment persistence with the amivantamab component of treatment of the SC formulation. The EAG therefore considers this to be an area of unresolved uncertainty that may lead to either better or worse cost-effectiveness than predicted by the company's modelling if ami-laz is recommended for use in clinical practice and the SC formulation is preferred.

6 References

1. National Institute for Health and Care Excellence. *Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-smallcell lung cancer : Draft Guidance for consultation* London, UK: National Institute for Health and Care Excellence,; 2025.
2. Johnson and Johnson Innovative Medicine. *Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]: Company response to the draft guidance document*. London, UK: National Institution for Health and Care Excellence,; 2025.
3. Electronic Medicines C. Rybrevant 1600 mg solution for injection. Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/101168/smpc [Accessed: July 2025].
4. Cho BC, Lu S, Felip E, Spira AI, Girard N, Lee JS*, et al.* Amivantamab plus Lazertinib in Previously Untreated EGFR-Mutated Advanced NSCLC. *N Engl J Med* 2024;**391**:1486-98. https://doi.org/10.1056/NEJMoa2403614
5. Chih-Hsin Yang J. et al. Amivantamab Plus Lazertinib vs Osimertinib in First-line (1L) EGFR-mutant (EGFRm) Advanced NSCLC: Final Overall Survival (OS) from the Phase 3 MARIPOSA Study. Presented at: European Lung Cancer Congress (ELCC); March 26-29, 2025. Paris, France.
6. European Medicines Agency (EMA). *Lazcluze assessment report. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/lazcluze. [Accessed: July 2025]*.).
7. Cho BC, Lu S, Felip E, Spira AI, Girard N, Lee JS*, et al.* Amivantamab plus Lazertinib in Previously Untreated EGFR-Mutated Advanced NSCLC. *N Engl J Med* 2024;**391**:1486-98. https://doi.org/10.1056/NEJMoa2403614
8. Johnson & Johnson Data on File. MARIPOSA Clinical Study Report. DCO: 11 August 2023.
9. Johnson & Johnson Data on File. MARIPOSA Clinical Study Report. DCO: 4 December 2024.
10. Gemeinsamer Bundesausschuss. Osimertinib in combination with pemetrexed and platinum-based chemotherapy for the first-line treatment of adult patients with advanced NSCLC whose tumors harbor EGFR mutations as a deletion in exon 19 or a substitution mutation in exon 21 (L858R). Module 4a - Appendix 4G. Available at: https://www.g-ba.de/downloads/92-975-7842/2024_07_23_Modul4A_Osimertinib_Anhang_4G.pdf. [Accessed: July 2025].
11. Planchard D, Jänne PA, Cheng Y, Yang JC, Yanagitani N, Kim SW*, et al.* Osimertinib with or without Chemotherapy in EGFR-Mutated Advanced NSCLC. *N Engl J Med* 2023;**389**:1935-48. https://doi.org/10.1056/NEJMoa2306434

12. National Institute for H, Care E. Osimertinib with pemetrexed and platinum-based chemotherapy for untreated EGFR mutation-positive advanced non-small-cell lung cancer. Available at: https://www.nice.org.uk/guidance/ta1060 [Accessed: July 2025].
13. Leighl NB, Akamatsu H, Lim SM, Cheng Y, Minchom AR, Marmarelis ME, *et al.* Subcutaneous Versus Intravenous Amivantamab, Both in Combination With Lazertinib, in Refractory Epidermal Growth Factor Receptor-Mutated Non-Small Cell Lung Cancer: Primary Results From the Phase III PALOMA-3 Study. *J Clin Oncol* 2024;**42**:Jco2401001. https://doi.org/10.1200/jco.24.01001
14. Baldwin A, Hughes A, Greystoke A. 99 Patient experiences of atezolizumab subcutaneous formulation compared to intravenous in Newcastle, and the impact on services delivering systemic anti-cancer treatments. *Lung Cancer* 2025;**200**. https://doi.org/10.1016/j.lungcan.2025.108209
15. National Health Service (NHS). *National Schedule of NHS Costs 2023/24 (2025). Available at: https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/ [Accessed: February 2025]*.).

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256] - Additional analysis request

1 **Decision problem** – The committee reiterated that the decision problem for current standard of care is Osimertinib therapy with or without chemotherapy, the choice of which would be based on fitness and other patient factors. If recommended, amivantamab with lazertinib would likely displace most osimertinib plus chemotherapy treatment and some osimertinib monotherapy, therefore the committee does not think it is appropriate to give a recommendation against only 1 comparator. The committee requested that **all modelling assumptions in the analysis should reflect this decision problem** (i.e. starting age, utility values, subsequent treatments may differ based on fitness).

2 **Indirect treatment comparison OS/PFS** – The committee considered that none of the analysis presented (Osimertinib monotherapy-based ITC company approach and naïve comparison) was appropriate, neither was the rationale for the company approach justified. It requested analysis that explored time-varying hazards and population adjustment where appropriate, including:

a) Parametric curves fitted to the data, using different curve extrapolation fits to those previously agreed for FLAURA2 (as per DSU TSD14). Alternative extrapolation curves may also be explored from MARIPOSA as long as their fit is appropriate and long-term predictions are adequate. The committee considered there may be curves that provided a reasonable fit to data from both trials and extrapolation curve selection from previous appraisals does not constitute fixed precedent for rejecting standard ITC approaches.
b) If parametric curve fits are inappropriate, then fractional polynomials can be used to explore time varying assumptions (as per DSU TSD21)
c) Other population adjustment could include an anchored MAIC to adjust the MARIPOSA population before fitting curves to each arm.
d) Alternatively, both the time-varying hazards and population adjustment could be explored through multi-level network meta-regression (ML-NMR)

Ideally, all the suggested analysis would be explored, but where it has not been done, there should be a full explanation and evidence for methods which were used or rejected. It also noted that the final analysis of FLAURA2 was complete and the KM data may become available which would allow for an updated data cut for OS.

3 **Indirect treatment comparison adverse events** – The committee requested an adjusted comparison of the adverse events of amivantamab with lazertinib compared with osimertinib plus chemotherapy. It noted that amivantamab with lazertinib in combination had produced some unexpected adverse events compared to previous trials of amivantamab and lazertinib as monotherapies which is why a protocol amendment was implemented for prophylactic anticoagulation in the MARIPOSA trial. It requested consideration of the adverse events profiles of both treatments compared and modelled or a full explanation and justification of why this wasn't possible or appropriate.

4 **Indirect treatment comparison TTD** – The committee was uncertain about the appropriate TTD curve for the osimertinib component of osimertinib plus chemotherapy. It requested exploration of modelling based upon ITC compared TTD values for the comparison with osimertinib plus chemotherapy if possible, noting that updated data from FLAURA2 may be available. If not available, the committee noted that the TTD curves should be reasonable when considering PFS curves from the updated ITC (see section 2), the clinical plausibility of assumptions (e.g. the EAG capping scenario) and the adverse event profiles of the different treatments (see section 3).

5 **Utility values** – The committee reiterated its preference for treatment dependent utility values in the progression-free health state, noting that the subcutaneous formulation of amivantamab would still require hospital attendance and the PALOMA-3 trial reported increases in some adverse events between the subcutaneous and IV formulations of amivantamab but decreases in others. It requested exploration of different progression-free utility values for the three treatment arms in the model, noting that an indirect treatment comparison that compared adverse events between the three treatments could help inform these values (see section 3). It also requested

consideration of the time period that these effects would be suitable, for example, discontinuation of platinum doublet chemotherapy in the osimertinib plus chemotherapy arm would likely improve utility.

For progressed disease, the committee considered the value from TA1060 would be more appropriate than MARIPOSA but requested exploration of differences in subsequent treatments between arms (see section 6). Explanation and justification of all chosen utility values should be provided.

6 **Subsequent treatments** – The committee heard from clinical experts at the meeting that the choice of second line therapy for people receiving osimertinib plus chemotherapy was inconsistent and estimated there would be a roughly equal split between platinum-based chemotherapy and docetaxel. The committee agreed with the EAGs assumptions around subsequent treatment modelling assumptions. So, the committee's preferred assumptions were:

- 50% of treatment at second line should be platinum-based chemotherapy and 50% should be docetaxel
- treatment at third line should be 100% best supportive care
- subsequent treatments should be aligned with the osimertinib component's time to treatment discontinuation curve
- EAG's assumption for the administration costs for subsequent treatments.

It also requested scenario analyses that explored the proportion of nintedanib use with docetaxel and an appropriate proportion of people using atezolizumab with bevacizumab, carboplatin and paclitaxel as a third line treatment.

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Additional Analyses Request

September 2025

1. Executive Summary

1.1 Background and context

In the initial Draft Guidance Document (DGD) published by NICE, a comparison was requested by the Committee between amivantamab-lazertinib and osimertinib-chemotherapy. To determine the best approach for this comparison, the Company evaluated the proportional hazards assumption for overall survival (OS) and progression-free survival (PFS) within the MARIPOSA and FLAURA2 trials. The proportional hazards assumption was violated in both trials and therefore hazard ratio (HR)-based ITCs were considered inappropriate. An alternative parametric ITC approach was also deemed unsuitable because the interventions required different distribution models, which were fundamentally incompatible. As a result, the Company responded in alignment with the Committee's preferred assumptions for amivantamab-lazertinib and osimertinib monotherapy (ID6256; the MARIPOSA indication), as well as NICE's final positions for osimertinib-chemotherapy (TA1060; the FLAURA2 indication). This approach was applied to practically all endpoints, with intervention only when a clear and justified rationale for deviation arose, such as removing settings that were contradictory or clinically implausible.

Consequently, the Company adopted a method where osimertinib-chemotherapy was modeled using independently fitted parametric distributions based on reconstructed individual patient data (IPD) from Kaplan-Meier (KM) curves in FLAURA2. The Company assumed any potential differences between trials would be reflected in outcomes with the osimertinib monotherapy arms from both trials (MARIPOSA and FLAURA2). As such the Company adjusted the osimertinib-chemotherapy arm by applying HRs reflecting the minor difference between outcomes with osimertinib monotherapy in MARIPOSA and FLAURA2 for each outcome (PFS, OS, TTD). Although the Economic Assessment Group (EAG) preferred unadjusted curves, the impact was limited due to the similarity of populations, as the HRs were close to 1. Nevertheless, during the second Committee meeting, concerns about the validity of these analyses were raised, prompting the Committee to request further exploration of additional ITC methods and clinical validation, especially with the updated OS data for FLAURA2 published on September 7th.

The Company maintains that the initial analyses were sufficient, given:

- two robust methods for ITC were considered and ruled out on methodological grounds,
- the similarity between trial populations of MARIPOSA and FLAURA2,
- alignment with Committee preferred assumptions (ID6256) and NICE guidance for TA1060
- extensive clinical validation of extrapolations for each outcome

The Company are, however, committed to working with NICE to ensure UK patients gain access to innovative, targeted therapies that offer benefits superior to current standard of care. In response to the Committee's specific requests, the Company has provided detailed analyses, including re-assessment of survival assumptions with updated FLAURA2 OS data, and an ITC comparison of adverse events. An updated cost-effectiveness analysis based on the most clinically plausible ITC approach has also been provided, aiming to comprehensively clarify and address the Committee's concerns.

1.2 Summary of FLAURA2 updated data, safety and comparative insights

The recent update on the FLAURA2 trial offers insights into longer-term clinical outcomes, safety, and treatment patterns for patients with untreated EGFR mutation-positive advanced non-small-cell lung cancer

(NSCLC). The results provide further insight into the evolving role of osimertinib as an EGFR mutation targeted therapy, either alone or in combination, and provide a basis for comparison with emerging treatments like amivantamab-lazertinib:

- With a median follow-up of 51.2 months, the median OS was 47.5 months in the osimertinib-chemotherapy arm versus 37.6 months in the osimertinib monotherapy arm (HR=0.77). This is a clinically meaningful improvement in survival benefit for these patients. The increased hazard ratio versus the previous data cut (HR=0.75) and the persistent narrowing of the KM survival curves with the longer follow-up suggest some uncertainty about the long-term durability of this benefit (median follow-up of 51.2 months).

- Osimertinib-chemotherapy is associated with higher rates of adverse events than osimertinib monotherapy, particularly Grade ≥3 and serious AEs. In FLAURA-2, treatment-related AEs led to treatment discontinuations in 12% of patients for osimertinib,17% for the platinum agent and 50% for pemetrexed in the intervention arm. These safety considerations, although expected, are important as they influence the ability to maintain patients on pemetrexed which is an important treatment component in order to achieve the survival results.

- In the osimertinib-chemotherapy arm, 127 patients had discontinued treatment due to progressed disease at the 12th June 2025 DCO, of which 69% (n=88) went on to receive subsequent treatment. At 2L following osimertinib-chemotherapy, the majority of patients were treated with chemotherapy (74%), either platinum-based (44%) or non-platinum-based (30%). More patients in the osimertinib-chemotherapy arm did not receive further active anticancer therapies (31% for osimertinib-chemotherapy versus 23% for osimertinib monotherapy), this can potentially contribute to the observed reduction in treatment benefit of osimertinib-chemotherapy when compared to osimertinib monotherapy from 3 years onward.

- Patients receiving the combination of osimertinib-chemotherapy had a median total exposure of 30.5 months (range: 0.1–59.0 months) to osimertinib. By contrast, patients on osimertinib monotherapy had a shorter median exposure of 21.2 months (range: 0.1–59.2 months) to osimertinib. However, exposure is a different endpoint from TTD, and only limited exposure data (medians and ranges) are available. Consequently, it was not possible to update the TTD in the cost-effectiveness analysis.

Overall, the updated FLAURA2 data shows a benefit in combining chemotherapy with osimertinib versus osimertinib monotherapy. However, consideration should be given to the fact that the initial benefit does not appear to be sustained over time, and a safety profile that appears to prevent the delivery of the maintenance chemotherapy component.

The new overall survival data, safety and subsequent treatments have been updated in the model. The exposure data (only medians and ranges) differs from TTD as endpoint, and the model therefore relies on TTD data from the previous data cut. PFS was not updated in the recent FLAURA2 data cut.

1.3 Summary of clinical advantages of amivantamab-lazertinib: Resistance Management, Response Durability, and Survival Benefits in EGFR-Mutated NSCLC

Recent advances in targeted therapies have revolutionised EGFR-mutated NSCLC treatment, including amivantamab-lazertinib and osimertinib-chemotherapy. These new treatment strategies consist of combining a third generation TKI (lazertinib or osimertinib) with an additional active agent(s) to achieve synergetic effect

and improve survival beyond the current standard of care. These additional therapies differ in mechanisms of action, resistance mechanisms, and long-term outcomes:

- The combined extracellular and intracellular blockade employed by amivantamab-lazertinib effectively addresses key resistance pathways, notably reducing the incidence of MET amplification and secondary EGFR mutations, as demonstrated in the MARIPOSA trial. Additionally, there was less complex secondary resistance mechanisms with amivantamab-lazertinib on progression than osimertinib monotherapy. By contrast, osimertinib, does not target MET pathways extracellularly, limiting its ability to prevent or delay resistance mechanisms such as MET amplification. Despite the addition of chemotherapy, resistance mechanisms remained largely similar across treatment groups, with MET amplification unaffected. This difference could contribute to explaining the long-term advantage of amivantamab-lazertinib versus osimertinib-chemotherapy.

- Waterfall plots from FLAURA, FLAURA-2 and MARIPOSA showed that while the addition of chemotherapy to osimertinib resulted in some incremental benefit in terms of response rate in target lesions, the addition of amivantamab to lazertinib demonstrated significantly deeper tumour responses. These findings highlight the potential of amivantamab-lazertinib to provide improved and durable response, positioning it as a promising and more effective treatment option for patients with EGFR-mutated NSCLC than osimertinib or osimertinib-chemotherapy.

- Pre-clinical in vitro and in vivo data provided evidence of the immune-modulatory effect of the active Fc domain of amivantamab. Recent early-stage clinical data from phase1b/2 OrigAMI-1 study, investigating amivantamab monotherapy in refractory metastatic colorectal cancer has provided supportive evidence pointing towards immune-mediated tumour effects as detected in participants of this study. Taking into consideration this evidence, within its' limitations, the additional mechanism of action of amivantamab could offer long-term effect that is not expected with chemotherapy.

Survival Outcomes

MARIPOSA curves demonstrate early separation and increasing benefit versus osimertinib monotherapy (survival difference at 24, 36, 42 months: 5%, 8%, 12%) while KM curves from FLAURA2 show survival gains that change over time and converge in the longer term (survival difference at 24, 36 and 48 months: 8%, 12%, 8%). The later time-points of the observed data further supports the long-term efficacy of amivantamab-lazertinib.

- In the MARIPOSA trial, mOS was not reached for amivantamab-lazertinib versus 36.73 months for osimertinib. The mOS for osimertinib in MARIPOSA closely aligns with that in FLAURA2 and can serve as basis to assess the incremental benefit of each combination.

- Statistical modelling projects a survival benefit of over 12 months for amivantamab-lazertinib compared to osimertinib. Although chemotherapy adds 9.9 months to osimertinib's mOS, this is less than the projected benefit with amivantamab-lazertinib. Overall, these data further support the long-term advantage of amivantamab-lazertinib versus osimertinib-chemotherapy.

Safety and Tolerability

With the updated safety data from FLAURA2, and when comparing osimertinib-chemotherapy and amivantamab-lazertinib it is important to understand that MoA plays a key role in shaping these profiles and the tolerability of treatments.

- The safety and tolerability profile of amivantamab-lazertinib is consistent with EGFR and MET inhibition and has been widely accepted as favourable across both intravenous (IV) and subcutaneous (SC) formulations. The safety profile and discontinuation rate of amivantamab-lazertinib as seen in MARIPOSA should also be assessed in the context of the additional body of evidence from the PALOMA programme and COCOON study where the SC formulation and the additional preventative measures led to significant reduction of frequency and severity of certain AEs of interest such as administration-related reaction, venous thromboembolism and most skin reactions. The SC formulation also has the additional benefit of potentially improving convenience and delivery efficiency without compromising clinical outcomes.

- Chemotherapy, being a broad-spectrum and non-selective treatment, as addition to osimertinib results in a higher incidence of Grade ≥3 AEs compared with osimertinib monotherapy, which is expected. Furthermore, the cytotoxic nature of chemotherapy is associated with cumulative toxicity profile including haematologic, gastrointestinal AEs, fatigue and dermatological AEs. Despite the familiarity with these AEs and their management among clinicians, they are associated with treatment delays, increased hospital visits and impact on patients' quality of life.

These differences highlight the importance of considering both efficacy and tolerability when assessing long-term outcomes.

1.4 Summary of assessment of comparative efficacy

Based on prior NICE appraisals, conclusions about more complex ITC methodologies support proceeding with caution and prioritising robustness and clinical plausibility over statistical flexibility. The appraisals show that in many settings, more flexible ITC methods did not improve decision-making certainty and, in several cases, led to greater uncertainty or implausible extrapolations. Where time-varying effects were genuinely needed, NICE sometimes accepted fractional-polynomial (FP) network meta-analysis (NMA), but only when the PH assumption was violated and the FP approach offered a clearly more clinically plausible fit; otherwise, simpler approaches (e.g., PH-based NMAs or observed KM data) were preferred.

Nevertheless, the Company conducted a comprehensive assessment of all relevant statistical methods to determine the most clinically plausible approach to formally assessing comparative effectiveness of amivantamab-lazertinib and osimertinib-chemotherapy:

- Piecewise Cox models: results show that the hazard ratios fluctuate markedly across intervals and results differ substantially depending on the time periods chosen, highlighting sensitivity to cut-points with intervals sometimes based on few events. Consequently, estimates are unstable with wide confidence intervals. Further, the long-term survival projections for osimertinib-chemotherapy fall in the lower band of what is considered clinically plausible illustrating that this method is not fit for purpose. A scenario has been provided to demonstrate this impact.

- Fractional polynomial models: aligned with findings from prior NICE appraisals, the FP models do not capture the complexity of the observed data and as a result lack clinical plausibility and visual fit,

therefore, making them unsuitable for decision making in the context of this appraisal. Practically no FP aligned with clinical expectations or had a good visual fit; however, a scenario has been provided to illustrate the potential impact.

- Parametric ITCs: were also found to be unsuitable as the longer-term OS in FLAURA2 shows an even more complex evolution of hazard over time, which can be captured only with flexible distributions. Goodness of fit and plausibility of long-term extrapolations with different distributions for the OS of osimertinib-chemotherapy suggest that it is not possible to conduct a parametric ITC for OS without selecting a distribution for osimertinib-chemotherapy with poor fit to the data and implausible long-term predictions.

Based on exploration of the methods presented above, it is concluded that any attempt to perform a different form of ITC or NMA in this context is a purely academic exercise that would only introduce additional uncertainty and potential bias. Therefore, having thoroughly assessed all approaches requested by the Committee, the Company have employed an unanchored matching-adjusted indirect comparison (MAIC) in the base case. This approach to ITC provides clinically plausible results with greater certainty than the other methods explored and is therefore more appropriate for clinical decision making and in line with earlier conclusions from prior appraisals.[34-36, 40]

1.5 Summary of findings of safety ITC assessment

The safety ITC between amivantamab-lazertinib and osimertinib-chemotherapy indicates that amivantamab-lazertinib has a more favourable safety profile. Multiple comparison methods, including Bayesian NMA and anchored MAIC, consistently reinforce this trend in favour of amivantamab-lazertinib. The Bayesian NMA specifically suggests that osimertinib-chemotherapy is associated with a worse safety profile, evidenced by lower risks of grade 3+ adverse events (AEs) and serious adverse events (SAEs) with amivantamab-lazertinib. These findings are further supported by forest plots, which visually show the favourable safety outcomes associated with amivantamab-lazertinib. Besides the ITC itself, other factors might contribute to an even more profound safety benefit of amivantamab-lazertinib over osimertinib-chemotherapy, as the MARIPOSA trial did not include:

- The FLAURA2 trial likely underestimates AE incidences for osimertinib, possibly due to differences in trial design or measurement methods, which may underreport the safety profile in FLAURA2 and could introduce bias against amivantamab-lazertinib.

- Prophylactic dermatologic management, such as COCOON DM, which significantly reduces dermatologic adverse events with amivantamab-lazertinib without impacting efficacy

- Subcutaneous administration of amivantamab, which offers advantages over intravenous delivery, including fewer IRRs and shorter administration times, which improve patient convenience and quality of life.

In conclusion, the evidence supports that amivantamab-lazertinib is safer and better tolerated than osimertinib-chemotherapy. This conclusion is without accounting for the differences in AE measurement methods in FLAURA2 and MARIPOSA, proactive treatment management and the subcutaneous administration for amivantamab-lazertinib. These findings support amivantamab-lazertinib as the preferred treatment over osimertinib-chemotherapy from a safety perspective, which could lead to an assumption of higher utility values.

1.6 Summary of the clinical validation

A clinical validation exercise was conducted with three independent Thoracic Oncology experts to evaluate the updated FLAURA2 data and the long-term extrapolations, in the context of amivantamab-lazertinib and its relative efficacy versus osimertinib-chemotherapy. The aim of this validation was to ensure the clinical plausibility, robustness of the scientific rationale and credibility of the long-term extrapolations presented in this analysis.[1] The validation involved a series of three independent consultations with clinical experts selected for their extensive experience in thoracic oncology, drug development, and prior involvement in NICE health technology assessments. Detailed minutes from each expert meeting are included as part of this resonse.[1] The consultation meetings took place in September 2025, soon after the new FLAURA2 was released (7th September 2025). Where applicable, insights and feedback obtained during these consultations have been integrated and highlighted throughout the document to reflect the outcome of the validation process. Below is a summary of the clinical validation:

- The biological rationale and differences in mechanism of action between the treatments provide a clear and plausible explanation for the long-term benefit of amivantamab-lazertinib over osimertinib-chemotherapy. Amivantamab's resistance mechanisms, response quality, and immunomodulatory effects offer a scientifically supported basis for its sustained survival benefit.

- Despite challenges in interpreting long-term estimates from smoothed time-varying hazard curves and fractional polynomial (FP) analyses, clinicians agree that the observed trends and biological understanding support a sustained survival benefit of amivantamab-lazertinib over osimertinib-chemotherapy. The validated clinical assumptions from TA1060 in relation to the latest MARIPOSA data should guide curve selection with the updated FLAURA2 data, with complex models serving as supportive evidence. Despite uncertainties inherent in long-term extrapolation, the clinical validation confirms that these survival benefit amivantamab-lazertinib over osimertinib-chemotherapy is both robust and plausible, aligning with the biological rationale.

- When evaluating FLAURA2 extrapolations, most extrapolations were dismissed due to poor fit or clinical implausibility. Extrapolations were either too pessimistic (Gompertz or Generalised Gamma) or too optimistic. The 1- and 2-knot hazard models were unanimously selected as clinically plausible, given their long-term survival prediction and fit to the KM curve. The survival estimates at 5, 10, and 15 years derived from clinical validation closely align with these 1- and 2-knot hazard extrapolations.

- In the clinical assessment for time to treatment discontinuation, the clinical validation highlighted that the TTD for osimertinib (as part of osimertinib-chemotherapy) would not fall below the TTD curve for osimertinib monotherapy. Additionally, they noted that TTD for osimertinib (as part of osimertinib-chemotherapy) for should be higher than the PFS curve for osimertinib-chemotherapy. Based on these insights, the Gompertz curve was deemed clinically implausible, whereas the Gomma curve was considered plausible. These insights are crucial for TTD discussion and have been incorporated into the cost-effectiveness analysis.

1.7 Summary of cost-effectiveness results

In line with the results presented in the initial DGD response, the base case results continue to demonstrate that, at amivantamab and lazertinib PAS prices, amivantamab-lazertinib is a cost-effective use of NHS resources when compared to both comparators at its list price, dominating both osimertinib monotherapy and osimertinib-chemotherapy (Table 1). This conclusion holds across a variety of sensitivity and scenario analyses, presented in Sections 6.2 and 6.3.

Table 1: Deterministic cost-effectiveness results

	Total Costs	Total LYs	Total QALYs	Incremental Costs	Incremental LYs	Incremental QALYs	ICER versus amivantamab-lazertinib (£/QALY)
Amivantamab-lazertinib	[redacted]	5.10	[redacted]	-	-	-	-
Osimertinib	[redacted]	3.77	[redacted]	[redacted]	1.33	[redacted]	−135,124.56
Osimertinib-chemotherapy	[redacted]	4.75	[redacted]	[redacted]	0.35	[redacted]	−987,103.32

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life years; NHB: net health benefit; PAS: patient access scheme; QALYs: quality-adjusted life years.

2. Clinical effectiveness results: Updated data from FLAURA2

Since the second Committee meeting on 13th August 2025, updated data for osimertinib with pemetrexed and platinum-based chemotherapy (osimertinib-chemotherapy) and osimertinib monotherapy have become available from the FLAURA2 trial, presented on 7th September 2025 at the International Association for the Study of Lung Cancer (IASLC) 2025 World Conference on Lung Cancer (WCLC).[2]

Based on the updated data, the aspects presented include overall survival (OS), safety, exposure to individual treatment component per arm and subsequent treatment data. No new information pertaining to progression-free survival (PFS) or time-to-treatment discontinuation (TTD) was provided. Given that no new insights regarding PFS and TTD are available, the emphasis was placed on OS, safety, and subsequent treatment data derived from FLAURA2. Median exposure was presented and is briefly discussed below; however, OS, safety, and subsequent treatment data constitute the foundation of the update for the draft guidance response and will be elaborated upon in the subsequent sections.

2.1 Updated OS data from FLAURA2

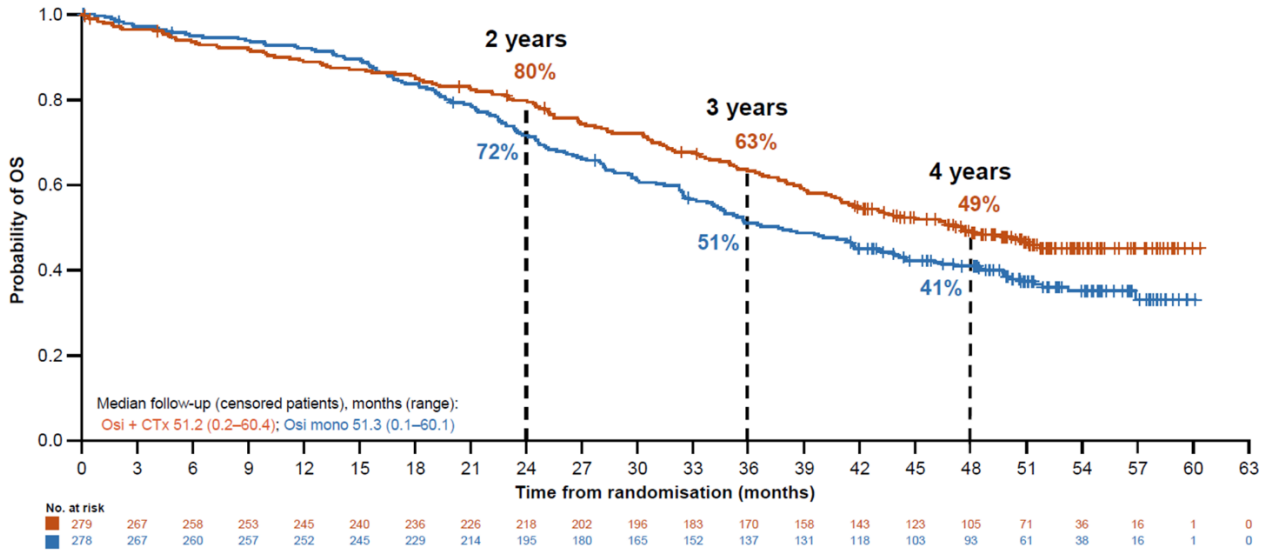
The updated OS data from 12th June 2025 data cut-off (DCO), which have a median follow up of 51.2 months (range: 0.1, 60.1), are presented in Table 2, alongside data from the previous 8th January 2024 DCO which informed the economic model previously submitted for consideration at the second Committee meeting of this appraisal process.[3] The corresponding Kaplan-Meier (KM) curves for the latest DCO are presented in Figure 1.

Table 2: FLAURA2 OS results based on 8th January 2024 and 12th June 2025 DCOs

	DCO: 12th June 2025[2]		DCO: 8th January 2024[3]	
	Osimertinib-chemotherapy (N=279)	Osimertinib monotherapy (N=278)	Osimertinib-chemotherapy (N=279)	Osimertinib monotherapy (N=278)
Event, n (%)	144 (51.6)	171 (61.5)	100 (35.8)	126 (45.3)
mOS, months (95% CI)	47.5 (41.0, NC)	37.6 (33.2, 43.2)	NR (38.0, NC)	36.7 (33.2, NC)
HR (95% CI)	0.77 (0.61, 0.96)		0.75 (0.57, 0.97)	
p-value	0.0202		0.0280	

Abbreviations: CI: confidence interval; DCO: data cut-off; HR: hazard ratio; mOS: median overall survival; NC: not calculable; NR: not reported; OS: overall survival.
Source: Planchard *et al.* (2025);[2] Valdiviezo *et al.* (2024).[3]

Figure 1: KM plot of OS (12th June 2025 DCO; FAS)



Abbreviations: FAS: full analysis set; KM: Kaplan-Meier; OS: overall survival.
Source: Adapted from Planchard *et al.* (2025).[2]

Although osimertinib-chemotherapy demonstrates a statistically significant improvement in OS versus osimertinib monotherapy at the final OS analysis of FLAURA2, the increasing hazard ratio and persistent narrowing of the curves around 39 months, despite the longer follow-up, implies an uncertainty around the long-term durability of survival benefit (further discussed in Section 4.1.1).

2.2 Updated safety data from FLAURA2

Updated data on the adverse events (AE) experienced by patients in the FLAURA2 trial at the timepoint of the final OS analysis (12th June 2025) were also presented at the IASLC 2025 WCLC. A summary of these AE data from the June 2025 DCO is presented in Table 3. Additional data on the most common AEs, recorded as Grade 3 or higher, are presented in Table 4 alongside the AE data published for the previous FLAURA2 DCO (3rd April 2023 DCO). AE data from the 3rd April 2023 DCO of FLAURA2 informed the cost-effectiveness model (CEM) submitted by the Company during the initial DGD response.

Table 3: Summary of AEs observed in FLAURA2 (12th June 2025 DCO, SAS)

AE any cause, n (%)	Osimertinib-chemotherapy (N=276)	Osimertinib monotherapy (N=275)
Any grade	276 (100)	269 (98)
Grade ≥3	193 (70)	94 (34)
Serious	126 (46)	75 (27)
Outcome of death	22 (8)	10 (4)
Considered possibly related to treatment	5 (2)	2 (1)
Leading to discontinuation of osimertinib	34 (12)	20 (7)
Leading to discontinuation of pemetrexed	137 (50)	NA
Leading to discontinuation of platinum chemotherapy	46 (17)	NA

Abbreviations: AE: adverse event; DCO: data cut off; NA: not applicable; SAS: safety analysis set
Source: Planchard *et al.* (2025)[2]

Table 4: FLAURA2 Grade 3+ AEs based on 3rd April 2023 and 12th June 2025 DCOs

AE, (%)	DCO: 12th June 2025[2]		DCO: 3rd April 2023[4]	
	Osimertinib-chemotherapy (N=276)	Osimertinib monotherapy (N=275)	Osimertinib-chemotherapy (N=276)	Osimertinib monotherapy (N=275)
Anaemia	20	1	20	<1
Diarrhoea	3	<1	3	<1
Nausea	1	0	1	0
Decreased appetite	3	1	3	1
Constipation	<1	0	<1	0
Rash	1	0	<1	0
Fatigue	3	<1	3	<1
Vomiting	1	<1	1	0
COVID-19	1	0	1	0
Stomatitis	<1	<1	1	<1
Paronychia	1	<1	1	<1
Neutropenia	14	1	14	1
Neutrophil count decreased	12	1	11	1
ALT increased	2	1	1	<1

Abbreviations: AE: adverse event; ALT: alanine transaminase; DCO: data cut off.
Source: Planchard *et al.* (2025);[2] Planchard *et al.* (2023).[4]

A higher proportion of patients receiving osimertinib-chemotherapy reported Grade ≥3 and serious AEs compared to osimertinib (70% versus 34% and 46% versus 27%, respectively), and AEs leading to discontinuation of osimertinib occurred in 12% of patients in the combination arm versus 7% of patients in the monotherapy arm.[2] Furthermore, AEs leading to death was twice as high for patients receiving osimertinib-chemotherapy compared to osimertinib monotherapy (8% versus 4%).[2]

Overall, no new safety signals were reported in the updated final analysis for FLAURA2, with the safety profile of the combination being considered manageable and consistent with the known profiles of the individual treatments. A more in-depth discussion around AEs associated with osimertinib-chemotherapy in the context of a comparison with amivantamab-lazertinib is provided in Section 3.6.

2.3 Updated subsequent treatment data from FLAURA2

Updated data on the first subsequent treatments received by patients in the FLAURA2 trial at the timepoint of the final OS analysis (DCO: 12th June 2025) were also presented at the IASLC 2025 WCLC (Table 5).

In FLAURA2, 127 patients receiving osimertinib-chemotherapy had discontinued treatment due to progressed disease at the 12th June 2025 DCO, of which 69% (n=88) went on to receive subsequent treatment. At 2L following osimertinib-chemotherapy, the majority of patients were treated with chemotherapy (74%), either platinum-based (44%) or non-platinum-based (30%). The majority of patients in the osimertinib monotherapy arm of the FLAURA2 trial received 2L platinum-based chemotherapy, in line with the 2L treatments received by patients in the osimertinib monotherapy arm of the MARIPOSA trial (see Table 18, Section B.2.6.5 of the original submission).[2]

Table 5: Summary of subsequent treatments received by patients in FLAURA2 following disease progression (12th June 2025 DCO)

Subsequent treatment (%)	DCO: 12th June 2025[2]	
	Osimertinib-chemotherapy (N=88)	Osimertinib monotherapy (N=143)
Platinum-based chemotherapy	44	72
Non-platinum-based chemotherapy	30	3
EGFR targeted therapy (not including osimertinib)	8	7
Osimertinib + targeted agent/investigational drug (not including chemotherapy)	5	3
Other[a]	14	14

Abbreviations: DCO: data cut off.
Footnotes: [a] Other included ADCs, immunotherapies [PD-(L)1 inhibitors], other investigational anticancer therapies, antiangiogenic therapies [VEGF(R) inhibitors], catequentinib hydrochloride, savolitinib, and unspecified herbal and traditional anticancer medicines.
Source: Planchard *et al.* (2025).[2]

In conclusion, chemotherapy is the most frequent first subsequent therapy in both treatment arms, with patients in the control arm receiving significantly higher rates of platinum-based chemotherapy. On progression, more patients in the osimertinib-chemotherapy arm did not receive further active anticancer therapies (31% for osimertinib-chemotherapy versus 23% for osimertinib monotherapy), potentially explaining the narrowing of the survival curves as previously described.

Of note, during the initial DGD response stage, the Company-submitted CEM aligned the 2L and 3L+ treatments for the osimertinib-chemotherapy arm with those used for the osimertinib monotherapy arm in the original submission, which were sourced from the MARIPOSA trial.

The methodology for modelling subsequent treatments for osimertinib-chemotherapy remains consistent with that used for osimertinib monotherapy, as initially outlined. However, the updated model now reflects revised proportions of patients receiving specific subsequent treatments at 2L and 3L+ after osimertinib-chemotherapy, in line with the Committee's preferences and the latest FLAURA2 data (see Section 5.4). Additionally, in accordance with the preferences of the EAG and Committee, patients are now modelled to receive subsequent treatment after discontinuing the osimertinib component, based on the TTD curve.

2.4 Updated median exposure from FLAURA2

In the updated data for FLAURA2 (DCO 12 June 2025), patients receiving the combination of osimertinib-chemotherapy (n=276) had a median total exposure of 30.5 months (range: 0.1–59.0 months) to osimertinib, along with 2.8 months (range: 0.7–4.1 months) of platinum-based therapy and 8.3 months (range: 0.7–58.9 months) of pemetrexed.[2] By contrast, patients on osimertinib monotherapy (n=275) had a shorter median exposure of 21.2 months (range: 0.1–59.2 months) to osimertinib.[2] Overall, the data suggests that combination therapy results in a longer exposure to osimertinib. The available exposure information (medians and ranges) is insufficient to support a quantitative assessment of cost-effectiveness and exposure is a different endpoint than TTD, so the model relies on the TTD data from the previous data cut. A discussion of the qualitative impact of exposure to pemetrexed on disease progression is further discussed in Section 3.6.

3. Amivantamab-lazertinib and osimertinib-chemotherapy: different mechanism of action, different impact

In MARIPOSA and FLAURA2, the new treatment strategies consist of combining a third generation TKI (lazertinib and osimertinib) with an additional active agent(s) to achieve synergetic effect and improve survival beyond the current standard of care. These additional therapies differ in mechanisms of action, resistance mechanisms, and long-term outcomes.

In MARIPOSA, the addition of amivantamab provides a combined inhibition of both epidermal growth factor receptor (EGFR) and MET pathways, as well as immune cell-mediated cytotoxicity. This innovative approach leads to deeper tumour response and addresses key resistance pathways that limit the long-term efficacy of osimertinib.[5] By contrast, the added value of chemotherapy to osimertinib is a systemic effect which reduces the number of cancer cells via a broad-spectrum and non-selective approach. The distinction in the mechanisms of action between amivantamab-lazertinib and osimertinib-chemotherapy is observed in the impact of the treatments on disease biology and OS and additionally feeds into the management of treatment-related AEs.

3.1 Resistance mechanisms as plausible explanation for durable responses

Patients with non-small cell lung cancer (NSCLC) treated with EGFR TKIs may acquire resistance through secondary mutations[6]. Alterations in the EGFR tyrosine kinase family contribute to resistance, such as EGFR and HER2 amplification and acquisition of additional EGFR mutations (C797, G724, L792, L718 and G719).[7] In addition to EGFR mutations, EGFR-positive tumours may also undergo activation of the MET intracellular signalling pathway through *MET* gene amplification and increased MET expression, accounting for up to 26% of resistance to osimertinib monotherapy. This leads to acquired resistance, as stimulation of this pathway provides an alternative mechanism to bypass the TKI block of EGFR and facilitate the survival of cancer cells.[8]

As an EGFR TKI, osimertinib offers intracellular inhibition of EGFR, with activity against the common EGFR mutations and specifically designed to overcome EGFR T790M resistance mutation.[9] Nevertheless, almost all patients treated with 1L osimertinib will develop resistance to the treatment, the most common mechanisms of which are secondary alterations in the EGFR pathway and MET alterations.[10, 11] Chemotherapy agents have a non-selective anti-tumour effect, reducing the number of cancer cells without additional targeted blockage of the EGFR or MET receptor. As such, adding chemotherapy agents (pemetrexed and cisplatin or carboplatin) to osimertinib does not prevent EGFR and MET-based resistance mechanisms to osimertinib treatment from occurring, and therefore the combination is unlikely to provide a marked alteration to resistance mechanisms upon progression. In the FLAURA2 trial, while the incidence of certain secondary EGFR resistance mutations was reduced with osimertinib-chemotherapy compared with osimertinib (4.0% versus 14.0%), the incidence of MET amplification was unaffected (12.0% versus 11.0%).[12] Furthermore, acquired resistance mechanisms were broadly similar between the osimertinib monotherapy group and the osimertinib-chemotherapy group, with both treatment arms exhibiting a high proportion of patients with more than one acquired resistance mutation (46% and 40%, respectively).[12]

By contrast, alongside the intracellular inhibition of EGFR by lazertinib, the innovative mechanism of action (MoA) of amivantamab offers extracellular inhibition of both EGFR and MET, leading to inhibition of pathways independent of their intracellular mutations. This multi-targeted MoA targets and significantly reduces key acquired resistance mutations, including secondary EGFR mutations and MET amplifications, and enhances immune engagement. This is supported by head-to-head data versus osimertinib from the MARIPOSA trial. In an updated analysis, recently presented at WCLC 2025, amivantamab-lazertinib significantly reduced the

incidence of MET amplifications and secondary EGFR resistance alterations versus osimertinib (reduction in MET amplification: 3.4% versus 13.1% [p=0.002]; EGFR resistance mutation: 1.4% versus 7.6% [p=0.014]).[13] These reductions were not associated with any clear compensatory resistance mechanism.[13] Furthermore, amivantamab-lazertinib demonstrated a substantial reduction in the incidence of complex resistance, defined as ≥2 resistance pathway alterations, compared with osimertinib (27.8% versus 42.6%).[14] Complex resistance mechanisms are associated with harder to treat disease on progression, especially in the absence of genotype-matched therapies.[15] This illustrates that amivantamab-lazertinib can change the disease biology while providing a chemotherapy-free treatment option to patients with common EGFR-mutated (cEGFRm) NSCLC, thus preserving future treatment options.

In summary, resistance to EGFR TKIs like osimertinib mainly involves secondary mutations such as secondary EGFR resistance mutations and activation of alternative pathways like MET amplification. Despite adding chemotherapy in the FLAURA2 trial, resistance mechanisms—particularly MET amplification—remained largely unaffected, and the overall pattern of resistance was similar across treatment groups. By contrast, amivantamab's extracellular MoA targets both EGFR and MET pathways simultaneously, offering a promising strategy to overcome these resistance mechanisms. Head-to-head data from the MARIPOSA trial show that amivantamab-lazertinib significantly reduces the incidence of key resistance mutations, including MET amplification and secondary EGFR mutations, and decreases complex resistance profiles. This suggests that amivantamab-lazertinib can change the biology of the disease, delay or prevent resistance development, potentially leading to improved long-term outcomes for patients with EGFR-mutated NSCLC. Its multi-targeted approach represents a significant advancement over current EGFR TKI therapies.

3.2 Quality of responses as plausible explanation for durable responses

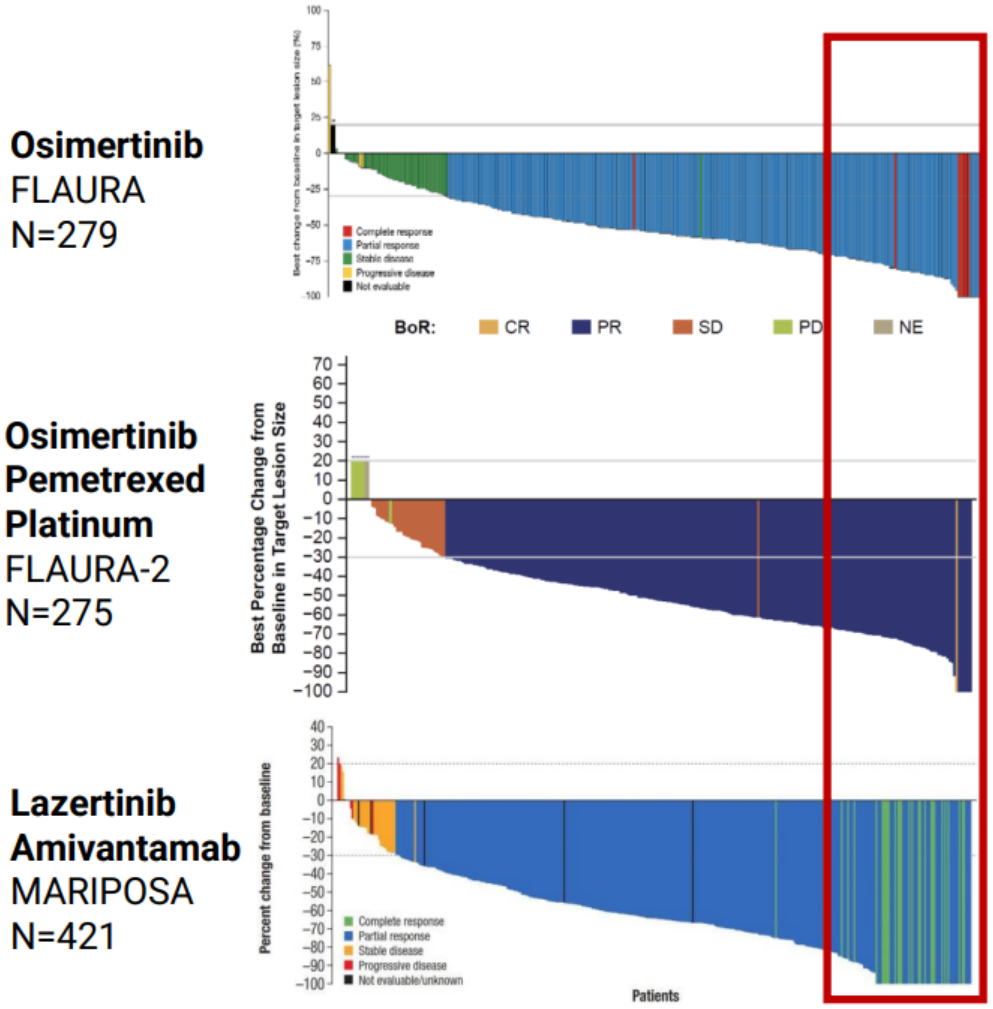
Alongside the final OS analysis of the FLAURA2 trial (DCO: 12th June 2025), presented at the IASLC 2025 WCLC, a comprehensive discussion on osimertinib-chemotherapy, contextualised within the spectrum of available treatments, including amivantamab-lazertinib, and osimertinib monotherapy, was also available.[2, 15]

A key focus of the discussion was the quality of responses, as illustrated by the various waterfall plots (Figure 2).[4, 15-17] When considering treatment effect in metastatic disease, one area to focus on is the quality of the radiological response. The addition of chemotherapy to osimertinib had a small effect on radiological responses as evidenced by the best percent change from baseline in target lesions. By contrast, the impact of amivantamab-lazertinib led to a greater degree of change from baseline in these target lesions.[15]

These data clearly indicate that the combination of amivantamab and lazertinib results in more profound and deeper response in a larger proportion of patients, compared with the responses seen with osimertinib-based regimens.

In conclusion, the FLAURA2 trial data demonstrate that while adding chemotherapy to osimertinib offers limited uplift in response depth, amivantamab-lazertinib produces significantly deeper tumour responses. These findings highlight the potential of amivantamab-lazertinib to provide improved and durable response, positioning it as a promising and more effective treatment option for patients with EGFR-mutated NSCLC. Its ability to induce profound tumour shrinkage underscores its potential to improve long-term outcomes.

Figure 2: Quality of radiological response in the FLAURA, FLAURA2 and MARIPOSA studies



Abbreviations: BoR: best objective response; CR: complete response; NE: not estimable; PD: progressed disease; PR: partial response; SD: stable disease
Source: Tan (WCLC 2025);[15] Cho *et al.* (2023);[16] Planchard *et al.* (2023);[4] Ramalingam *et al.* (2020).[17]

3.3 Immune mediate effect of amivantamab as plausible explanation for durable responses

Amivantamab, a fully human Fc-active immunoglobulin G1 (IgG1) bispecific antibody, has an immune cell-directing activity, such as antibody-dependent cellular cytotoxicity and trogocytosis that could contribute to the treatment effect for patients treated with this treatment. The binding of the Fc region of amivantamab to immune cells induces several effector functions. This important MoA hinges on the activation of these immune cells through amivantamab-Fc binding to their Fcγ receptors (FcγRs) on immune cells.[16] The impact of effector functions on the overall efficacy of amivantamab has been studied extensively in *in vitro* and *in vivo* models and compared with that of an EGFR- and MET-targeting bispecific Fc-silent antibody (referred to as amivantamab-Fc-silent). For example, in an EGFR- and MET-driven xenograft model, treatment with amivantamab resulted in nearly 80% tumour growth inhibition, while treatment with amivantamab-Fc-silent resulted in <10% tumour growth inhibition.[16] Moreover, amivantamab-Fc-silent had reduced ability to inhibit receptor phosphorylation, demonstrating that in addition to driving efficacy, binding of the Fc region of amivantamab to FcγRs on immune cells also plays an important role in receptor and signal downmodulation. Notably, trogocytosis was recently identified as a novel Fc-mediated effector function for amivantamab.[16] Trogocytosis, or “cellular gnawing,” is a process in which cell surface proteins from the tumour cell membrane

are removed by immune effector cells, such as monocytes, macrophages, and neutrophils. Amivantamab led to monocyte- and macrophage-dependent downmodulation of EGFR and MET through trogocytosis in cell culture and xenograft mouse models.[26] It has been hypothesised that this mechanism may extend to other nearby receptors, such as other human EGFR family members, which could contribute to suppression of signalling pathways that lead to resistance.

Recently, results from the Phase 1b/2 dose expansion OrigAMI-1 study, investigating amivantamab in refractory metastatic colorectal cancer has provided supportive evidence implying immune-mediated tumour effects seen in participants of this study.[18] Tumour biopsy samples were collected at screening and Cycle 3 Day 1 (C3D1). Whole transcriptome RNA-sequencing data of paired baseline and C3D1 tumour samples were studied. Gene expression data were analysed using standard bioinformatic methods to identify gene signatures associated with amivantamab treatment in baseline tumour samples (n=76) and paired baseline and C3D1 tumour samples (n=17). The authors concluded that:

- A significant upregulation of dendritic cell (P<0.005) and T cell–inflamed (P<0.05) signature scores was observed with amivantamab treatment, potentially implying increased immune cell infiltration of the tumour microenvironment[18]
- Amivantamab increased the cytolytic (P<0.05) and NK cell–mediated cytotoxicity pathway (P<0.05) scores, implying an increase in cytotoxic immune cells[18]
- AREG and EREG baseline mRNA levels were associated with response, and median PFS showed improvement for participants with high AREG expression in Cohort A (P<0.01)[18]
- Downregulation of cell cycle signatures was observed following amivantamab treatment, implying reduced tumour cell proliferation[18]

Although this is early data from a different tumour type, it's crucial evidence of the plausibility of the immune-mediated effect of amivantamab beyond the pre-clinical setting. In conclusion, the quality of radiological response, the qualitative and quantitative alteration of resistance mechanisms on progression, as well as the immuno-modulatory effects of amivantamab provide a strong argument that the amivantamab-lazertinib combination could provide long-term benefits that are not expected when combining chemotherapy with a third generation TKI.

In summary, the immunomodulatory mechanisms of amivantamab, such as trogocytosis and immune cell activation, demonstrate its potential to enhance long-term tumour control beyond direct receptor inhibition. Early clinical evidence suggests increased immune infiltration and reduced proliferation, supporting its immune-mediated effects. The superior depth of response and alteration of resistance pathways indicate that the amivantamab-lazertinib combination could offer sustained long-term benefit versus osimertinib and osimertinib-chemotherapy. Furthermore, clinical experts agree that these biological advantages can plausibly translate into improved survival outcomes, positioning amivantamab-lazertinib as a promising therapy with potential for durable, meaningful benefits over existing treatments.

3.4 Survival differences

In the final OS analysis of FLAURA2, osimertinib-chemotherapy demonstrated a median OS (mOS) of 47.5 months compared with 37.6 months with osimertinib monotherapy, over a median follow up of 51.2 months (range: 0.1, 60.1).[2] After a median follow-up of 37.8 months at the timepoint of final OS analysis of MARIPOSA (4th December 2024 DCO), mOS was not estimable (NE) in the amivantamab-lazertinib arm

(95% CI: 42.94, NE) and 36.73 months (95% CI: 33.41, 41.03) in the osimertinib arm.[19] The results show that the 95% CIs for the two MARIPOSA treatment arms are mutually exclusive: the lower 95% CI of the amivantamab-lazertinib arm is higher than the upper 95% CI for the osimertinib arm.[20] This indicates that a significantly greater proportion of patients are surviving within the amivantamab-lazertinib arm during the trial period, in stark contrast to the osimertinib arm and serves to underscore the clinically meaningful and superior efficacy of amivantamab-lazertinib when compared with osimertinib.[20] The mOS for osimertinib of 36.73 months (median follow-up in osimertinib arm: [redacted] months) is comparable to that reported in the osimertinib monotherapy arm of the FLAURA2 trial (37.6 months) over an extended follow-up period (51.2 months).[2, 19]

Additionally, it is projected that the benefit in mOS with amivantamab–lazertinib over osimertinib is projected to exceed 12 months[21]. This figure was supported by statistical calculations and widely used parametric models.[19] In FLAURA2, the concomitant use of chemotherapy and osimertinib yielded and additional 9.9 months of mOS. This is clearly a significant benefit over the sequential use of both treatments; it remains however inferior to the anticipated benefit in MARIPOSA.

In fact, a survival benefit is anticipated with amivantamab-lazertinib compared with osimertinib-chemotherapy given its innovative MoA and is supported by the differences in the survival rates towards the end of the observed data. When evaluating the KM curves in the final OS analysis of the FLAURA2 trial (Figure 1), the benefit increases from 8.2% at 24 months to 12.3% peak at 36 months. It then stabilises between 8–10% until 54 months (Table 6).[2] This is further supported by time-dependent hazard ratios (HRs) (which will be discussed in Section 4.1), and the choice of long-term extrapolation curves in TA1060, in addition to the clinical validation done as part of the new FLAURA2 data (see Section 4.1). By contrast, the KM curves for amivantamab-lazertinib at the final OS analysis of the MARIPOSA trial separated early and widened continuously over time at every landmark, before amivantamab-lazertinib starts to plateau after 42 months of treatment (Figure 3), highlighting the durable survival benefit of amivantamab-lazertinib.[19]

Table 6: The difference in rates of patients alive between intervention and osimertinib monotherapy for MARIPOSA and FLAURA2

Months	MARIPOSA	FLAURA2	Absolute Difference (%)	Ratio of absolute differences
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

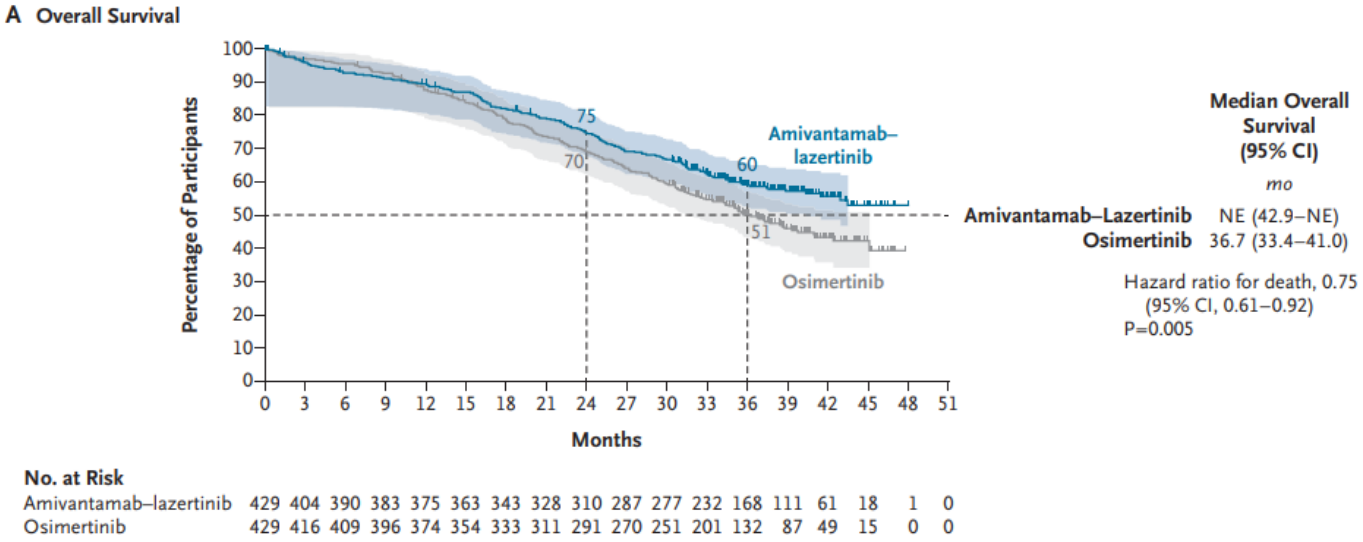
*Estimations from the KM curves, number at risk are low at 48 months for MARIPOSA and 60 months for FLAURA2
Source: Yang *et al.* (2025);[21] Planchard *et al.* (WCLC 2025)[2]

In conclusion, data from MARIPOSA demonstrate a median overall survival (mOS) projected to exceed 12 months favouring amivantamab-lazertinib over osimertinib[21], supported by non-overlapping confidence intervals and survival tail analyses. The MARIPOSA trial further underscores the durable survival benefit, with the KM curves showing early separation and emergent plateauing of the amivantamab-lazertinib curve after 42 months. These findings suggest that amivantamab-lazertinib offers a significant and clinically meaningful long-term survival advantage, driven by its innovative mechanism of action and favourable survival tail, positioning it as a promising treatment for EGFR-mutated NSCLC.

3.5 Clinical insights on the resistance, quality of responses, immune mediated effect and survival differences

The resistance mechanisms, quality of responses, immune mediated effects and insights in the observed data as shown in Table 6 have all been validated in the clinical validation process. Clinical experts state that the benefits observed in the MARIPOSA and FLAURA2 trials differ, with the survival curves following distinct trajectories in each trial. These observations do not focus solely on relative differences; rather, they highlight that, within the observed period, both treatments exhibit different presumed effects compared to osimertinib monotherapy, which were described as clinically plausible in explaining the long-term clinical benefit of amivantamab-lazertinib over osimertinib-chemotherapy.[1] All three clinical experts found that the biological rationale, difference in the mechanisms of action, the higher quality of responses and the difference in resistance mechanisms with amivantamab versus standard cytotoxic chemotherapy to be a strong scientific and plausible clinical argument to explain the expected long-term benefit in favouring amivantamab-lazertinib.[1]

Figure 3: KM plot of OS for amivantamab-lazertinib and osimertinib monotherapy in the MARIPOSA trial (4th December 2024 DCO; FAS)



Abbreviations: CI: confidence interval; DCO: data cut-off; FAS: full analysis set; HR: hazard ratio; KM: Kaplan-Meier; mo: months; NE: not estimable; OS: overall survival.
Source: Yang *et al.* (2025)[21]

In conclusion, the observed differences in resistance mechanisms, response quality, and immunomodulatory effects are plausible explanations for the long-term survival benefits of amivantamab-lazertinib. Clinical experts consulted during the clinical validation process agreed that these arguments provide a plausible scientific and clinical rationale for the improved long-term outcomes amivantamab-lazertinib over osimertinib-chemotherapy.

3.6 Adverse events profiles

With the updated safety data from FLAURA2, there is a need to explain the differences in AE profiles between the two treatments and give an in-depth analysis of the differences. This will also feed into the safety indirect treatment comparison (ITC) in Section 4.6.

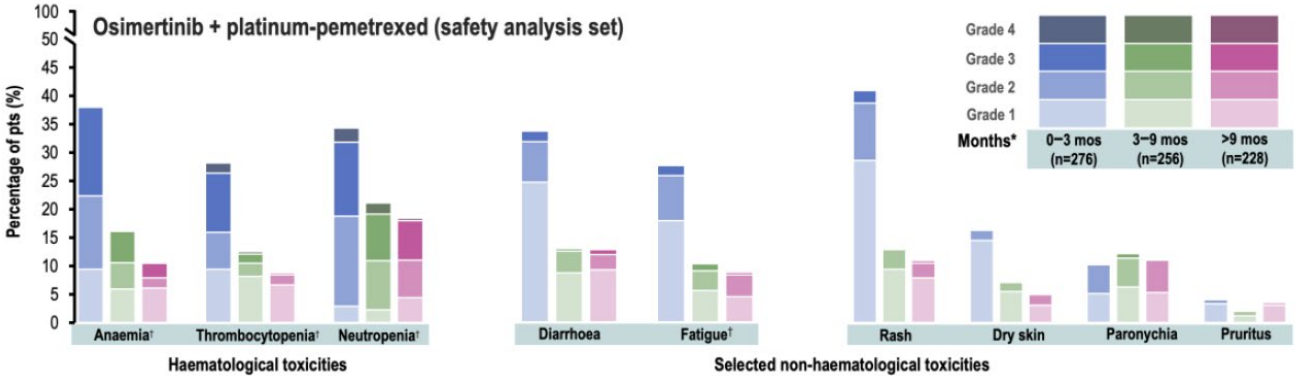
The MoA has a large impact on the adverse effects profile observed with any particular treatment. The safety and tolerability profile of amivantamab-lazertinib is consistent with EGFR and MET inhibition and has been

widely accepted as favourable across both intravenous (IV) and subcutaneous (SC) formulations. Treatment-related AEs leading to discontinuations of all agents occurred in 23% of patients treated with amivantamab-lazertinib. For additional context, discontinuation rates due to AEs are reported in up to 8% of patients receiving monotherapy erlotinib, gefitinib, or osimertinib and up to 29% of patients receiving monotherapy afatinib in clinical trials.[22]

Data from the PALOMA-3 trial show that SC amivantamab is associated with a reduced incidence of certain AEs compared with IV amivantamab, a five-fold reduction in the incidence of infusion related reactions (IRRs) compared with IV amivantamab (13% versus 66%, respectively) and a reduced incidence of venous thromboembolisms (VTE) compared with the IV formulation (9% versus 14%, respectively).[23] In addition, ongoing studies proactively assessing the prophylactic management of AEs associated with IV amivantamab demonstrate that incidence of IRRs, dermatologic events and VTEs can be significantly reduced using established protocols, ensuring continuity of treatment and minimising the burden placed on both healthcare providers and patients (see Section 4.6.3).[24, 25] The SC formulation of amivantamab offers an administration route that reduces IRRs and thromboembolic events as compared with the previous IV formulation, while potentially improving convenience and delivery efficiency without compromising clinical outcomes.

In FLAURA2, and with the updated safety data, the safety profile is consistent with the expected safety profile of osimertinib and cytotoxic chemotherapy with myelosuppression, gastro-intestinal side effects, fatigue and skin adverse events being the most frequents AEs (Figure 4).

Figure 4: Haematological and selected non-haematological toxicities with osimertinib-chemotherapy treatment in FLAURA2 (12th June 2025 DCO; final analysis)

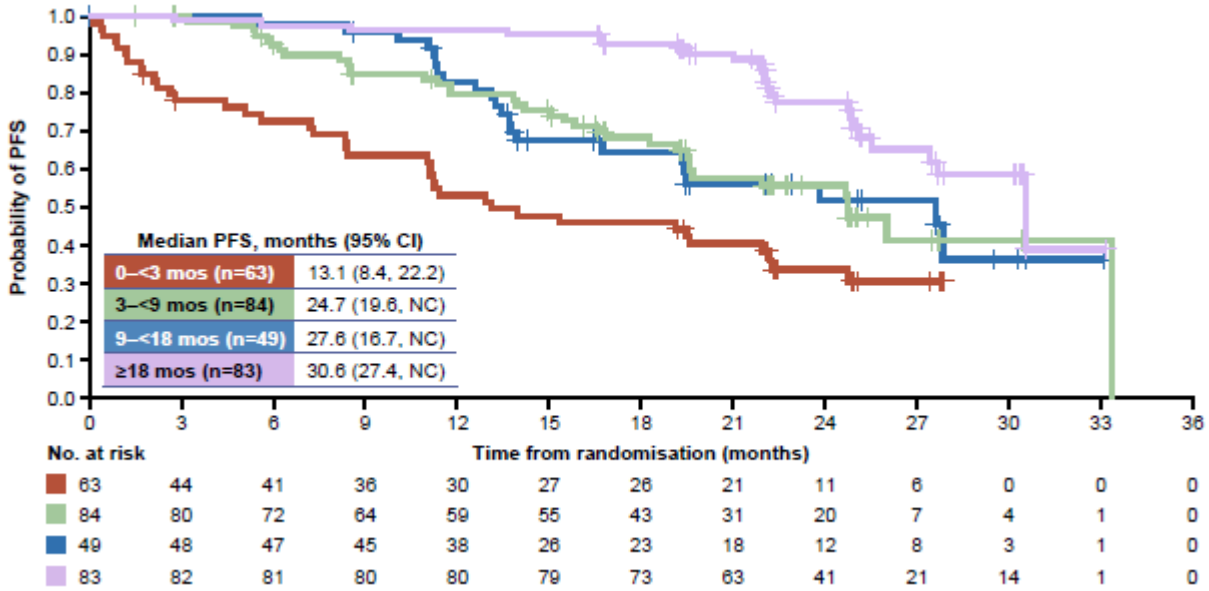


Abbreviations: AE: adverse event; DCO: data cut-off; mos: months.
Source: Tan (WCLC 2025);[15] Planchard *et al.* (ELCC 2025)[26]

As chemotherapy is a broad-spectrum and non-selective treatment approach, the addition of chemotherapy to osimertinib results in a higher incidence of Grade ≥3 AEs compared with osimertinib monotherapy (70% versus 34%, respectively).[4] In a recently published network meta-analysis of RCTs evaluating first-line EGFR TKIs in combination with chemotherapy, including the FLAURA2 trial, Grade ≥3 AEs were up to five-fold more frequent in patients treated with TKIs in combination with chemotherapy than in patients treated with EGFR TKIs alone.[27] Furthermore, cytotoxic chemotherapies are associated with cumulative toxicity profiles, with long-term AEs that worsen over time, including haematologic AEs which are a key driver of AE-related costs due to hospitalisation and intensive care support needs.[28] In the FLAURA2 trial, persistent haematologic AEs, including anaemia, thrombocytopenia and neutropenia, were frequent Grade ≥3 toxicities for patients treated with osimertinib-chemotherapy (Table 3).[2, 4] Chemotherapy therefore requires additional preventative prophylactic therapies to manage AEs, and may be better suited to the 2L setting when resistance becomes more heterogenous.

Treatment-related AEs leading to discontinuations occurred in 12% of patients for osimertinib[1],17% for the platinum agent[29] and 50% for pemetrexed[1]. In fact, the median duration of pemetrexed is only 8.3 months, as opposed 30.5 months for osimertinib in the intervention arm. This is because the chemotherapy is withheld or stopped due to unmanageable adverse events while the disease is still in progression free state. Additional post-hoc exploratory analysis from FLAURA2 showed an observed association between longer PFS and longer duration of pemetrexed treatment (Figure 5).[26] Consequently, the adverse event profile of pemetrexed may represent a limiting factor in optimising the efficacy outcomes of the osimertinib-chemotherapy regimen.

Figure 5: PFS according to pemetrexed exposure (FLAURA2)



Abbreviations: CI: confidence interval; mos: months; PFS: progression-free survival.
Source: Yang (AALC 2024);[29] Planchard *et al.* (ELCC 2025)[26]

The limited number of later-line treatment options and early reliance on chemotherapy in the osimertinib-chemotherapy regimen additionally underscores the need for more sustainable first-line approaches. At the final OS analysis (12th June 2025) of the FLAURA2 trial, more patients in the osimertinib-chemotherapy arm did not receive further active anticancer therapies (31% for osimertinib-chemotherapy versus 23% for osimertinib monotherapy), [2] By contrast, a comparable number of patients who discontinued amivantamab-lazertinib and osimertinib treatment in the MARIPOSA trial at the December 2024 DCO due to disease progression received subsequent treatment (74% and 76% respectively). This implies that receiving amivantamab-lazertinib did not impede patient fitness or willingness to receive 2L treatment.

4. Requested additional analysis of comparative clinical and cost-effectiveness

The Company have systematically addressed the Committee's concerns by providing thorough analyses in response to a series of specific requests stipulated in the document, 'Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256] - Additional analysis request' (hereby referred to as additional analyses request document).[30] In essence, to ensure utmost clarity in the way in which the Committee's requests are addressed, the Company have aligned as closely as possible to the structure of the additional analyses document while also ensuring a logical flow is maintained.

The Company maintains that the initial analyses were sufficient, given:

- two robust methods for ITC were considered and ruled out on methodological grounds,
- the similarity between trial populations of MARIPOSA and FLAURA2,
- alignment with Committee preferred assumptions (ID6256) and NICE guidance for TA1060
- extensive clinical validation of extrapolations for each outcome

The Company are, however, committed to working with NICE to ensure UK patients gain access to innovative, targeted therapies that offer benefits superior to current standard of care. In response to the Committee's specific requests, the Company has provided detailed analyses, including re-assessment of survival assumptions with updated FLAURA2 OS data, and an ITC comparison of adverse events. An updated cost-effectiveness analysis based on the most clinically plausible ITC approach has also been provided, aiming to comprehensively clarify and address the Committee's concerns.

The availability of updated OS data from the FLAURA2 trial has been used to re-assess and re-evaluate survival assumptions (including PFS and TTD, although updated data for these endpoints are not available for FLAURA2, survival assumptions have been reassessed in light of the updated OS data available) for osimertinib-chemotherapy when compared to amivantamab-lazertinib. Therefore, as a first step, the Company have incorporated the updated OS data from the FLAURA2 trial (presented in Section 2.1) and have thoroughly assessed the clinical plausibility of each of the ITC approaches proposed by the Committee (see Sections 4.2, 4.3, 4.4). Additionally, the Company have also provided an adjusted comparison of the adverse events of amivantamab-lazertinib compared with osimertinib-chemotherapy. Following an in-depth analysis of the appropriateness of the requested analyses, the Company have provided updated cost-effectiveness inputs and survival assumptions (including OS, PFS, TTD and PF utility values) based on the most clinically plausible ITC approach.

4.1 The evolution of OS in FLAURA2 in comparison to MARIPOSA

Final OS data from the MARIPOSA trial (DCO: 4th December 2024) are presented in Table 1 of the Addendum that was submitted alongside the original Company submission. Final OS data from the FLAURA2 trial (DCO: 12th June 2025) are presented in Table 2 in Section 2.1 of the current document.

Following ACM 1, at the initial DGD response stage, the time-dependency of treatment effects was investigated by analysis of the Schoenfield residual plots with smoothed HRs over time. These plots, at the time of interim analysis for FLAURA2, suggested an increasing treatment effect in favour of amivantamab-lazertinib versus osimertinib monotherapy over time in MARIPOSA, and a decreasing treatment effect for

osimertinib-chemotherapy versus osimertinib monotherapy in FLAURA2 over time (Figure 6). This analysis also demonstrated an increasing treatment effect in favour of amivantamab-lazertinib over osimertinib-chemotherapy in the long term, supporting the observed long-term OS benefit suggested for amivantamab-lazertinib.

Updating this time-dependent treatment effects graph using the final analysis from FLAURA2 indicates the same direction, trend and magnitude of an increasing treatment effect of amivantamab-lazertinib over osimertinib-chemotherapy (Figure 7). The time-dependant treatment effect of amivantamab-lazertinib versus osimertinib-chemotherapy continues to exhibit a crossing within the observed period, now with more patients at risk in the osimertinib-chemotherapy arm than in the previous data cut. This observation aligns with the findings from the initial DGD and continues to reinforce the long-term benefit of amivantamab-lazertinib over osimertinib-chemotherapy, thereby further reducing the level of uncertainty. This trajectory of time-dependent treatment effect has been corroborated by several clinical experts.[1]

Figure 6: Time-dependent treatment effect in MARIPOSA and IA2 FLAURA2

Abbreviations: AMILAZ: amivantamab-lazertinib; OSI: osimertinib; OSICP: osimertinib-chemotherapy.

Figure 7: Time-dependent treatment effect in MARIPOSA and FA FLAURA2

Abbreviations: AMILAZ: amivantamab-lazertinib; F2: FLAURA2; HR: hazard ratio; M: MARIPOSA; OS: overall survival; OSI: osimertinib; OSICP: osimertinib-chemotherapy.

Based on this evidence, the assumption of proportional hazards still cannot be supported and, consequently, an ITC based on constant HRs would not be appropriate. The approach to modelling osimertinib-chemotherapy used in the initial DGD response remains a valid option that can adequately capture the evolution of survival outcomes in FLAURA2. However, at the request of the Committee, alternative approaches have been explored to estimate the relative treatment effect of amivantamab-lazertinib in comparison to osimertinib-chemotherapy. These approaches are outlined below.

The focus of this section is to illustrate the evolution of OS and to provide context regarding the changes in the FLAURA2 data. However, in response to the additional analyses request document, the Company have also explored the same methods for assessing PFS and TTD, albeit based on the data previously provided in the earlier draft response. In the case of TTD, most of the newly explored methods are not applicable, as numbers of patients at risk are not reported, which meant that it was not feasible to properly reconstruct FLAURA2 IPD for this outcome, and therefore new models could not be fitted and only comparisons based on standard parametric distributions were possible.

4.1.1 Clinical insights into the long-term treatment effect of amivantamab-lazertinib when compared to the updated OS results of osimertinib-chemotherapy

An extensive clinical validation was conducted to ensure the assumptions driving the analyses requested by NICE were not only clinically plausible for the observed data but also for the long-term survival estimates.[1] To ensure NICE's key concerns around uncertainty in the long-term survival estimates were addressed, the Company explored the impact of applying various time-varying methods to best understand how the treatment effect of amivantamab-lazertinib compared to the treatment effect for the updated osimertinib-chemotherapy OS. All three clinicians were in agreement that both the time-varying hazards and fractional polynomial NMA (FP-NMA) results, although challenging to interpret, are indicative of a long-term survival benefit for patients treated with amivantamab-lazertinib compared to those treated with osimertinib-chemotherapy.[1]

The clinicians all agreed that the smoothed time-dependent hazards show a change in risk over time favouring amivantamab-lazertinib over osimertinib-chemotherapy, with the overall shape and clear crossing of

the curves supporting the hypothesis that the treatment effect of amivantamab-lazertinib improves over time, aligning with the biological rationale for a long-term survival benefit over osimertinib-chemotherapy (also described in Section 3.5).[1] Similarly, all three clinicians were unanimous in their understanding of the overall results of the FP-NMAs which they agreed showed a benefit favouring amivantamab-lazertinib after approximately 30 months. Although there was an acknowledgement of the limitation of such approach due to the uncertainty associated with extrapolation beyond the observed data, all clinicians agreed that the results were clearly in support of the long-term benefit of amivantamab-lazertinib over osimertinib-chemotherapy.[1]

Therefore, despite the challenges associated with interpreting long-term estimates derived using time-varying methods (such as FP-NMAs discussed below in Sections 4.2.2 and 4.3.2), all three clinicians confirmed that the graphs and visual trend observed along with a comprehensive understanding of the biology of the treatments in question, are indicative of a long-term and sustained survival benefit of amivantamab-lazertinib over osimertinib-chemotherapy.[1] Not only were the clinical assumptions for osimertinib-chemotherapy validated and concluded during the TA1060 appraisal, they are now re-assessed with the updated FLAURA2 data and in relation to the MARIPOSA data. Therefore, the long-term clinical estimates should be driving the decisions around curve selection, with the more complex analytical methods providing supportive evidence, where relevant. Exploration of more complex approaches to modelling comparative efficacy do not directly address the need to arrive at clinically plausible extrapolations, and as will be seen, either depend on very strong and implausible assumptions in case of parametric methods or confirm amivantamab-lazertinib benefit over osimertinib-chemotherapy when assumptions are relaxed through use of semi-parametric methods. However, the Company is willing to work with NICE and has provided a detailed analysis of all relevant methods to identify the best way to reduce long-term survival estimate uncertainties for amivantamab-lazertinib versus osimertinib monotherapy.

4.1.2 Long term clinical extrapolations of osimertinib-chemotherapy (FLAURA2; DCO 12th June 2025)

In the clinical validation, clinicians were also questioned to assess the long-term extrapolations of FLAURA2, based on the new OS data (FLAURA2; DCO 12th June 2025).

The details are provided in Table 7, with the long-term extrapolations that were considered for TA1060 as reference. The average of the clinical validation position for overall survival is slightly higher than what was determined in TA1060. This is consistent with the observed data from the final analysis results of FLAURA2. In the validation of all standard parametric curves, the clinicians stated that the curves have a very poor fit to the KM data and that the curves presented were either too optimistic or too pessimistic. The Gompertz and Generalised Gamma extrapolations were considered pessimistic overall, as they failed to exhibit a tail in the survival curve. All other parametric extrapolations were seen as too optimistic. When assessing the spline extrapolations, all curves, besides the 1- or 2-hazard knot extrapolations, were unanimously dismissed due to their clinical implausibility, primarily because they predicted excessively high survival rates at 10 and 15 years. Further details on the choice of OS curves as a result of the clinical validation are in Section 5.2.1.

Table 7: Long-term extrapolations from TA1060 (FLAURA2 IA2) and the clinically validated long term extrapolations with the updated OS data from FLAURA2 (DCO: 12th June 2025)

Source	5 years OS			10 years OS			15 years OS		
	Lower	Av.	Upper	Lower	Av.	Upper	Lower	Av.	Upper
Clinical validation 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Clinical validation 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical validation 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Average of clinical validation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2-knot normal (company preference; TA1060)[49]		32.6%			6.8%			1.8%	
2-knot odds (EAG preference; TA1060)[49]		32.0%			7.8%			3.0%	

Abbreviations: Av.: average; EAG: External Assessment group; OS: overall survival.

4.1.3 Clinical insights into Time to Treatment Discontinuation for osimertinib as part of osimertinib-chemotherapy

As part of the clinical validation, the Company also validated the approach to modelling TTD, particularly in relation to the osimertinib component (as part of osimertinib-chemotherapy). Insights from the clinical assessment provided valuable understanding of how TTD is expected to behave, especially in relation to PFS, and clarified which concepts are deemed clinically plausible.

Although in the updated data from FLAURA2 (DCO 12th June 2025) TTD was not provided, clinicians did mention the gap in median of 9.3 months in treatment exposure as an important indicator that the osimertinib component (as part of osimertinib-chemotherapy) is expected to result in a higher TTD then osimertinib monotherapy.

The validation highlighted that the TTD for osimertinib within osimertinib-chemotherapy would not fall below the TTD curve for osimertinib monotherapy. Furthermore, it was noted that TTD for osimertinib as part of osimertinib-chemotherapy should be higher than the PFS curve for the same treatment. Based on these insights, the Gompertz curve for TTD (osimertinib as part of osimertinib-chemotherapy) was regarded as clinically implausible, whereas the alternative Gomma curve was considered plausible. These findings are essential to the ongoing discussion around TTD modelling and have been incorporated into the cost-effectiveness analysis.

4.2 ITC based on Cox regression models

4.2.1 Piecewise Cox regression models

Piecewise Cox models were fitted to estimate the HRs in different time intervals to allow the HR estimate to vary over time. HR estimates from these Cox models are provided in Table 8, and the relative treatment effect for amivantamab-lazertinib versus osimertinib-chemotherapy by time interval is presented in Table 9. Intervals were identified using the method described in Wong *et al.* (2017) and described further in the Supplementary Appendix document.[31] The *Wong et al* publication, was employed to identify the primary cutoff points at which the HR changes over time for each trial individually. Subsequently, the cutoff points from both trials were combined to form a unified set. This combined set was then used to calculate the time-dependent HR within each trial, segmented by intervals. These interval-specific HRs were subsequently used to determine the ITC HR between amivantamab-lazertinib and osimertinib-chemotherapy over time. Relative treatment effects over time were applied to the amivantamab-lazertinib extrapolation to obtain osimertinib-chemotherapy extrapolations. Figure 8 presents the OS extrapolations for osimertinib-chemotherapy from applying the piecewise Cox model time-dependent HRs to amivantamab-lazertinib and demonstrates that osimertinib-chemotherapy extrapolations are sensitive to the time cutoff point selection. The PFS extrapolations for osimertinib-chemotherapy from applying the piecewise Cox model is presented in Appendix 1.1. attached to this document.

Table 8: Piecewise Cox models, OS, MARIPOSA and FLAURA2

Period (months)	MARIPOSA (amivantamab-lazertinib vs. osimertinib)			FLAURA2 (osimertinib-chemotherapy vs. osimertinib)		
	HR (95% CI)	Number of events - Number at risk AMILAZ	Number of events, Number at risk OSI	HR (95% CI)	Number of events - Number at risk OSICP	Number of events - Number at risk OSI
4-interval model						
≤7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>7 – ≤15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>15 – ≤26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5-interval model						
≤7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>7 – ≤15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>15 – ≤ 26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>26 – ≤35	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>35	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; HR: hazard ratio; OS: overall survival.

Table 9: Relative treatment effect for osimertinib-chemotherapy vs. amivantamab-lazertinib based on piecewise Cox models.

Period (months)	HR (95% CI)
4-interval model	
≤7	[redacted]
>7 – ≤15	[redacted]
>15 – ≤26	[redacted]
>26	[redacted]
5-interval model	
≤7	[redacted]
>7 – ≤15	[redacted]
>15 – ≤26	[redacted]
>26 – ≤35	[redacted]
>35	[redacted]

Abbreviations: CI: confidence interval; HR: hazard ratio.

Figure 8: OS Extrapolations for osimertinib-chemotherapy obtained by applying piecewise Cox model HRs to amivantamab-lazertinib

Abbreviations: HR: hazard ratio; KM: Kaplan-Meier; OS: overall survival; CP: chemotherapy; pw: piecewise.

HRs estimated in different intervals were in line with increasing treatment effect in favour of amivantamab-lazertinib vs. osimertinib, and a less marked treatment effect over time for osimertinib-chemotherapy vs. osimertinib. This difference in the trend of time-dependent HR between the two trials supports the conclusion that the treatment effect of amivantamab-lazertinib vs. osimertinib-chemotherapy, improves over time, as illustrated in Table 9Figure 9. Additional details and the cumulative hazard plots used to identify cut off points for the OS and PFSINV endpoints are provided in Appendix Section 1.2.

The 5-interval HR estimate led to osimertinib-chemotherapy OS extrapolations below that of osimertinib monotherapy and was not further considered in the health economic model. The survival long-term projections for osimertinib-chemotherapy derived from the 4-interval piece-wise approach fall in the lower band of what is considered clinically plausible (based on clinical validation; see Section 4.1.2), illustrating that the later described base case is not the most optimistic scenario. To provide some insight into the impact, we have conducted a scenario based on the 4-period piecewise cox model (see Section 6.3).

In addition to the piecewise analysis conducted on OS, the company also performed the same analysis on PFS. The relevant tables and graphs are provided in Appendix Section 1.1.

4.2.2 Fractional polynomial ITC using Cox regression

Within the Committee requests, fractional polynomials (FPs) are listed as a potential method of modelling time-varying treatment effects. Across NICE appraisals, FP-NMAs have been considered primarily where the proportional hazards (PH) assumption was violated or where time-varying treatment effects were plausible enough to merit exploration. However, in practice, FP-NMAs rarely reduced uncertainty in the decision process.

In TA595 (dacomitinib),[32] the Committee concluded that results from the FP-NMA were uncertain, with the Evidence Review Group (ERG) highlighting how FP extrapolations could over-fit the tail and yield clinically

implausible survival estimates; a large number of models had to be rejected for these reasons. In TA858 (levantinib with pembrolizumab),[33] the EAG warned that flexible FP models can be hard to interpret and may produce very different long-term survival estimates despite similar short-term fit, and it did not regard FP-NMA results as appropriate for clinical decision making, preferring more conventional approaches. In TA530 (nivolumab),[34] FP was described as non-conventional for an NMA; concerns were raised about robustness and the sensitivity of incremental cost-effectiveness ratios (ICERs) to model parameterisation, leading to uncertainty about the relative-effectiveness estimates. By contrast, TA964 explicitly preferred FP-NMA in a PH-violated context because it provided a better, clinically plausible fit for time-varying hazards.[35] Taken together, these appraisals illustrate that while FP-NMAs can improve certainty within the observed data, they can introduce substantial extrapolation uncertainty. As a result, NICE often prioritise alternative models or observed KM data and clinical validation over FP-based approaches. This context is of paramount importance for this appraisal, particularly given the extensive alignment already achieved regarding long-term survival outcomes that were already finalised by NICE for osimertinib-chemotherapy (TA1060) and amivantamab-lazertinib (ID6256). The significance of clinically validated and plausible outcomes is essential, especially when evaluated within the framework of complex FP-NMAs.

A Cox model with time-dependent treatment effect assumes the following form for hazards:

$$\lambda(t) = \lambda_0 e^{\beta(t)X}$$

Where $\boldsymbol{\beta(t)}$ indicates that the impact of treatment (i.e. X=1) depends on time. Time-dependent treatment effects in MARIPOSA and FLAURA2 were estimated by assuming a FP functional form for $\boldsymbol{\beta(t)}$. In order to capture the potentially complex shape of the hazard ratio, as indicated by the smoothed regression curve on the Schoenfeld residual plot (Figure 3), fFPs of order 1, 2, and 3 were used. Powers were selected from the set proposed in Royston *et al*. (1994) (−2, −1, −0.5, 0, 0.5, 1, 2, 3) where 0 indicates log transformation.[36] A total of 164 FP-based Cox models were fitted to both MARIPOSA and FLAURA2 data to estimate time-dependent treatment effect of amivantamab-lazertinib versus osimertinib monotherapy, and osimertinib-chemotherapy versus osimertinib monotherapy, one for each possible combination of powers: 8 first-order FPs, 36 second-order FPs, and 120 third order FPs. Third order FPs were explored for the Cox model in order to explore options that may better capture the complex shape of the treatment effect estimated by the smoothed Schoenfeld residuals shown in Figure 7. Relative treatment effect of osimertinib-chemotherapy versus amivantamab-lazertinib was then estimated as the difference between the estimated coefficient values from models fitted to FLAURA2 and MARIPOSA. An example is given below:

For a second order FP with powers *p1* and *p2*, first, the following model was estimated for MARIPOSA:

$$\log(HR_{amilaz\ vs.osi}) = \beta_1(t)X$$

$$= (\beta_{10} + \beta_{11}t^{p1} + \beta_{12}t^{p2})X$$

The same model was then estimated for FLAURA2:

$$\log\left(HR_{osicp\ vs.osi}\right) = \beta_2(t)X$$

$$= (\beta_{20} + \beta_{21}t^{p1} + \beta_{22}t^{p2})X$$

The time-dependent relative effect of osimertinib-chemotherapy versus amivantamab-lazertinib was then estimated as:

$$\log\left(HR_{osicp\ vs.\ amilaz}\right) = \left(\beta_2(t) - \beta_1(t)\right)X$$

$$= \left((\beta_{20} - \beta_{10}) + (\beta_{21} - \beta_{11})t^{p1} + (\beta_{22} - \beta_{12})t^{p2}\right)X$$

Covariance matrix of the relative treatment effect was estimated as the element-wise sum of the covariance matrices from the FP models estimated from FLAURA2 and MARIPOSA data. The *coxph* function in R package *survival* was used with the appropriate time-transform specification for each of the 164 models.

The time-dependent relative treatment effect was then applied to the hazard of amivantamab-lazertinib (unadjusted Weibull) to derive overall survival probabilities for osimertinib-chemotherapy. Log-transformed OS HRs from all the fitted models are shown in Figure 9 and Figure 10, and they span a wide range of trajectories (red horizontal zero line indicates no treatment effect. Trajectories below the zero-line favour amivantamab + lazertinib vs. osimertinib monotherapy in MARIPOSA in Figure 9 and trajectories below zero-line favour osimertinib + chemotherapy vs. osimertinib monotherapy in FLAURA2 in Figure 10). The relative effects of osimertinib-chemotherapy vs. amivantamab-lazertinib are presented in Figure 11 (trajectories above the zero-line favour amivantamab + lazertinib vs. osimertinib + chemotherapy). Treatment effect plots for PFSINV are provided in Appendix 2.1.

Figure 9: MARIPOSA amivantamab-lazertinib versus osimertinib monotherapy, time-dependent treatment effect on OS with FP-based Cox models

Abbreviations: amilaz: amivantamab-lazertinib; FP: fractional polynomial; HR: hazard ratio; M1AMILAZ: MARIPOSA amivantamab-lazertinib; osi: osimertinib monotherapy

Figure 10: FLAURA2 osimertinib-chemotherapy versus osimertinib monotherapy, time-dependent treatment effect on OS with FP-based Cox models

Abbreviations: FP: fractional polynomial; F2OSICP: FLAURA2 osimertinib-chemotherapy; HR: hazard ratio; osi: osimertinib monotherapy; osicp: osimertinib-chemotherapy

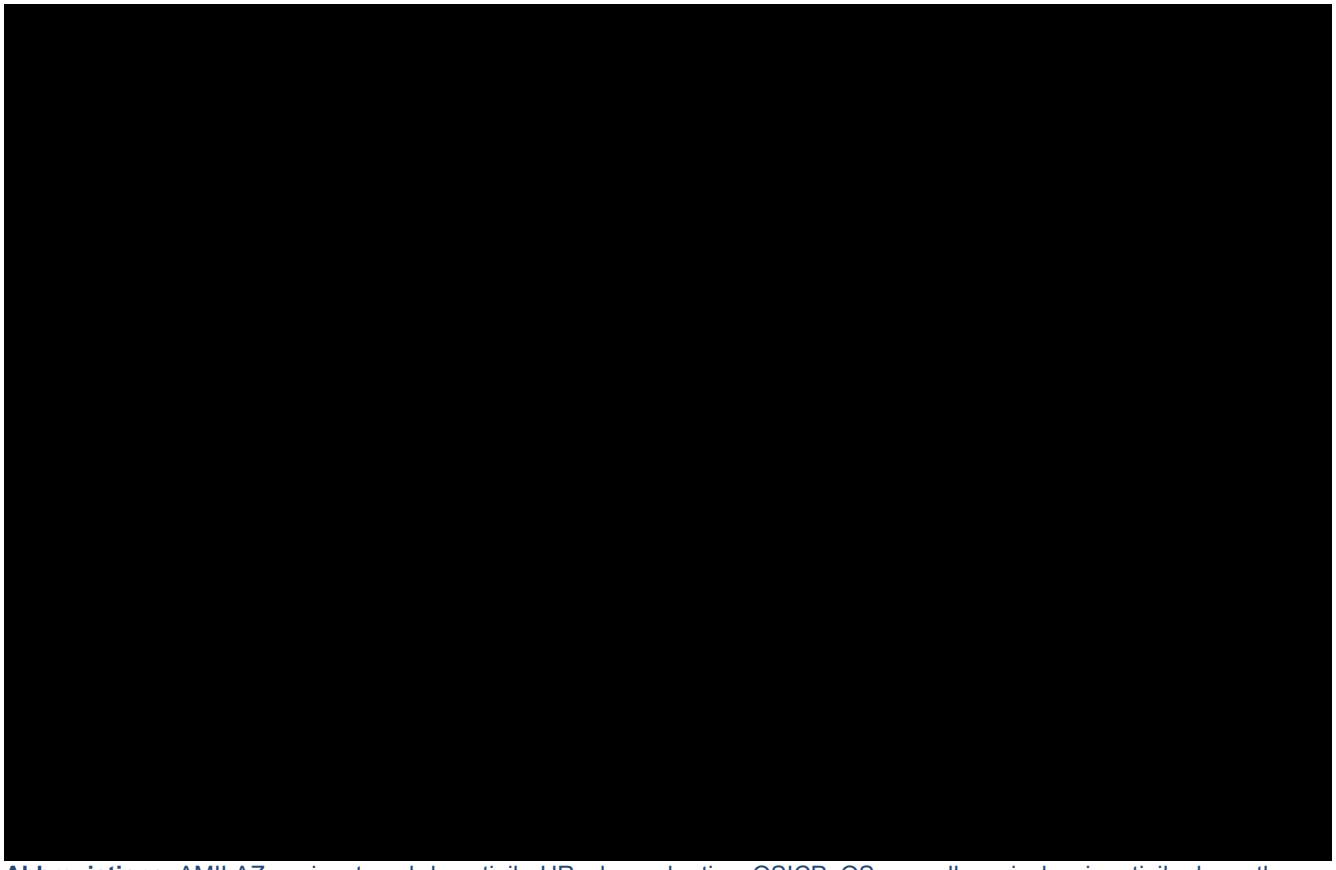
Figure 11: Osimertinib-chemotherapy versus amivantamab-lazertinib, time-dependent relative treatment effect on OS with FP-based Cox models

Abbreviations: amilaz: amivantamab-lazertinib; FP: fractional polynomial; F2OSICP: FLAURA2 osimertinib-chemotherapy; HR: hazard ratio; M1AMILAZ: MARIPOSA amivantamab-lazertinib; NMA: network meta-analysis; osicp: osimertinib-chemotherapy

Appendix 2.2 includes additional information on the 164 Cox FP models. For many of the Cox FPs, treatment effect estimates near time 0 went to extreme values, a behaviour referred to as 'end effects' in the Royston et. al. study that introduced FPs.[51] Extreme behaviour near 0 was considered as an exclusion criterion, as it led to survival estimates for osimertinib-chemotherapy that dropped very sharply in the first cycle. The sharp

drops in survival estimates for many of the curves are due to extreme HR estimates near time 0. Even FPs with comparable goodness-of-fit, when extrapolated beyond the observed period, lead to very different survival estimates for osimertinib-chemotherapy (Figure 12).

Figure 12: Osimertinib-chemotherapy OS extrapolations obtained from applying 164 Cox FP models on amivantamab-lazertinib Weibull and osimertinib-chemotherapy base case extrapolation (dark orange)



Abbreviations: AMILAZ: amivantamab-lazertinib; HRs: hazard ratios; OSICP: OS: overall survival; osimertinib-chemotherapy.

The results from the FP models demonstrate that while goodness-of-fit criteria can inform model selection, the clinical plausibility of extrapolations is paramount for health-economic analyses and must be considered when modelling long-term outcomes. Prior NICE appraisals demonstrate that there are significant limitations associated with the use of FP models, including high uncertainty, making other more conventional models preferred for decision making. The FP models mostly lack clinical plausibility and visual fit to treatment effect estimate obtained through smoothing of Schoenfeld residuals, therefore, making them unsuitable for decision making in the context of this appraisal. Only the [redacted] polynomial with power [redacted] was considered close to the average of the clinically plausible range for the OS endpoint, this extrapolation is plotted against amivantamab-lazertinib (unadjusted Weibull) and osimertinib (unadjusted Weibull) in Figure 13, and was included as a scenario in the cost-effectiveness analysis. In the same scenario, first order polynomial with power 0 (i.e. log transformation of time) was considered most plausible among the Cox FP models for PFSINV. Extrapolations from this model are provided in Appendix 2.1. Further details about model selection for Cox FPs are provided in Appendix Section 2.2.

Figure *13*. OS Extrapolations for osimertinib-chemotherapy obtained by Cox FP {power [redacted]} relative treatment effect estimate applied to amivantamab-lazertinib

Abbreviations: FP: fractional polynomial; KM: Kaplan-Meier; OS: overall survival; CP: chemotherapy.

4.3 ITC based on parametric models

4.3.1 Parametric ITC

At the previous DGD response stage, the Company explained that a parametric ITC of amivantamab-lazertinib and osimertinib-chemotherapy could not be conducted because there was no common distribution type that would adequately model outcomes in all four arms of MARIPOSA and FLAURA2, especially in the case of OS and TTD.[37, 38] Weibull was accepted by the Committee as the most clinically plausible and statistically robust distribution choice to model OS for amivantamab-lazertinib and osimertinib monotherapy arms. However, none of the standard parametric distributions provided good fits to OS in FLAURA2, and this conclusion had been supported by the EAG in TA1060. In that TA, the EAG's preferred base case (accepted by the Committee) for modelling the OS was spline on odds scale with 2 knots for osimertinib-chemotherapy and a spline on normal scale with 1 knot for osimertinib monotherapy.

In order to thoroughly examine the Committee's request, the Company has investigated ways to relax the common distribution requirement of parametric ITC. This can be achieved to some extent by observing that several standard survival distributions (exponential, Weibull, gamma and log-normal) are special cases of the generalised gamma distribution. Parametrising them as generalised gamma (either by fitting generalised gamma models with certain parameter values fixed, or by deriving generalised gamma parameters from fitted exponential, Weibull, gamma or log-normal models) allows indirect comparisons across any combination of these distributions. However, this still places important restrictions on model selection, as Gompertz and log-logistic distributions cannot be converted to generalised gamma distribution. Comparisons including a mix of standard distributions and different spline models are also not possible within the parametric ITC framework.

With the requirement of common distribution type relaxed, parametric ITC is feasible for PFS despite different distribution types selected for amivantamab-lazertinib and osimertinib (gamma) and osimertinib-chemotherapy (Weibull), as both can be parametrised as generalised gamma distributions. On the other

hand, in the case of TTD, the Committee accepted different types of splines for amivantamab, lazertinib and osimertinib, whereas the preferred choices for osimertinib and chemotherapy components of osimertinib-chemotherapy were Gompertz and exponential distributions. While the Company disagrees with the selection of Gompertz distribution for the TTD of osimertinib in osimertinib-chemotherapy, the selection of splines for MARIPOSA interventions precludes conducting a parametric ITC for this outcome.

Re-evaluation of the feasibility of parametric ITC for OS in light of the updated data from FLAURA2 does not alter the conclusion from the previous DGD response regarding this outcome. The longer-term OS in FLAURA2 shows an even more complex evolution of hazard over time, which can be captured only with flexible distributions. Goodness of fit and plausibility of long-term extrapolations with different distributions for the OS of osimertinib-chemotherapy are discussed in detail in Section 5.2.1 (individual plots for each standard parametric distribution fit to OS and PFSINV of FLAURA2 osimertinib-chemotherapy and osimertinib arm KM are presented in Appendix 1.3). Therefore, it is not possible to conduct a parametric ITC for OS without selecting a distribution for osimertinib-chemotherapy with poor fit to the data and implausible long-term predictions.

Despite these conclusions, functionality that allows the use of parametric ITC (conditional on selecting an appropriate mix of distributions) has been included for all survival outcomes in the updated cost-effectiveness model, and two scenarios using the parametric ITC are presented (see Section 6.3). The reference treatment to which the treatment effect of osimertinib-chemotherapy is applied can be either amivantamab-lazertinib or osimertinib; if the latter is used, treatment effect of osimertinib-chemotherapy versus osimertinib estimated from FLAURA2 data is used. The choice of reference has no impact on the resulting distribution of osimertinib-chemotherapy but selecting osimertinib as reference allows greater flexibility in selection of amivantamab-lazertinib distribution.

Long-term outcomes with osimertinib-chemotherapy derived using treatment effects from parametric ITC applied to selected distributions of amivantamab-lazertinib and osimertinib are shown in Table 16, Table 17, Table 18 & Table 19.

Figure 14: Long-term OS projections of osimertinib-chemotherapy from parametric ITC based on Weibull distributions for amivantamab-lazertinib, osimertinib (MARIPOSA) and osimertinib (FLAURA2)

Abbreviations: ITC: indirect treatment comparison; OS: overall survival.

Figure 15: Long-term PFS projections of osimertinib-chemotherapy from parametric ITC based on gamma distributions for amivantamab-lazertinib and osimertinib (MARIPOSA), and Weibull distribution for osimertinib (FLAURA2)

Abbreviations: ITC: indirect treatment comparison; PFS: progression-free survival.

Figure 16: Long-term TTD projections of osimertinib in osimertinib-chemotherapy from parametric ITC based on Weibull distributions for osimertinib (MARIPOSA) and osimertinib (FLAURA2)

Abbreviations: ITC: indirect treatment comparison; TTD: time to discontinuation.

Figure 17: Long-term TTD projections of chemotherapy in osimertinib-chemotherapy from parametric ITC based on Weibull distributions for osimertinib (MARIPOSA) and osimertinib (FLAURA2)

Abbreviations: ITC: indirect treatment comparison; TTD: time to discontinuation.

4.3.2 Fractional polynomial ITC using parametric models

In addition to parametric ITC that relies on standard parametric models, FP models were also used to model the relative treatment effect over time.

FPs model the log hazard as a flexible function of the form[52]:

$$\log(h_{trt,t}) = \mu_0 + \mu_1 \cdot t^{p1}$$

Where μ_0 and μ_1 are model parameters to be estimated from the data, P1 is the power term and was selected from the following set: $\{-2, -1, -0.5, 0, 0.5, 1, 2, 3\}$ (0 denotes log transformation of time), $h_{trt,t}$ is the time-dependent hazard of the modelled treatment arm. In addition to these 8 1st order polynomials, 2nd order polynomials of the following form were also tested:

$$\log(h_{trt,t}) = \mu_{trt,0} + \mu_{trt,1} \cdot t^{p1} + \mu_{trt,2} \cdot t^{p2}$$

Where same powers are used (i.e. p1=p2), the second term is multiplied by log transformation of time, and the FP takes the following form:

$$\log(h_{trt,t}) = \mu_{trt,0} + \mu_{trt,1} \cdot t^{p1} + \mu_{trt,2} \cdot t^{p2} \cdot \log(t)$$

There are 36 different 2nd order FPs (2 select from 8 with replacement). Together with the 8 first order FPs, 44 FPs were tested. For both OS and PFSINV endpoints, for each of the 44 FPs, the FP was first fit to the four treatment arms (MARIPOSA amivantamab + lazertinib, MARIPOSA osimertinib, FLAURA2 osimertinib + chemotherapy, and FLAURA2 osimertinib) separately. The mean FP parameters that model the time-dependent treatment effect in FLAURA2 and MARIPOSA were then estimated as:

$$\begin{pmatrix} d_{F2osicp\ vs\ osi,0} \\ d_{F2osicp\ vs\ osi,1} \end{pmatrix} = \begin{pmatrix} \mu_{F2osicp,0} \\ \mu_{F2osicp,1} \end{pmatrix} - \begin{pmatrix} \mu_{F2osi,0} \\ \mu_{F2osi\ 1} \end{pmatrix}$$

$$\begin{pmatrix} d_{Mamilaz\ vs\ osi,0} \\ d_{Mamilaz\ vs\ osi,1} \end{pmatrix} = \begin{pmatrix} \mu_{Mamilaz,0} \\ \mu_{Mamilaz,1} \end{pmatrix} - \begin{pmatrix} \mu_{Mosi,0} \\ \mu_{Mosi\ 1} \end{pmatrix}$$

Mean parameters for time-dependent relative treatment effect of osimertinib + chemotherapy vs. amivantamab + lazertinib was then estimated as:

$$\begin{pmatrix} d_{osicp\ vs\ amilaz,0} \\ d_{osicp\ vs\ amilaz,1} \end{pmatrix} = \begin{pmatrix} d_{F2osicp\ vs.osi,0} \\ d_{F2osicp\ vs.osi\ ,1} \end{pmatrix} - \begin{pmatrix} d_{Mamilaz\ vs.osi,0} \\ d_{Mamilaz\ vs.osi\ 1} \end{pmatrix}$$

Covariance matrix of the relative treatment effect was estimated as the element-wise sum of the covariance matrices from the parametric FP models estimated from the FLAURA2 and MARIPOSA data.

Time-dependent relative treatment effect was then estimated as:

$$\log\left(\frac{h_{osicp,t}}{h_{amilaz,t}}\right) = d_{osicpvs.amilaz,0} + d_{osicpvs.amilaz,1} \cdot t^{p1}$$

This time-dependent relative-treatment effect was then applied to the per-cycle hazard of amivantamab-lazertinib OS (unadjusted, Weibull) to model the osimertinib-chemotherapy OS. PFSINV relative treatment

effect estimates were applied to the per-cycle hazard of amivantamab-lazertinib PFSINV (unadjusted, gamma) to model the osimertinib-chemotherapy PFSINV.

Most parametric FPs estimated extremely high or low hazards close to time 0, many of them implied osimertinib-chemotherapy OS and PFSINV curves falling below that of osimertinib monotherapy, or had extremely rapidly increasing hazards, or estimated extreme hazard ratios either near time 0 or during extrapolation period. None of the remaining FPs provided adequate fit to all four treatment arms, therefore these were not included in the health economic models. Appendix 2.2. includes detailed description of parametric FP results, and plots providing further details on each parametric FP are provided in supplementary materials.

4.4 Population adjustment

4.4.1 Matching-adjusted indirect comparison

The Committee suggested that ITC with population adjustment, such as an anchored MAIC, could be explored. MAIC is not an alternative to the previously described ITC methods, but rather an additional step that could be combined with any of them. Therefore, it does not remove any of the challenges described in previous sections. Its use would be warranted if imbalance in treatment effect modifiers (TEMs) between MARIPOSA and FLAURA2 populations was suspected. Given the similarity of these populations, noted previously, this seems unlikely, and the EAG did not put forward any potential TEMs in its criticism of the Company's approach in the response to the initial DGD.

Nevertheless, MAIC was explored by matching MARIPOSA patients to the FLAURA2 population on the following baseline characteristics: ECOG, exon 19 deletion, L858 mutation, liver metastases, bone and locomotor system metastases, age, race, sex, smoking status and histologic tumour type. After matching on all characteristics, 841 patients remained in the MARIPOSA cohort (amivantamab-lazertinib arm: 418; osimertinib arm: 423), with an effective sample size of 693. Comparison of baseline characteristics before and after matching and in FLAURA2 is presented in

Table ***10***. The baseline characteristics in the two trials were similar even before matching, and thus the matching was successful. Figure 18 and Figure 19 present Kaplan-Meier estimates of OS and PFS (INV), respectively, before and after matching. As both observed trial populations were similar (illustrated as well by the high effective sample size after matching compared to the original sample), matching had no impact on the HR, and only a minor impact on the CI, effectively leading to no impact on the treatment effect in MARIPOSA, with OS HR of [redacted] after matching, compared to 0.75 (95% CI: 0.61 to 0.92) before matching. Similar lack of impact of matching on HR was observed for PFS (INV), with the HR after matching of [redacted] compared to [redacted] after matching. This suggests lack of treatment effect modification by differences in measured baseline characteristics. Therefore, anchored MAIC was not considered further as a scenario.

Table 10. Baseline characteristics before and after matching MARIPOSA patients to the FLAURA2 population.

Baseline characteristic	FLAURA2	MARIPOSA, before matching	MARIPOSA, after matching
ECOG 0 (%)	37	34	[redacted]
ECOG 1–2 (%)	63	66	[redacted]
Exon 19 deletion (%)	62	60	[redacted]

L858 mutation (%)	38	40	[redacted]
Liver metastases (%)	19	16	[redacted]
Bone and locomotor system metastases (%)	49	46	[redacted]
Age, median	61.5	63	[redacted]
Race: Asian (%)	63	59	[redacted]
Race: white (%)	28	38	[redacted]
Race: other (%)	9	3	[redacted]
Sex: male (%)	38	39	[redacted]
Current or former smoker (%)	33	31	[redacted]
Histologic type: adenocarcinoma (%)	99	97	[redacted]
Histologic type: other (%)	1	3	[redacted]

Abbreviations: ECOG: Eastern Cooperative Oncology Group.

Figure 18. Amivantamab-lazertinib and osimertinib OS before and after matching to FLAURA2 population

Abbreviations: OS: overall survival.

Figure 19. Amivantamab-lazertinib and osimertinib PFS before and after matching to FLAURA2 population

Abbreviations: PFS: overall survival.

4.4.2 Multi-level network meta-regression (ML-NMR)

Multilevel network meta-regression (ML-NMR) was not explored as only expected to have advantages over MAIC in case of a broader network, but not in the current context of 2 trials.

4.5 Selected base case approach to comparative efficacy

Considering that the ITC approaches discussed so far had several limitations or resulted in implausible long-term projections of survival with osimertinib-chemotherapy, and the Committee did not consider a naive comparison to be acceptable, an alternative method based on unanchored comparison with population adjustment was selected for the base case.

In this approach, OS, PFS and TTD of amivantamab-lazertinib and osimertinib were modelled by fitting standard parametric and spline-based distributions to MARIPOSA patients weighted with MAIC-derived weights (i.e., matched to the FLAURA2 population), while osimertinib-chemotherapy was modelled with distributions fitted individually to the FLAURA2 data without any adjustment. Therefore, all three interventions were modelled in the FLAURA2 population, allowing a fair comparison.

This approach shares assumptions with unanchored MAIC, namely that the matching can compensate for potential differences in both prognostic factors and TEMs between both trials. Given the high similarity between both observed trial populations, this assumption was deemed more appropriate than accepting lack of fit to data, induced by the anchored approaches described before, which lead to biased treatment effect estimates and implausible extrapolations.

In this exploration, an assessment was required for the appropriate curve choices for the OS curve of osimertinib-chemotherapy considering the final analysis results. This is detailed further in Section 5.2. As applying the MAIC weights to the MARIPOSA produces new survival data, survival distributions fitted to the weighted cohort are also presented in Figure 20 and Figure 21.

Figure 20. Parametric Fits to MAIC-weighted amivantamab-lazertinib cohort OS

Abbreviations: KM: Kaplan-Meier; MAIC: matching-adjusted indirect comparison; OS: overall survival.

Figure 20. Parametric Fits to MAIC-weighted osimertinib cohort OS

Abbreviations: KM: Kaplan-Meier; MAIC: matching-adjusted indirect comparison; OS: overall survival.

To facilitate discussion on the impact of population adjustments, alternative scenarios have been conducted using both the naïve comparison (EAG preference) and the population adjustment based on HRs of osimertinib in MARIPOSA vs. osimertinib in FLAURA2 applied to the osimertinib-chemotherapy outcomes (company's preference) as presented in the DGD and during the 2nd ACM. Additionally, a scenario has been incorporated to limit the population adjustment based on HRs to the observed period per respective endpoint.

These scenarios do not assume the MAIC weighting as described above. The results from the base case and the alternative scenarios consistently follow a similar trend, demonstrating significant similarities, which is an expected outcome given the comparable nature of the trials. This collectively suggests that any form of population adjustment exerts only a minimal influence on the overall results.

4.5.1 Conclusion

Overall, the results of the additional analyses conducted by the Company to determine the most clinically plausible approach to formally assessing comparative effectiveness of amivantamab-lazertinib and osimertinib-chemotherapy are as follows:

- Piecewise Cox models: results show that the hazard ratios fluctuate markedly across intervals and results differ substantially depending on the time periods chosen, highlighting sensitivity to cut-points with intervals sometimes based on few events. Consequently, estimates are unstable with wide confidence intervals. Further, the long-term survival projections for osimertinib-chemotherapy fall in the lower band of what is considered clinically plausible illustrating that this method is not fit for purpose. A scenario has been provided to demonstrate this impact.

- Fractional polynomial models (Cox and parametric models): aligned with findings from prior NICE appraisals, the FP models do not capture the complexity of the observed data and as a result lack clinical plausibility and visual fit, therefore, making them unsuitable for decision making in the context of this appraisal. Practically no FP aligned with clinical expectations or had a good visual fit; however, a scenario has been provided to illustrate the potential impact.

- Parametric ITCs: were also found to be unsuitable as the longer-term OS in FLAURA2 shows an even more complex evolution of hazard over time, which can be captured only with flexible distributions. Goodness of fit and plausibility of long-term extrapolations with different distributions for the OS of osimertinib-chemotherapy suggest that it is not possible to conduct a parametric ITC for OS without selecting a distribution for osimertinib-chemotherapy with poor fit to the data and implausible long-term predictions.

Based on exploration of the methods presented above, it is concluded that any attempt to perform a different form of ITC or NMA in this context is a purely academic exercise that would only introduce additional uncertainty and potential bias. Therefore, having thoroughly assessed all approaches requested by the Committee, the Company have employed an unanchored MAIC in the base case. This approach to ITC provides clinically plausible results with greater certainty than the other methods explored and is therefore more appropriate for clinical decision making in line with earlier conclusions from prior appraisals.[34-36, 40]

4.6 Safety ITC assessment

Final AE data from the MARIPOSA trial (DCO: 13th May 2024) are presented in Table 7 of the document submitted in response to clarification questions on the original Company submission. Final safety data from the FLAURA2 trial (DCO: 12th June 2025) are presented in Table 4 in Section 2.2 of the current document.

As per the Committee's request, the Company explored an adjusted comparison of the AEs of amivantamab-lazertinib compared with osimertinib-chemotherapy and osimertinib monotherapy. The safety profiles of amivantamab-lazertinib versus osimertinib-chemotherapy are different, with different types of adverse events being prevalent for each treatment regimen (Figure 21 and Figure 22). As a result of the difference in the leading MOA for toxicities between the two treatment arms, a comparison of specific events becomes biased

in favour of one of the two regimens. Therefore, a broader comparison on the overall incidence and impact of toxicity was conducted.

Figure 21: Risk difference for AEs of any grade in MARIPOSA versus FLAURA2*

Footnote: *Based on MARIPOSA FA and FLAURA2 FA
Abbreviations: AE: adverse event; ALT: alanine transaminase.

Figure 22: Risk difference for Grade ≥3 AEs in MARIPOSA versus FLAURA2*

Footnote: *Based on MARIPOSA FA and FLAURA2 FA
Abbreviations: AE: adverse event; ALT: alanine transaminase.

A summary of the relative proportion of Grade ≥3 AEs and SAEs in osimertinib-chemotherapy compared to amivantamab-lazertinib is presented in Table 11. Overall, osimertinib-chemotherapy has a higher relative incidence of Grade ≥3 AEs and SAEs compared to amivantamab-lazertinib.

Table 11: Relative proportion of Grade ≥3 AEs and SAEs in the MARIPOSA and FLAURA2 trials

	MARIPOSA	FLAURA2

	AMI-LAZ	OSI	OSI-CT	OSI
Median follow-up, months	38		51	
Grade ≥3 AEs, %	80	52	70	34
% difference, intervention versus comparator arm	+54		+106	
SAEs, %	55	41	46	27
% difference, intervention versus comparator arm	+34		+70	

Abbreviations: AE: adverse event; AMI-LAZ: amivantamab-lazertinib; OSI: osimertinib; OSI-CT: osimertinib-chemotherapy; SAE: serious adverse event.

Importantly, the incidence of AEs over time was comparable across both trials, with most events taking place in the first 4 months of treatment.[15,21] This is indicative of AEs for both treatments being time-dependent rather than combination dependent.

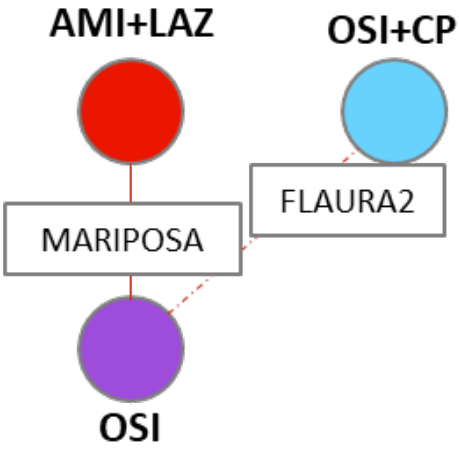
Further, the two osimertinib monotherapy arms across both trials have different rates of AEs despite being the same regimen in the same population. This implies potential differences between the trials in the way in which AEs were measured, which could introduce bias against amivantamab-lazertinib

4.6.1 Comparative safety using a Bayesian NMA

In order to compare the safety profile of amivantamab-lazertinib and osimertinib-chemotherapy, a Bayesian NMA was set up. The application of a comparative Bayesian NMA for safety was deemed appropriate, given that it involves the assessment of a binary endpoint at a comparable time point. Conversely, for efficacy, this approach was considered unsuitable due to the presence of time-dependent hazard ratios.

The network diagram and data inputs informing this NMA are provided in Figure 23 and Table 12. Since the proportion of patients reporting any AEs was close to 100% across both trial arms, a comparison was not deemed to be informative. Results will instead focus on Grade ≥3 AEs and SAEs.

Figure 23: Bayesian NMA network diagram



Abbreviations: AMI+LAZ: amivantamab-lazertinib; NMA: network meta-analysis; OSI: osimertinib; OSI+CP: osimertinib-chemotherapy

Table 12: Data input availability for Bayesian safety NMA

	MARIPOSA (PA, IA2, FA DC)	FLAURA2 (PA, FA DC)
Any AEs*	✓	✓
Grade 3+	✓	✓
SAEs	✓	✓

*Any AEs is close to 100% for both treatments and therefore a comparison is not very informative. Results will focus on grade 3+ and SAEs.
Abbreviations: AE: adverse events; DC: data cut; FA: final analysis; IA2: second interim analysis; NMA: network meta-analysis; PA: primary analysis; SAE: serious adverse event

Frequentist ITCs are often underpowered and therefore a Bayesian analysis was considered to provide clearer probability statements, which provide more tangible results such as, 'Treatment A is better than Treatment B with a probability of 90%'. For this reason, the Bayesian method is considered to be the most interpretable approach for assessing the comparative benefit of and most useful for decision making in HTA, evidence by its alignment aligns with the ISPOR guidelines.[39]

Results of the Bayesian methodology are presented below: Hazard Plot Matrix diagrams (Figure 24) and the forest plots comparing Grade 3+ safety across MARIPOSA and FLAURA2 (Figure 25 and Figure 26). The results clearly indicate that osimertinib-chemotherapy has a worse safety profile among combination treatments, with a trend in favour of amivantamab-lazertinib for Grade ≥3 AEs and 'favourable' results for amivantamab-lazertinib in terms of SAEs.

Figure 24: Hazard plot matrix diagrams for Bayesian safety NMA

Abbreviations: AE: adverse event; AMI+LAZ: amivantamab-lazertinib; DC: data cut; FE: fixed effect; NMA: network meta analysis; OSI: osimertinib; OSI-CP: osimertinib-chemotherapy; SAE: serious adverse event.

Figure 25: Forest plot comparing SAEs across MARIPOSA and FLAURA2 from the Bayesian NMA

Abbreviations: AMI+LAZ: amivantamab-lazertinib; CrI: credible interval; DC: data cut; FE: fixed effects; NMA: network meta analysis; OR: odds ratio; OSI: osimertinib; OSI+CP: osimertinib-chemotherapy; SAE: serious adverse event; SUCRA: surface under the cumulative ranking curve

Figure 26: Forest plot comparing Grade 3+ AEs across MARIPOSA and FLAURA2 from the Bayesian NMA

Abbreviations: AE: adverse event; AMI+LAZ: amivantamab-lazertinib; CrI: credible interval; DC: data cut; FE: fixed effects; NMA: network meta analysis; OR: odds ratio; OSI: osimertinib; OSI+CP: osimertinib-chemotherapy; SUCRA: surface under the cumulative ranking curve.

4.6.2 Comparative safety using an anchored MAIC

An anchored MAIC was applied to the Bayesian method for completeness. From comparing the matched baseline characteristics across the patient populations in MARIPOSA and FLAURA2, it was clear that the populations were relatively well balanced, except for a minor imbalance in race. An initial assessment of the matched baseline characteristics suggests that the impact of matching on results may be negligible, which was also concluded when this matching was done for OS.

A summary of the MAIC results for Grade ≥3 AEs and SAEs is presented in Figure 27 and Figure 28 below which represent comparative results by incrementally including additional covariates from top to bottom. As expected, the impact on the conclusions drawn from the ITC, after having matched baseline characteristics, is minimal and moving in different directions for Grade 3+ AEs and SAEs, as the results suggest a trend in favour of amivantamab-lazertinib for SAEs and favourable results for Grade ≥3 AEs.

Figure 27: MAIC results for Grade ≥3 AEs

Abbreviations: AE: adverse event; AMI+LAZ: amivantamab-lazertinib; OR: odds ratio; OSI: osimertinib; OSI+CP: osimertinib-chemotherapy.

Figure 28: MAIC results for SAEs

Abbreviations: AE: adverse event; AMI+LAZ: amivantamab-lazertinib; OR: odds ratio; OSI: osimertinib; OSI+CP: osimertinib-chemotherapy.

4.6.3 Impact on progression-free (PF) utilities

Based on the above analysis, the Company conclude that the use of treatment-specific utilities could be considered appropriate in this context. However, while the Company agree that the PF-utility for osimertinib monotherapy could be higher than in the combination treatment arms, the PF utility for amivantamab-lazertinib and osimertinib-chemotherapy should be the same or higher for amivantamab-lazertinib. The analysis unequivocally demonstrates that the safety ITC favours amivantamab-lazertinib over osimertinib-chemotherapy, which may translate into higher utility values in the PF state. This is supported by the suggestion of higher utilities for osimertinib monotherapy within the PF state due to less side effects.

This is especially true given that any treatment-specific differences in utilities are due to AEs, were already incorporated into the model separately. This is demonstrated by the observed quality-adjusted life years (QALY) decrements from AEs within the model, which are the greatest for amivantamab-lazertinib ( ), followed by osimertinib-chemotherapy ( ) and then osimertinib monotherapy ( ).

The outcomes and impact of the safety ITC are reflected in the updated base case and scenario (see Sections 6.1 and 6.3).

FLAURA2 may underestimate the incidence of Grade ≥3 AEs and serious AEs (SAE) associated with osimertinib monotherapy

Besides the results from the Safety ITC, as noted by the EAG in response to the initial draft guidance response, the Company agree that the incidences of Grade ≥3 AEs and SAEs are lower in the osimertinib monotherapy arm of the FLAURA2 trial (Grade ≥3 AEs: 27%; SAEs: 19%) than in the osimertinib monotherapy arm of the MARIPOSA trial (Grade ≥3 AEs: 52%; SAEs: 41%), which is in turn reflected in a lower rate of discontinuations in this arm of the FLAURA2 trial than in the MARIPOSA trial (11% versus 16%, respectively).[40] The EAG suggested that this could be attributed to the population in the MARIPOSA trial being more prone to having a Grade ≥3 AEs or SAEs reported, but it may instead be the case that the

FLAURA2 trial is underestimating the incidence of Grade ≥3 AEs and SAEs.[40] This is supported by the rate of Grade ≥3 AEs observed in the osimertinib monotherapy arm of the FLAURA trial (42%) aligning much more closely with the data from the MARIPOSA trial than with the data from the FLAURA2 trial.[17] As a result, it is suggested that the FLAURA2 trial overestimates the PF HSUV for osimertinib monotherapy by underestimating AEs.

In the case that the PF HSUV derived from the FLAURA2 trial is overestimated for osimertinib monotherapy, then the pooled osimertinib monotherapy and osimertinib-chemotherapy PF HSUV from FLAURA2 (0.794) is consequently likely to be artificially inflated. Despite this, it is nevertheless lower than the pooled osimertinib monotherapy and amivantamab-lazertinib PF HSUV derived from the MARIPOSA trial [redacted] Given osimertinib monotherapy is the common contributor to both pooled values, this indicates that osimertinib-chemotherapy has a lower treatment-specific PF HSUV than amivantamab-lazertinib, and that this difference may be even larger than a comparison of the pooled values from FLAURA2 and MARIPOSA suggests. Therefore, it is suggested that the application of equal PF HSUVs for osimertinib-chemotherapy and amivantamab-lazertinib in the Company updated model represents a conservative approach, given the data suggest that osimertinib-chemotherapy may have a lower PF HSUV than amivantamab-lazertinib.

This is additional support that, the PF utility value for osimertinib-chemotherapy and amivantamab-lazertinib could be considered as different and in favour of amivantamab-lazertinib, especially in light the safety ITC.

SC amivantamab is associated with fewer AEs than IV amivantamab

Efficacy data from the PALOMA trials demonstrates that SC amivantamab is associated with fewer AEs than IV administration, as presented in the initial DGD response.[23] In the PALOMA-3 trial, the most frequently reported treatment-emergent adverse events (TEAE) (>5% of participants in any arm) were comparable between administration routes, with the notable exception of IRRs which were substantially lower in incidence in the SC amivantamab-lazertinib arm (13.%) than in the IV amivantamab-lazertinib arm (66%).[23] Despite similar rates of anticoagulation use (80% for SC amivantamab-lazertinib and 81% for IV amivantamab-lazertinib), the incidence of VTE was lower in the SC amivantamab-lazertinib arm (9%) compared with the IV amivantamab-lazertinib arm (14%).[23]

TEAEs associated with the on-target activity of amivantamab against the EGFR and MET pathways were comparable between the SC and IV amivantamab-lazertinib treatment arms (Table 13). While the all-grade incidence of hypoalbuminemia was notably higher in the SC amivantamab-lazertinib arm of PALOMA-3 in comparison to IV amivantamab-lazertinib, these events were mostly low grade, and did not result in treatment discontinuation. The incidence of Grade ≥3 hypoalbuminemia between the two treatment arms was similar (2% versus 3%, respectively).[23] The differences in hypoalbuminemia, in the absence of difference in peripheral oedema rates, is unlikely to have a large impact on utility values.

Table 13: Summary of AEs observed in PALOMA-3 (3rd January 2024 DCO, SAS)

AE (%)	All grades		Grade ≥3	
	SC amivantamab-lazertinib (N=206)	IV amivantamab-lazertinib (N=210)	SC amivantamab-lazertinib (N=206)	IV amivantamab-lazertinib (N=210)
Related to the on-target activity of amivantamab against the EGFR pathway				
Rash	46	43	4	4
Dermatitis acneiform	31	33	9	6
Paronychia	54	51	4	1

Stomatitis	28	33	0.5	2
Diarrhoea	21	19	1	1
Related to the on-target activity of amivantamab against the MET pathway				
Hypoalbuminemia	[redacted]	[redacted]	[redacted]	[redacted]
Peripheral oedema	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE: adverse event; DCO: data cut off; NA: not applicable; SAS: safety analysis set
Source: Leighl *et al.* (2024).[23]

In addition to the TEAEs described above, an incidence difference of ≥5% was observed between the SC amivantamab-lazertinib arm and the IV amivantamab-lazertinib arm for myalgia (16% versus 6%), weight decreased ([redacted]% versus [redacted]%), and hypotension ([redacted]% versus [redacted]%).[23, 41] Although there was a substantial difference in the rates of myalgia and weight loss, the overall incidence remained below [redacted] of patients.[41] In conclusion, the treatment-related adverse event (TRAE) profile of SC amivantamab-lazertinib is largely comparable to IV amivantamab-lazertinib, except for a reduction in rates of IRRs and VTE with the SC formulation where the profile is more favourable for SC administration.

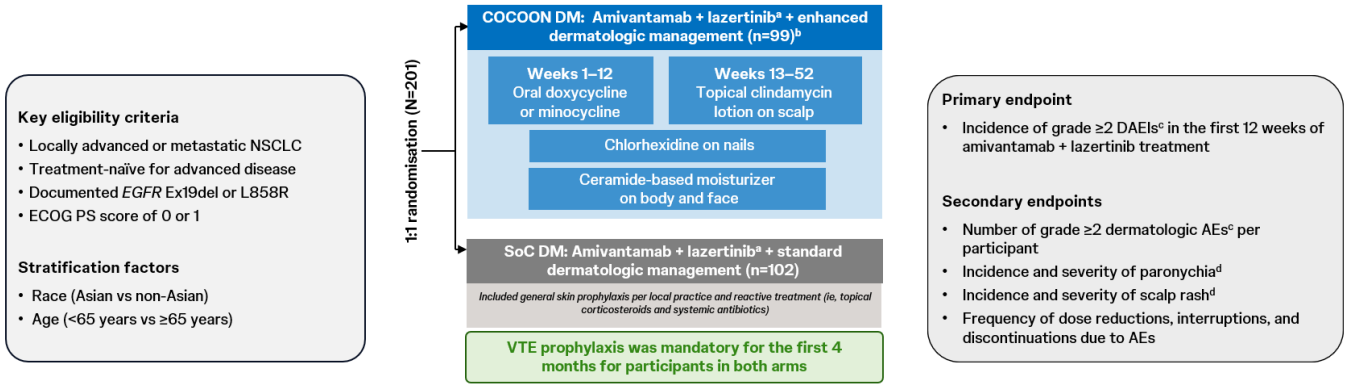
Furthermore, the use of SC amivantamab would result in significantly less time spent by a patient in a clinical setting, as compared with osimertinib-chemotherapy which is administered intravenously.[23] In the context of the tolerability profile of both SC amivantamab-lazertinib and IV amivantamab-lazertinib, the short administration time for SC amivantamab-lazertinib as compared with IV amivantamab-lazertinib, and the patient preference for SC administration over IV administration, it is expected that the PF HSUV for SC amivantamab in combination with oral lazertinib would be higher than for IV chemotherapy in combination with oral osimertinib. As such, applying the same treatment-specific HSUVs for the PF health state across amivantamab-lazertinib and osimertinib-chemotherapy treatment arms is considered conservative.

Treatment with enhanced dermatologic management significantly reduces the burden of dermatologic AEs on patients treated with amivantamab and lazertinib, reducing the apparent differences in AE disutility between amivantamab-lazertinib and osimertinib monotherapy

As previously discussed in Section B.2.11 of the original Company submission, the COCOON trial (NCT06120140) was designed to evaluate the impact of enhanced dermatologic management (COCOON DM) versus standard dermatologic management (SoC DM) on the incidence of dermatological AEs among patients with cEGFRm advanced or metastatic NSCLC receiving first line IV amivantamab in combination with lazertinib i.e., the MARIPOSA population.[42] COCOON is a Phase 2, open-label, multicentre trial and patients were randomised (1:1) to COCOON DM (N=99) or SoC DM (N=100).[43]

All patients, regardless of arm, received general skincare recommendations, including avoiding exposure to sunlight, wearing protective clothing (including a hat and sunglasses), using broad spectrum sunscreen (SPF>30), and avoiding alcohol-based topical agents, and could receive reactive treatment upon occurrence of skin toxicity per local practice.[43] Patients in the COCOON DM arm received prophylactic antibiotics (twice-daily oral doxycycline or minocycline 100 mg during weeks 1–12; once-daily topical clindamycin 1% lotion on the scalp before bedtime starting at week 13 and onward), once-daily chlorhexidine 4% to wash the fingernails and toenails, and a ceramide-based moisturiser on the body and face at least once daily for skin moisturisation for the duration of the study. Patients in the SoC DM arm were managed according to local clinical practice, and there was no standard preventive regimen. The COCOON study design is presented in Figure 29 below.[43]

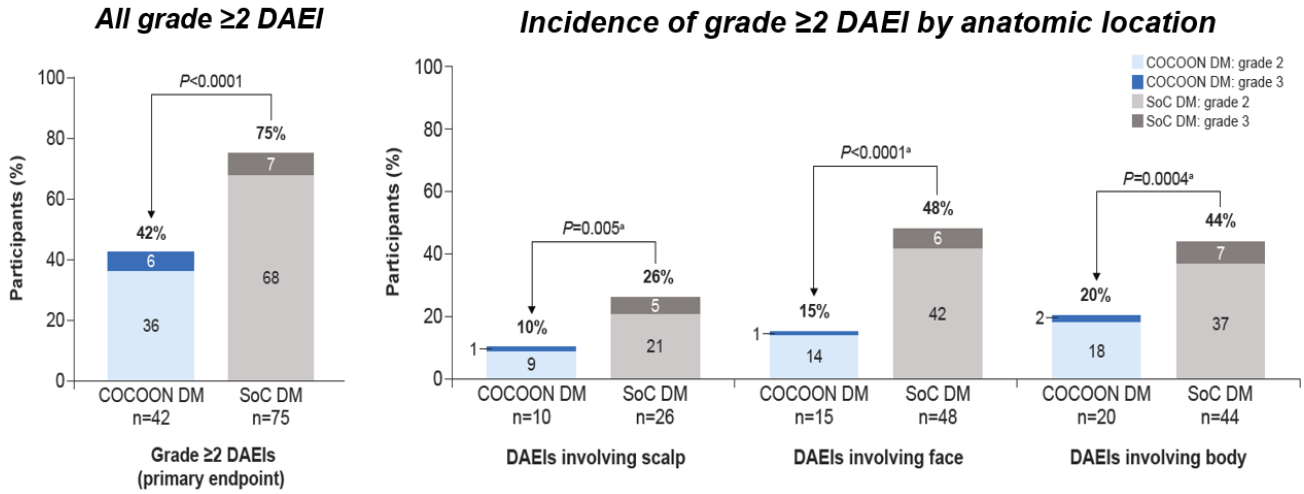
Figure 29: COCOON study design



Footnotes: [a]IV amivantamab was administered at 1050 mg (1400 mg if ≥80 kg) once weekly for 4 weeks and every 2 weeks thereafter; lazertinib was orally administered daily at 240 mg. [b]Prophylactic antibiotics: oral doxycycline or minocycline 100 mg BID; topical clindamycin lotion 1% on scalp QD before bedtime. Paronychia prophylaxis: chlorhexidine 4% on the fingernails and toenails QD. Skin moisturization: La Roche Posay Lipikar AP+M moisturiser on the body and face at least QD. [c]DAEIs include rash, dermatitis acneiform, pruritus, skin fissures, acne, folliculitis, erythema, eczema, maculopapular rash, skin exfoliation, skin lesion, skin irritation, dermatitis, rash erythematous, rash macular, rash papular, rash pruritic, rash pustular, dermatitis contact, dermatitis exfoliative generalised, drug eruption, dyshidrotic eczema, eczema asteatotic, and paronychia. [d]AE severity per NCI CTCAE v5.0.
Abbreviations: AE: adverse event; BID: twice daily; CTCAE: Common Terminology Criteria for Adverse Events; DAEI: dermatologic adverse event of interest; DM: dermatologic management; ECOG: European Cooperative Oncology Group; EGFR: epidermal growth factor receptor; Ex19del: exon 19 deletion; IV: intravenous; L858R: exon 21 L858R substitution; NCI: National Cancer Institute; NSCLC: non-small cell lung cancer; QD: once a day; SoC: standard of care; VTE: venous thromboembolism.
Source: Adapted from Cho *et al.* (2025)[44]

The primary endpoint in COCOON, incidence of Grade 2 or higher dermatologic AEs of interest (DAEI), was evaluated at the pre-planned interim analysis after 12 weeks of study follow-up. Results for the primary endpoint from the pre-planned interim analysis of COCOON are presented in Figure 30. Notably, during the first 12 weeks of treatment with amivantamab-lazertinib, the incidence of Grade 2 or higher DAEI was significantly lower for patients treated with COCOON DM compared to those treated with SoC DM (42% versus 75% respectively; odds ratio [OR]: 0.24 [95% CI, 0.13–0.45]; P<0.0001).[43] A significant reduction of Grade ≥2 skin DAEI (excluding paronychia) incidence was also observed, consistent by anatomical location (see Figure 30).[43]

Figure 30: Results from COCOON (pre-planned 12-week interim analysis)



Footnotes: [a]Nominal *P* value

Abbreviation: CI: confidence interval; DAEI: dermatologic adverse event of interest; DM: dermatologic management; OR: odds ratio; SoC: standard of care.
Source: Cho *et al.* (2025)[43]

These results are indicative of the utility of COCOON DM in mitigating the DAEI that are associated with treatment with amivantamab-lazertinib. The COCOON DM prophylactic regimen is uncomplicated and widely available in routine clinical practice. Discontinuations and modifications to the COCOON DM regimen were rare and the use of COCOON DM over SoC DM did not have any material impact on the antitumour effect (ORR) of amivantamab-lazertinib (82% [95% CI, 73–89] versus 75% [95% CI, 65–83], respectively, at a median follow-up of 7.1 months).[43, 44]

As reported in Section B.2.10.2 of the original Company submission, treatment with amivantamab-lazertinib was associated with a greater incidence of dermatologic AEs such as rash compared to treatment with osimertinib monotherapy in the MARIPOSA trial. The frequency and duration of dermatologic AEs observed in MARIPOSA were a key – and highly significant – component informing the pooled AE disutilities used in the Company model. The significant reduction in DAEI observed for patients treated with amivantamab-lazertinib and COCOON DM in the COCOON trial is indicative of an appropriate and effective prophylactic management approach to DAEI for patients who are seeking treating with amivantamab-lazertinib. Patients in UK clinical practice who would be treated with amivantamab-lazertinib with COCOON DM for cEGFRm advanced or metastatic NSCLC would therefore be expected to experience fewer DAEI compared to those in MARIPOSA, with incidence rates more similar to those observed in COCOON. It therefore follows that the contribution of DAEI to health state disutilities would decrease for patients treated with amivantamab-lazertinib in combination with COCOON DM as compared with the values calculated from the MARIPOSA trial.

Impact of chemotherapy exposure on osimertinib-chemotherapy PF HSUVs

The median duration of exposure to pemetrexed in the FLAURA2 trial was 8.3 months; however, many patients remained on pemetrexed treatment for longer (range: 0.7–58.9 months).[2] Data from FLAURA2 has shown an observed positive association between the duration of pemetrexed exposure and PFS.[2] Forty-nine (17.5%) and 83 (30%) patients received pemetrexed for 9–18 months and ≥18 months, respectively, meaning that overall, nearly half (49.3%) of patients in the osimertinib-chemotherapy arm of the FLAURA2 trial remained on maintenance pemetrexed beyond the reported 8.3 month median exposure. Additionally, among the 63 (22.5%) patients who received ≤3 months of chemotherapy in total, the median PFS (13.1 months [95% CI: 8.4, 22.2]) was significantly shorter than in the ITT analysis (25.5 months [95% CI: 24.7, not calculable]).[2] As such, the FLAURA2 data do not support that patients who stop pemetrexed early and remain on osimertinib monotherapy would achieve the same PFS as reported in the ITT population. Furthermore, there is no publicly available evidence to suggest a difference in quality-of-life for patients who discontinue chemotherapy in the osimertinib-chemotherapy arm, as this was not captured in TA1060, meaning that it is not possible to account for the discontinuation of chemotherapy in this treatment arm in the PF HSUV in an evidence-based manner.

Therefore, and in conclusion, the approach of applying a higher PF utility to osimertinib monotherapy and maintaining the same treatment-specific PF utilities for amivantamab-lazertinib and osimertinib-chemotherapy is appropriate, if conservative. This is reflected within the updated model and base case. However, considering the evidence from the safety ITC, alongside the greater clinical burden with IV chemotherapy, differences in safety events across the various trials, and the impact of COCOON and SQ not being reflected in the analysis, it is reasonable to assume that osimertinib-chemotherapy would have a lower utility value in the PF health state compared to amivantamab-lazertinib. Consequently, a scenario was included that is clinically plausible, reflecting a PF utility value for amivantamab-lazertinib that is higher than that of

osimertinib-chemotherapy but lower than that of osimertinib alone, to account for the various factors that have been described in Section 5.3.

5. Updated cost-effectiveness inputs

5.1 Background and context

The updates made to the CEM as compared with the model provided by the Company along with the first DGD response are are discussed below. The CEM previously submitted and considered by the Committee during the second Committee meeting is referred to as the 'previous model'. The updated model presented alongside this document is referred to as the 'updated model'.

At the Committee's request, the Company have provided an updated CEM, with survival inputs informed by various ITCs between amivantamab-lazertinib and osimertinib-chemotherapy. The model starting age has been updated to 68.5 years old, in line with the Committee's request to align with the Systemic Anti-Cancer Therapy (SACT) dataset at the first DGD stage; all other baseline characteristics within the updated model have been maintained as per the previous model. When considering all the analyses presented in Section 4, alongside the clinical expert opinion of the FLAURA2 final analysis, the unanchored MAIC is deemed to be most suitable for decision making. This has been selected for the Company base case, but scenarios utilising the other relevant methods of comparison are provided in Section 6.3. The incorporation of these indirect comparison results within the economic model means pairwise comparisons of amivantamab-lazertinib versus osimertinib monotherapy and amivantamab-lazertinib versus osimertinib-chemotherapy are now available. All updated input data informing the updated model are presented in Sections 5.2 – 5.4, and all updated economic results versus osimertinib-chemotherapy and osimertinib monotherapy are presented in Section 6.

In the updated model base case, OS data were sourced from the respective arms of the MARIPOSA (DCO: 4th December 2024) and FLAURA2 (DCO: 12th June 2025) trials (see Table 1 of the Addendum that was submitted alongside the original Company submission, and Table 2 in Section 2.1 of the current document, respectively), with estimated relative efficacy of amivantamab-lazertinib versus osimertinib-chemotherapy being derived via various ITCs (see Section 4). The more mature overall survival data now available from the FLAURA2 trial reduces overall uncertainty in long-term OS extrapolations. With the updated data and applying the MAIC weights, the KM curves for amivantamab-lazertinib and osimertinib-chemotherapy continue to exhibit a crossing within the observed period, now with more patients at risk in the osimertinib-chemotherapy arm than in the previous data cut. This observation aligns with the findings from the initial DGD and continues to reinforce the long-term benefit of amivantamab-lazertinib over osimertinib-chemotherapy, thereby further reducing the level of uncertainty.

5.2 Survival inputs and assumptions

5.2.1 Overall survival (OS)

Osimertinib-chemotherapy

The OS KM curve and independently fitted parametric and spline extrapolations for osimertinib-chemotherapy are presented in Figure 31. Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) of each of the osimertinib-chemotherapy OS distributions is provided in Table 15. The smoother hazard plots can be found in Figure 32 and Figure 33.

The best-fitting models were selected based on visual inspection, statistical criteria (AIC and BIC), clinical plausibility, and face validity, with expert clinical validation and the results from TA1060 guiding the process. Smoothed hazard plots were used to aid in model selection and ensure hazard functions aligned with clinical expectations.

As described in Section 4.1.2 clinicians dismissed most long-term extrapolations, citing reasons such as poor fit to the data (all parametric curves), too pessimistic (Gompertz or Generalised Gamma), or too optimistic, excluding the 1- or 2-knot hazard models. Based on this assessment, further guided by visual inspection, statistical fit, and the conclusions from TA1060, the 2-knot hazard model was selected as the base case.

Table 14 presents the averages derived from clinical validation, alongside the 1- and 2-knot hazard extrapolations. These models closely align with the averages of clinical validation.

Table 14: Long-term extrapolations from TA1060 (FLAURA2 IA2) and the clinically validated long term extrapolations with the updated OS data from FLAURA2 (DCO: 12th June 2025)

Source	5 years OS			10 years OS			15 years OS		
	Lower	Av.	Upper	Lower	Av.	Upper	Lower	Av.	Upper
Average of clinical validation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2-knot hazard (company preference)		39.5%			8.4%			1.2%	
1-knot hazard		39.4%			8.1%			1.1%	

Abbreviations: Av.: average; EAG: External Assessment Group; OS: overall survival.

Figure 31: Long-term OS projections of osimertinib-chemotherapy

Abbreviations: CP: chemotherapy; KM: Kaplan-Meier; OS: overall survival; OSI: osimertinib.

Table 15: AIC and BIC of osimertinib-chemotherapy OS (FLAURA2 distributions)

Distribution	AIC	BIC	AIC Rank	BIC Rank
Exponential	1524.04	1527.67	14	5
Weibull	1520.10	1527.36	12	4
Lognormal	1548.94	1556.20	16	16
Loglogistic	1527.75	1535.01	15	15
Gompertz	1515.77	1523.03	5	1
Gamma	1521.74	1529.00	13	6
Generalised gamma	1518.55	1529.44	10	7
1-knot hazard scale	1515.70	1526.59	4	2
2-knot, hazard scale	**1517.78**	**1532.31**	**8**	**13**
3-knot, hazard scale	1514.13	1532.29	3	12
1-knot, odds scale	1516.42	1527.31	6	3
2-knot, odds scale	1517.55	1532.08	7	11
3-knot, odds scale	1513.83	1531.99	2	10
1-knot, normal scale	1518.94	1529.84	11	8
2-knot, normal scale	1518.31	1532.83	9	14
3-knot, normal scale	1513.36	1531.51	1	9

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; OS: overall survival.

Figure 32: Osimertinib-chemotherapy OS standard parametric and smoothed hazard plots

Abbreviations: OS: overall survival.

Figure 33: Osimertinib-chemotherapy OS splines smoothed hazard plots

Abbreviations: OS: overall survival.

Amivantamab-lazertinib and osimertinib monotherapy

The selected base case extrapolations for OS for amivantamab-lazertinib and osimertinib monotherapy are presented in Table 16. The data informing these arms of the model have not been updated as compared with the previous model, with data derived from the most recent DCO of the MARIPOSA trial (4th December 2024).

Table 16: Selected base case extrapolations for amivantamab-lazertinib and osimertinib monotherapy in the updated model

	Selected base case extrapolation	Rationale
Amivantamab-lazertinib	Weibull	Aligned with Committee preference and no change when assessed within the unanchored MAIC
Osimertinib monotherapy	Weibull	Aligned with Committee preference and no change when assessed within the unanchored MAIC

Abbreviations: OS: overall survival; MAIC – matching-adjusted indirect comparison.

Summary

Long-term OS projections of amivantamab-lazertinib, osimertinib monotherapy and osimertinib-chemotherapy selected for the base case are presented in Figure 34. Throughout the analysis, the long-term OS projections are underpinned by a consistent and comprehensive body of evidence, all landing on the same conclusion, with amivantamab-lazertinib expected to have a survival benefit over osimertinib-chemotherapy. This includes the biological rationale, quality of response, mechanisms of resistance, insights from time-varying hazard plots, fractional polynomial network meta-analyses, assessment of the smoothed hazards, goodness of fit to

the KM data and overall clinical plausibility. Collectively, these factors provide a robust and credible foundation supporting the long-term projections and the survival benefit of amivantamab-lazertinib over osimertinib-chemotherapy.

Figure 34: Long-term OS projections of amivantamab-lazertinib, osimertinib monotherapy and osimertinib-chemotherapy selected for the base case in the updated model

Abbreviations: OS: overall survival; KM: Kaplan-Meier curve.

5.2.2 Progression-free survival (PFS)

A summary of the selected base case extrapolations for PFS for amivantamab-lazertinib, osimertinib monotherapy and osimertinib-chemotherapy is presented in Table 16 and in Figure 35. The data informing these arms of the model have not been updated as compared with the previous model given the absence of additional data. The selected curves do not change when considered as part of the unanchored MAIC.

Table 17: Selected base case extrapolations for PFS in the updated model

	Selected base case extrapolation	Rationale
Amivantamab-lazertinib	Gamma	Preferred by the EAG as part of the initial DGD response
Osimertinib monotherapy	Gamma	Preferred by the EAG as part of the initial DGD response
Osimertinib-chemotherapy	Weibull	Preferred by the EAG as part of the initial DGD response

Abbreviations: PFS: progression-free survival.

Figure 35: Long-term PFS projections of amivantamab-lazertinib, osimertinib monotherapy and osimertinib-chemotherapy selected for the base case

Abbreviations: PFS: progression-free survival.

5.2.3 Time to discontinuation (TTD)

A summary of the selected base case extrapolations for TTD for amivantamab-lazertinib, osimertinib monotherapy and osimertinib-chemotherapy is presented in Table 18 and in Figure 36. The data informing these arms of the model have not been updated as compared with the previous model. In light of the updated OS for osimertinib-chemotherapy, a higher TTD for the osimertinib component of osimertinib-chemotherapy than that suggested by the EAG is suitable. Therefore, the average of the Gompertz and gamma curves has been maintained by the Company as the base case. This aligns with the clinical validation, visual fits, and the curve comparison with osimertinib monotherapy TTD, osimertinib-chemotherapy PFS and osimertinib-chemotherapy OS (further described in Section 4.1.3).

Table 18: Selected base case extrapolations for TTD in the updated model

	Selected base case extrapolation	Rationale
Amivantamab	2-knot Normal	Committee preference
Lazertinib	1-knot Hazard	Committee preference
Osimertinib monotherapy	1-knot Normal	Committee preference
Osimertinib component of osimertinib-chemotherapy	Average of Gompertz and Gamma	Best fit to longer-term expectations, and aligns to PFS, OS, and the other accepted TTD curves
Chemotherapy component of osimertinib chemotherapy	Exponential	EAG preference

Abbreviations: TTD: time to discontinuation.

Figure 36: Long-term TTD projections of amivantamab-lazertinib, osimertinib monotherapy and osimertinib-chemotherapy selected for the base case

Abbreviations: TTD: time to discontinuation.

5.3 Health state utility values (HSUV)

5.3.1 Progressed disease (PD) health state

While the Company maintain that the MARIPOSA trial represents the most appropriate source of health state utilities available given that the utilities are obtained from the same source as the efficacy data, the Committee preference for progressed disease (PD) utility values to be aligned with the prior NICE appraisal of osimertinib-chemotherapy (TA1060; PD: 0.678) is acknowledged.[46] Therefore, the model has been updated to reflect this preference, with a PD utility value 0.678 applied across all three treatment arms in the updated model.

5.3.2 Progression-free (PF) health state

Based on a comprehensive analysis of the updated safety data from the FLAURA2 FA, as discussed in Section 4.6, the Company conclude that using treatment-specific PF utilities is defendable only when the utility value for amivantamab-lazertinib and osimertinib-chemotherapy remain the same. The assumption of a higher treatment-specific PF utility for osimertinib monotherapy, while maintaining equal PF HSUVs across amivantamab-lazertinib and osimertinib-chemotherapy is considered conservative, but could be perceived as suitable, for several reasons:

- The safety ITC in Section 4.6 clearly shows a more favourable safety profile for amivantamab-lazertinib versus osimertinib-chemotherapy
- FLAURA2 may underestimate the incidence of Grade ≥3 AEs and serious AEs (SAE) associated with osimertinib monotherapy, meaning the pooled osimertinib monotherapy and osimertinib-chemotherapy PF HSUV from FLAURA2 is higher than it would be if the osimertinib PF HSUV were accurately capturing AEs.
- SC amivantamab is associated with fewer AEs than IV amivantamab, and the use of SC amivantamab would result in significantly less time spent by a patient in a clinical setting, as compared with osimertinib-chemotherapy which is administered intravenously.[23] As such, the PF HSUV for SC amivantamab in combination with oral lazertinib would be expected to be higher, as was derived from the MARIPOSA trial.

- Treatment with enhanced dermatologic management significantly reduces the burden of dermatologic AEs on patients treated with amivantamab-lazertinib, reducing the apparent differences in AE disutility between amivantamab-lazertinib and osimertinib.[43]
- There is no publicly available evidence to suggest a difference in quality-of-life for patients who discontinue chemotherapy in the osimertinib-chemotherapy arm, meaning that it is not possible to account for the discontinuation of chemotherapy in this treatment arm in the PF HSUV in an evidence-based manner.

Additionally, a scenario analysis has been explored using treatment-dependent HSUVs for the PF health state, assuming 3 different PF utilities for all 3 treatments (see Section 6.3). This is in alignment with the various insights presented in this Section and Section 3.6 on the differences in AE impact, that favour amivantamab-lazertinib, which could lead to a higher PF utility value than osimertinib-chemotherapy.[40]

5.4 Other inputs and variables used in the updated cost-effectiveness model

All other inputs and variables that have been updated in the updated cost-effectiveness model are summarised in Table 19. All updates made are in alignment with the Committee's preferences following the second Committee meeting.

Table 19: All other inputs updated in the updated model

Input	Committee preference
Model characteristics	
Mean starting age	68.5 years
Drug administration costs	
IV administration within the osimertinib-chemotherapy	Average of SB13Z and SB15Z (NHS Reference Costs, Day Case; £477.00)
Platinum chemotherapy component of osimertinib-chemotherapy	Modelled as 100% carboplatin
SC administration of amivantamab	SB12Z OP (£133.39)
Continuation of oral treatment	Costed on a four-weekly schedule
Subsequent treatments	Alignment to 1L administration costing
Subsequent treatments	
Initiation of 2L treatments following osimertinib-chemotherapy	Aligned with the discontinuation of the osimertinib component (as per osimertinib TDD curve)
2L treatment distribution following osimertinib-chemotherapy	50% docetaxel, 50% platinum-based chemotherapy
3L treatment distribution following osimertinib-chemotherapy	100% BSC
Adverse events	
Incidence in the osimertinib-chemotherapy arm	Informed by the updated FLAURA2 DCO (see Section 2.2)

Abbreviations: 2L: second line; 3L: third line; BSC: best supportive care; IV: intravenous; NHS: National Health Service; SC: subcutaneous; TTD; time to treatment discontinuation.

Drug administration and acquisition costs

The drug administration and acquisition unit costs used in the updated cost-effectiveness model are aligned with those presented in Table 13 and Table 14, respectively, of the Company's initial DGD response. In

alignment with TA1060 and the Committee's preference in the Draft Guidance for this current appraisal (ID6256), an average of the SB13Z and SB15Z codes (NHS Reference Costs, Day Case) has been used to model the IV administration within the osimertinib-chemotherapy arm (£477.00).[46] In alignment with the value preferred by NHSE in the second Committee meeting, the SC administration of amivantamab has been modelled using the SB12Z code.[47] The continuation of oral treatment beyond the alternative treatment option is costed on a four-weekly cycle. In addition, the model has been updated to align with the Committee's preferred administration costs for subsequent treatments.

The drug acquisition unit costs used in the model for osimertinib-chemotherapy were sourced from the British National Formulary (BNF) and the UK Drugs and pharmaceutical electronic market information tool (eMIT). Following the NICE-agreed approach within TA1060, the platinum component of osimertinib-chemotherapy is modelled as 100% carboplatin.[46]

The Committee have raised no further concerns with the drug administration costs included within the model, so no further amendments have been made in this updated model as compared with the previous model.

Subsequent treatments

As per the initial DGD response, the methodology used to model the subsequent treatment costs for osimertinib-chemotherapy is aligned with the methodology used for osimertinib monotherapy. However, in the updated model submitted alongside this response, the proportion of patients receiving specific subsequent treatments at 2L and 3L+ following osimertinib-chemotherapy has been updated as presented in Table 20, in alignment with the Committee's preference and the updated FLAURA2 data (see Section 2.3). In further alignment with the preferences of the EAG and Committee, patients receiving osimertinib-chemotherapy are now modelled to receive subsequent treatment following discontinuation of the osimertinib component, as per the TTD curve.

All other inputs used to model the subsequent treatments for osimertinib-chemotherapy were aligned with those used for osimertinib monotherapy in the original submission. The methodology and inputs used to model the osimertinib monotherapy subsequent treatments remain unchanged from the original submission and are outlined in Section B.3.5.1.4 of Document B.

Table 20: Distribution and duration of subsequent treatments received by patients after osimertinib-chemotherapy

Subsequent treatment regimen	Distribution of treatments	Mean duration on treatment (weeks)	Source for duration of treatment
2L Regimen			
Platinum-based chemotherapy	50	[redacted]	[redacted]
Docetaxel	50	[redacted]	[redacted]
3L+ Regimen			
BSC	100	-	-

Abbreviations: 1L: first line; 2L: second line; 3L+: third-line or later; BSC: best supportive care.

Adverse events

For the osimertinib-chemotherapy arm, Grade 3 or higher TEAEs were included if they occurred in ≥5% of patients in the osimertinib-chemotherapy arm of the FLAURA2 trial. In the latest DCO available, values are rounded and more accurate values are not able to be sourced.[2, 4] Therefore, given the similarity between the rounded IA and FA incidence values (Table 4), the adverse events within the economic model have not been updated to the FA results. Table 21 shows the values that remain in the CEM. Additionally, Grade ≤2 VTE was included given that this is a clinically relevant consideration for amivantamab treatment. Incidence rates and durations of AEs for 1L treatment were sourced from the FLAURA2 trial for osimertinib-chemotherapy (Table 21).

Table 21: Incidence of AEs included in the osimertinib-chemotherapy arm of the CEM

Adverse Event	Osimertinib-chemotherapy (%)
Dermatitis acneiform	1.4%
Alanine aminotransferase increased	1.4%
Hypalbuminaemia	0.0%
Paronychia	0.7%
Infusion related reaction	0.0%
Rash	0.4%
Pulmonary Embolism	2.2%
Grade ≤2 VTE	0.0%
Pneumonia	2.2%
Anaemia	19.9%
Neutropenia	13.4%
Neutrophil count decreased	11.2%
Platelet count decreased	7.6%
Thrombocytopenia	6.9%

Abbreviations: AE: adverse event; CEM: cost-effectiveness model; VTE: venous thromboembolism.
Source: FLAURA2 (Planchard 2023).[4]

6. Updated cost-effectiveness results

6.1 Base case economic results

The base case pairwise results from the updated model at amivantamab and lazertinib patient access scheme (PAS) prices are presented in Table 22.

In line with the results presented in the initial DGD response, the base case results continue to demonstrate that, at amivantamab and lazertinib PAS prices, amivantamab-lazertinib is a cost-effective use of NHS resources when compared to both comparators at its list price, dominating both osimertinib monotherapy and osimertinib-chemotherapy. For completeness, the base case results at list prices are presented in Table 23.

Table 22: Pairwise deterministic DGD response base case results (at amivantamab and lazertinib PAS prices)

	Total Costs	Total LYs	Total QALYs	Incremental Costs	Incremental LYs	Incremental QALYs	ICER versus amivantamab-lazertinib (£/QALY)
Amivantamab-lazertinib	[redacted]	5.10	[redacted]	-	-	-	-
Osimertinib	[redacted]	3.77	[redacted]	[redacted]	1.33	[redacted]	−135,124.56
Osimertinib-chemotherapy	[redacted]	4.75	[redacted]	[redacted]	0.35	[redacted]	−987,103.32

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life years; NHB: net health benefit; PAS: patient access scheme; QALYs: quality-adjusted life years.

Table 23: Pairwise deterministic DGD response base case results (at amivantamab and lazertinib list prices)

	Total Costs	Total LYs	Total QALYs	Incremental Costs	Incremental LYs	Incremental QALYs	ICER versus amivantamab-lazertinib (£/QALY)
Amivantamab-lazertinib	[redacted]	5.10	[redacted]	-	-	-	-
Osimertinib	[redacted]	3.77	[redacted]	[redacted]	1.33	[redacted]	302,217.02
Osimertinib-chemotherapy	[redacted]	4.75	[redacted]	[redacted]	0.35	[redacted]	1,125,203.27

Abbreviations: ICER: incremental cost-effectiveness ratio; LY: life years; NHB: net health benefit; PAS: patient access scheme; QALYs: quality-adjusted life years.

6.2 Sensitivity analyses

Probabilistic sensitivity analysis

An updated probabilistic sensitivity analysis was conducted using the updated CEM. The incremental net monetary benefit (INMB) convergence plot is presented in Figure 37, which incorporates the PAS discounts for amivantamab and lazertinib. Additionally, the probabilistic cost-effectiveness planes for amivantamab-lazertinib versus osimertinib monotherapy and osimertinib-chemotherapy are presented in Figure 39 and Figure 40, respectively. The cost-effectiveness acceptability plane (CEAC) indicates that the probability of amivantamab-lazertinib being cost-effective [redacted] (Figure 38).

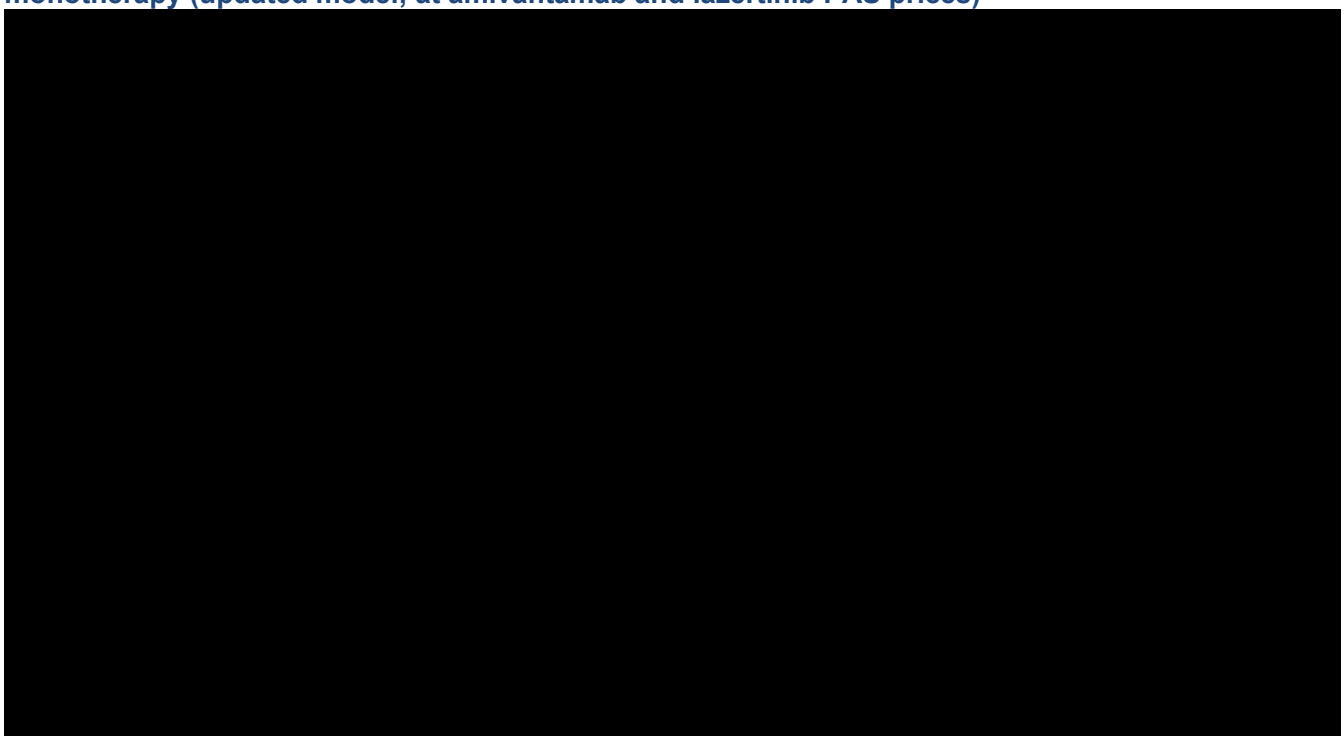
Figure 37: INMB convergence plot (updated model; at amivantamab and lazertinib PAS prices)

Abbreviations: CP: carboplatin-pemetrexed; INMB: incremental net monetary benefit; PAS: patient access scheme.

Figure 38: Cost-effectiveness acceptability curve for amivantamab-lazertinib versus osimertinib monotherapy and osimertinib-chemotherapy (updated model; at amivantamab and lazertinib PAS prices)

Abbreviations: CEAC: cost-effectiveness acceptability curve; CP: carboplatin-pemetrexed; PAS: patient access scheme.

Figure 39: Probabilistic cost-effectiveness plane for amivantamab-lazertinib versus osimertinib monotherapy (updated model; at amivantamab and lazertinib PAS prices)



Abbreviations: QALY: quality-adjusted life year; PSA: probabilistic sensitivity analysis

Figure 40: Probabilistic cost-effectiveness plane for amivantamab-lazertinib versus osimertinib monotherapy (updated model; at amivantamab and lazertinib PAS prices)

Abbreviations: QALY: quality-adjusted life year; PSA: probabilistic sensitivity analysis

Deterministic sensitivity analysis

Updated tornado diagrams showing the top 10 most influential parameters on the incremental net monetary benefit (INMB) in the updated model are provided in Figure 41 and Figure 42 for amivantamab-lazertinib versus osimertinib monotherapy and osimertinib-chemotherapy, respectively. Given the negative ICER, standard tornado diagrams on the ICER are not helpful for decision making. Therefore, the INMB has been chosen to show the most influential parameters on the results. The model is robust to variation in inputs and settings. In alignment with the results presented in the original CS, the Company response to Clarification questions and the Company response to draft guidance, all results generated from the deterministic sensitivity analysis (DSA) provide a positive INMB due to amivantamab-lazertinib (at amivantamab and lazertinib PAS prices) being dominant in all instances.

Figure 41: DSA tornado diagram for amivantamab-lazertinib versus osimertinib monotherapy (updated model; at amivantamab and lazertinib PAS prices)

Abbreviations: DSA: deterministic sensitivity analysis; INMB: incremental net monetary benefit; OS: overall survival; TTD: time to treatment discontinuation or death.

Figure 42: DSA tornado diagram for amivantamab-lazertinib versus osimertinib-chemotherapy (updated model; at amivantamab and lazertinib PAS prices)

Abbreviations: CP: carboplatin-pemetrexed; DSA: deterministic sensitivity analysis; HR: hazard ratio; INMB: incremental net monetary benefit; OS: overall survival; TTD: time to treatment discontinuation or death; SC - subcutaneous.

6.3 Scenario analyses

A number of scenario analyses were explored, in which model assumptions or parameters were altered. The robustness of the model results to changes in the following modelling approaches and assumptions were investigated:

- Mean age informed by MARIPOSA trial (62.3 years)
- Using treatment-specific PF HSUVs for all three treatments assuming none are equal, as described in Section 5.3. In this scenario, osimertinib remains as 0.813 and osimertinib-chemotherapy as 0.774, based on the MARIPOSA post-hoc analysis. However, the amivantamab-lazertinib PF utility value is 0.794, the value used within TA1060.
- Using a naïve comparison as was conducted by the EAG for ACM2.
- Using a population adjustment for each endpoint, as was conducted by the Company for ACM2:
    - OS: HR Adjustment = 1.05
    - PFS: HR adjustment = 0.93
    - TTD: HR adjustment = 1.04
- Using a population adjustment for each endpoint, as was conducted by the Company for ACM2, but with a time limit, based on the observed period follow-up in the respective endpoints:
    - OS: HR Adjustment = 1.05 – time limit: 47 months
    - PFS: HR adjustment = 0.93 – time limit: 33 months
    - TTD: HR adjustment = 1.04 – time limit: 33 months
- Using the piecewise cox regression model (4-interval method) as detailed in Section 4.2.1. In this scenario, the hazard ratio for amivantamab-lazertinib is acknowledged to change over time versus osimertinib-chemotherapy, as previously detailed. Here, the curve is split into time-points where the hazard ratio changes across time points. This is for [redacted], as shown in the Supplementary Appendix 1.1.

Table 24: Piecewise Cox regression model inputs utilised in scenario analysis

Endpoint	Time period	Value	Lower 95% CI	Upper 95% CI
MARIPOSA PFS HR	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
FLAURA2 PFS HR	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
MARIPOSA OS HR	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
FLAURA2 OS HR	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]

	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; HR: hazard ratio; OS: overall survival; PFS: progression-free survival.

- Using the standard parametric ITC as detailed in Section 4.3.1. The curves selected for this comparison are detailed in Table 25. Figure 43 shows the OS, PFS and TTD curves of osimertinib-chemotherapy resulting from these selections.

Table 25: Standard parametric curves explored in scenario analyses

Endpoint	Treatment	Curve Choice	Rationale
PFS	Amivantamab-lazertinib	Gamma	Maintains the accepted curve.
	Osimertinib monotherapy	Gamma	Maintains the accepted curve.
	Osimertinib-chemotherapy	Weibull	Maintains the accepted curve.
OS	Amivantamab-lazertinib	Weibull	Maintains the accepted curve.
	Osimertinib monotherapy	Weibull	Maintains the accepted curve.
	Osimertinib-chemotherapy	Weibull	Does not fit the shape of the KM curve, provides unrealistically high survival based on clinical validation, but is the least unfavourable fitting of the available options.
TTD	Amivantamab	Spline, normal scale, 2 knots	Maintains the accepted curve.
	Lazertinib	Spline, hazard scale, 2 knots	Maintains the accepted curve.
	Osimertinib monotherapy	Weibull	Previously presented by the Company as the most appropriate parametric curve.
	Osimertinib component of osimertinib-chemotherapy	Weibull	Does not fit the shape of the KM curve and is higher than earlier company base case but is the least unfavourable of the available options.
	Chemotherapy component of osimertinib-chemotherapy	Exponential	EAG preferred curve.

Abbreviations: EAG: External Assessment Group; OS: overall survival; PFS: progression-free survival; TTD: time-to-treatment discontinuation. Splines can be used for amivantamab and lazertinib TTD since the reference treatment for osimertinib-chemotherapy is osimertinib monotherapy.

Figure 43: Long-term OS, PFS and TTD projections of osimertinib-chemotherapy from parametric ITC with distributions selected for scenario analysis

Abbreviations: ITC: indirect treatment comparison; PFS: progression-free survival; OS: overall survival; TTD: time to discontinuation.

- Using the parametric fractional polynomial method as detailed in Section 4.2.2. In the absence of patient number at risk for FLAURA2 TTD, this method is only suitable for OS and PFS (Table 26). Both endpoints use amivantamab-lazertinib as the reference treatment. Further, this scenario is one of a very limited number of clinically plausible options for the fractional polynomials. All are included within the model for completeness but as previously described, results should be interpreted with caution.

Table 26: Parametric fractional polynomial inputs utilised in scenario analysis

Endpoint	Fractional Polynomial Order	Fractional Polynomial Power 1
PFS	[redacted]	[redacted]
OS	[redacted]	[redacted]

Abbreviations: OS: overall survival; PFS: progression-free survival.

- Given the standard parametric fits for PFS are suitable within the ITC, this could be incorporated alongside the base case, for PFS alone. This is not to suggest the OS or TTD standard parametric ITC should be used.

Results of the updated deterministic scenario analyses for the comparison of amivantamab-lazertinib against osimertinib monotherapy and osimertinib-chemotherapy are presented in Table 27 and Table 28, respectively.

In all analyses, amivantamab-lazertinib at PAS price remained dominant over osimertinib monotherapy and osimertinib-chemotherapy at list price, indicating that the cost-effectiveness of amivantamab-lazertinib versus osimertinib monotherapy and osimertinib-chemotherapy remains robust when altering key modelling assumptions and approaches.

Table 27: Scenario analysis results for amivantamab-lazertinib versus osimertinib monotherapy (updated model; deterministic; PAS prices)

Scenario		At amivantamab and lazertinib PAS prices		
		Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Base case		[redacted]	[redacted]	-135,124.56
Model characteristics				
1	Mean age informed by MARIPOSA trial (62.3 years)	[redacted]	[redacted]	-134,173.50
Utility				
2	Three treatment-specific PF HSUVs (amivantamab-lazertinib: [redacted]; osimertinib monotherapy: [redacted], osimertinib-chemotherapy: [redacted])	[redacted]	[redacted]	-132,851.52
Comparative effectiveness analyses				
3	Naïve comparison	[redacted]	[redacted]	-114,501.19
4	Population adjustment	[redacted]	[redacted]	-114,501.19
5	Population adjustment with time limit	[redacted]	[redacted]	-114,501.19
6	Piecewise hazard ratio indirect treatment comparison	[redacted]	[redacted]	-114,501.19
7	Standard parametric indirect treatment comparison	[redacted]	[redacted]	-97,427.19
8	Fractional polynomial indirect treatment comparison	[redacted]	[redacted]	-114,501.19
9	FLAURA2 population and PFS standard parametric indirect treatment comparison	[redacted]	[redacted]	-135,124.56

Abbreviations: ICER: incremental cost-effectiveness ratio; incr: incremental; PAS: patient access scheme; QALYs: quality-adjusted life years; PF HSUV: progression-free health state utility value

Table 28: Scenario analysis results for amivantamab-lazertinib versus osimertinib-chemotherapy (updated model; deterministic; PAS prices)

Scenario		At amivantamab and lazertinib PAS prices		
		Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Base case		[redacted]	[redacted]	-987,103.32
Model Characteristics				
1	Mean age informed by MARIPOSA trial (62.3 years)	[redacted]	[redacted]	-972,747.62
Utility				

Scenario		At amivantamab and lazertinib PAS prices		
		Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
2	Three treatment-specific PF HSUVs (amivantamab-lazertinib: [redacted]; osimertinib monotherapy: [redacted] osimertinib-chemotherapy: [redacted])	[redacted]	[redacted]	-710,926.68
Comparative effectiveness analyses				
3	Naïve comparison	[redacted]	[redacted]	-672,094.93
4	Population adjustment	[redacted]	[redacted]	-446,883.84
5	Population adjustment with time limit	[redacted]	[redacted]	-513,263.82
6	Piecewise hazard ratio indirect treatment comparison	[redacted]	[redacted]	-248,680.22
7	Standard parametric indirect treatment comparison	[redacted]	[redacted]	-1,095,916.44
8	Fractional polynomial indirect treatment comparison	[redacted]	[redacted]	-369,614.33
9	FLAURA2 population and PFS standard parametric indirect treatment comparison	[redacted]	[redacted]	-1,159,223.15

Abbreviations: ICER: incremental cost-effectiveness ratio; incr: incremental; PAS: patient access scheme; QALYs: quality-adjusted life years; PF HSUV: progression-free health state utility value

7. References

1. Johnson & Johnson Data on File. Amivantamab-lazertinib Clinical Validation Minutes. 18 September 2025.
2. David Planchard, Pasi A. Jänne, Kunihiko Kobayashi, et al. First-line Osimertinib + Chemotherapy Versus Osimertinib Monotherapy in EGFRm Advanced NSCLC: FLAURA2 Final Overall Survival, In IASLC 2025 World Conference on Lung Cancer, Barcelona, Spain, 2025.
3. Valdiviezo N, Okamoto I, Hughes BGM, et al. 4O First-line (1L) osimertinib (osi) ± platinum-pemetrexed in EGFR-mutated (EGFRm) advanced NSCLC: FLAURA2 post-progression outcomes. ESMO Open 2024;9.
4. Planchard D, Jänne PA, Cheng Y, et al. Osimertinib with or without Chemotherapy in EGFR-Mutated Advanced NSCLC. New England Journal of Medicine 2023;389:1935-1948.
5. Cho BC, Lu S, Felip E, et al. Amivantamab plus Lazertinib in Previously Untreated EGFR-Mutated Advanced NSCLC. N Engl J Med 2024;391:1486-1498.
6. Lin YT, Tsai TH, Wu SG, et al. Complex EGFR mutations with secondary T790M mutation confer shorter osimertinib progression-free survival and overall survival in advanced non-small cell lung cancer. Lung Cancer 2020;145:1-9.
7. Giaccone G, He Y. Current knowledge of small cell lung cancer transformation from non-small cell lung cancer. Seminars in Cancer Biology 2023;94:1-10.
8. Moores SL, Chiu ML, Bushey BS, et al. A Novel Bispecific Antibody Targeting EGFR and cMet Is Effective against EGFR Inhibitor-Resistant Lung Tumors. Cancer Res 2016;76:3942-53.
9. Reungwetwattana T, Nakagawa K, Cho BC, et al. CNS Response to Osimertinib Versus Standard Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors in Patients With Untreated EGFR-Mutated Advanced Non–Small-Cell Lung Cancer. Journal of Clinical Oncology 2018;36:3290-3297.
10. Schmid S, Li JJN, Leighl NB. Mechanisms of osimertinib resistance and emerging treatment options. Lung Cancer 2020;147:123-129.
11. Remon J, Besse B. Unravelling signal escape through maintained EGFR activation in advanced non-small cell lung cancer (NSCLC): new treatment options. ESMO Open 2016;1:e000081.
12. James Chih-Hsin Yang, Jacqulyne Robichaux, David Planchard, et al. FLAURA2: Resistance, and impact of baseline TP53 alterations in patients treated with first-line osimertinib with or without platinum-pemetrexed, In 2024 World Conference on Lung Cancer, San Diego, CA USA, 2024.
13. Hidetoshi Hayashi, Benjamin Besse, Se-Hoon Lee, et al. Mechanisms of Acquired Resistance to First-Line Amivantamab Plus Lazertinib Vs Osimertinib: Updated Analysis from MARIPOSA, In IASLC 2025 World Conference on Lung Cancer, Barcelona, Spain, 2025.
14. Besse B, Lee S, Lu S, et al. Mechanisms of Acquired Resistance to First-line Amivantamab Plus Lazertinib Versus Osimertinib in Patients With EGFR-mutant Advanced Non-Small Cell Lung Cancer An Early Analysis from the Phase 3 MARIPOSA Study. Presentation presented at: European Society for Medical Oncology (ESMO); September 13-17, 2024. Barcelona, Spain.
15. Tan DS. Navigating treatment choices in advanced EGFR mutated NSCLC: a balancing act, In IASLC 2025 World Conference on Lung Cancer, Barcelona, Spain, 2025.
16. Cho BC, Simi A, Sabari J, et al. Amivantamab, an Epidermal Growth Factor Receptor (EGFR) and Mesenchymal-epithelial Transition Factor (MET) Bispecific Antibody, Designed to Enable Multiple Mechanisms of Action and Broad Clinical Applications. Clinical Lung Cancer 2023;24:89-97.
17. Ramalingam SS, Vansteenkiste J, Planchard D, et al. Overall Survival with Osimertinib in Untreated, EGFR-Mutated Advanced NSCLC. New England Journal of Medicine 2020;382:41-50.
18. Eng C, Oberstein PE, Hecht JR, et al. Amivantamab treatment and intra-tumoral gene expression and immune cell changes in refractory metastatic colorectal cancer (mCRC): Whole transcriptome RNA-sequencing analysis from the OrigAMI-1 study. Journal of Clinical Oncology 2025;43:3550-3550.

19. Chih-Hsin Yang J. et al. Amivantamab Plus Lazertinib vs Osimertinib in First-line (1L) EGFR-mutant (EGFRm) Advanced NSCLC: Final Overall Survival (OS) from the Phase 3 MARIPOSA Study. Presented at: European Lung Cancer Congress (ELCC); March 26-29, 2025. Paris, France.
20. Johnson & Johnson Data on File. MARIPOSA Clinical Study Report. DCO: 4 December 2024.
21. Yang JC-H, Lu S, Hayashi H, et al. Overall Survival with Amivantamab-Lazertinib in EGFR-Mutated Advanced NSCLC. New England Journal of Medicine 2025;0.
22. Florez N, LeBoeuf NR, Rotow J, et al. Mitigation and management of adverse events associated with amivantamab therapy. Oncologist 2025;30.
23. Leighl NB, Akamatsu H, Lim SM, et al. Subcutaneous Versus Intravenous Amivantamab, Both in Combination With Lazertinib, in Refractory Epidermal Growth Factor Receptor-Mutated Non-Small Cell Lung Cancer: Primary Results From the Phase III PALOMA-3 Study. J Clin Oncol 2024;42:Jco2401001.
24. Spira AI, Paz-Ares L, Han JY, et al. Preventing Infusion-Related Reactions With Intravenous Amivantamab-Results From SKIPPirr, a Phase 2 Study: A Brief Report. J Thorac Oncol 2025;20:809-816.
25. Nicolas Girard, Weimin Li, Alexander I Spira, et al. Preventing Moderate to Severe Dermatologic Adverse Events in First-Line EGFR-Mutant Advanced NSCLC Treated With Amivantamab Plus Lazertinib: Early Success of the COCOON Trial, In Hematology/Oncology Pharmacy Association (HOPA) Annual Conference, Portland, OR, USA, 2025.
26. David Planchard, Ying Cheng, Kunihiko Kobayashi, et al. Characterisation of benefit-risk by pemetrexed exposure in patients with EGFR-mutated advanced NSCLC treated with first-line osimertinib plus platinum-pemetrexed chemotherapy in FLAURA2. Poster 53P., In European Lung Cancer Congress (ELCC), Paris, France, 2025.
27. Landre T, Assié JB, Chouahnia K, et al. First-line concomitant EGFR-TKI + chemotherapy versus EGFR-TKI alone for advanced EGFR-mutated NSCLC: a meta-analysis of randomized phase III trials. Expert Rev Anticancer Ther 2024;24:775-780.
28. Paly V, Hernandez LG, Howe A, et al. EE670 Management Costs of Grade 3/4 Adverse Events Associated with Emerging and Existing Systemic Therapies for Metastatic Colorectal Cancer with at Least Two Prior Lines of Therapy in Italy, Portugal, Spain, and the United States. Value in Health 2023;26:S182-S183.
29. Jincheng Yang, Damilola Olabode, Aarti Sawant, et al. Exposure Efficacy and Safety Analysis of Osimertinib in Combination with Pemetrexed and Platinum-based Chemotherapy for the First-Line Treatment of Locally Advanced or Metastatic NSCLC patients with EGFRm (FLAURA2), In American Association for Cancer Research, San Diego, California, 2024.
30. Johnson & Johnson Data on File. Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256] - Additional analysis request, 2025.
31. Wong GYC, Osborne MP, Diao Q, et al. Piecewise Cox models with right-censored data. Communications in Statistics - Simulation and Computation 2017;46:7894-7908.
32. National Institute for Health and Care Excellence (NICE). Dacomitinib for untreated EGFR mutation-positive non-small-cell lung cancer [TA595] Available at: https://www.nice.org.uk/guidance/TA595 [Accessed: September 2025].
33. National Institute for Health and Care Excellence (NICE). Lenvatinib with pembrolizumab for untreated advanced renal cell carcinoma [TA858] Available at: https://www.nice.org.uk/guidance/ta858 [Accessed: September 2025].
34. National Institute for Health and Care Excellence (NICE). Nivolumab for treating locally advanced unresectable or metastatic urothelial cancer after platinum-containing chemotherapy [TA530] Available at: https://www.nice.org.uk/guidance/ta530 [Accessed: September 2025].
35. National Institute for Health and Care Excellence (NICE). Cabozantinib with nivolumab for untreated advanced renal cell carcinoma [TA964] Available at: https://www.nice.org.uk/guidance/ta964 [Accessed: September 2025].
36. Royston P, Altman DG. Regression Using Fractional Polynomials of Continuous Covariates: Parsimonious Parametric Modelling. Journal of the Royal Statistical Society. Series C (Applied Statistics) 1994;43:429-467.

37. Ouwens MJNM, Philips Z, Jansen JP. Network meta-analysis of parametric survival curves. Research Synthesis Methods 2010;1:258-271.
38. Cope S, Chan K, Jansen JP. Multivariate network meta-analysis of survival function parameters. Research Synthesis Methods 2020;11:443-456.
39. Jansen JP, Fleurence R, Devine B, et al. Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 1. Value Health 2011;14:417-28.
40. Johnson & Johnson Data on File. 2nd Addendum: EAG critique of the company's response to draft guidance. 7th August 2025.
41. Johnson & Johnson Data on File. PALOMA-3 Clinical Study Report. DCO: 3 January 2024.
42. ClinicalTrials.gov. NCT06120140. Enhanced Dermatological Care to Reduce Rash and Paronychia in Epidermal Growth Factor Receptor (EGFR)-Mutated Non-Small Cell Lung Cancer (NSCLC) Treated First-line With Amivantamab Plus Lazertinib (COCOON). Available at: https://www.clinicaltrials.gov/study/NCT06120140?term=COCOON [Accessed: September 2025].
43. Cho BC, Li W, Spira AI, et al. Enhanced Versus Standard Dermatologic Management With Amivantamab-Lazertinib in EGFR-Mutated Advanced NSCLC: The COCOON Global Randomized Controlled Trial. Journal of Thoracic Oncology 2025.
44. Byoung Chul Cho, Weimin Li, Alexander I Spira, et al. Enhanced vs Standard Dermatologic Management with Amivantamab-Lazertinib in EGFRm Advanced NSCLC: the COCOON Global RCT, In World Conference on Lung Cancer 2025, Barcelona, Spain.
46. National Institute for Health and Care Excellence (NICE). Osimertinib with pemetrexed and platinum-based chemotherapy for untreated EGFR mutation-positive advanced non-small-cell lung cancer. Available at: https://www.nice.org.uk/guidance/ta1060 [Accessed: September 2025].
47. National Institute for Health and Care Excellence (NICE). Daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma (Managed Access Review of TA573) [ID4057]. Available at: https://www.nice.org.uk/guidance/ta897/documents/committee-papers [Accessed: September 2025].

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Additional Analyses Request

Supplementary Appendix

September 2025

1 Additional results from ITC methods

1.1 Piecewise HR PFSINV Results

Piecewise Cox model results for PFSINV, number of events and number of patients at risk at the beginning of the interval for the MARIPOSA and FLAURA2 trials are provided in Table 1, and the relative treatment effect per interval is provided in Table 2.

Table 1: Piecewise Cox models, PFSINV, MARIPOSA and FLAURA2

Period (months)	MARIPOSA (amivantamab-lazertinib vs. osimertinib)			FLAURA2 (osimertinib-chemotherapy vs. osimertinib)		
	HR (95% CI)	Number of events, Number at risk AMILAZ	Number of events, Number at risk OSI	HR (95% CI)	Number of events, Number at risk OSICP	Number of events, Number at risk OSI
3-interval model						
≤7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>7 – ≤19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4-interval model						
≤ 7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>7 – ≤19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>19 – ≤24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AMILAZ: amivantamab-lazertinib; CI: confidence interval; HR: hazard ratio; OSI: osimertinib; OSICP: osimertinib-chemotherapy; PFSINV: progression-free survival assessed by investigator.

Table 2: Relative Treatment Effect (PFSINV) for Osimertinib-chemotherapy vs. amivantamab-lazertinib based on piecewise Cox Models

Period (months)	HR (95% CI)
3-interval model	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
4-interval model	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Abbreviations: CI: confidence interval; HR: hazard ratio.

Figure 1. PFSINV Extrapolations for osimertinib-chemotherapy obtained by applying piecewise Cox model HRs to amivantamab-lazertinib

Abbreviations: CP: chemotherapy; HR: hazard ratio; KM: Kaplan-Meier; PFSINV: progression-free survival assessed by investigator.

1.2 Piecewise HR Approach Cut-off Points

Cut off points for the piecewise HR approach for each trial were identified by investigating the changes in the slope of the curve obtained by plotting the cumulative hazards of the two treatments against each other. After the cut off points were identified from the two trials separately, the cut off points from the two trials were combined and aligned to have common cut off points.

In each plot, the diagonal 45-degree yellow line denotes the trajectory the red curve should follow to indicate a HR of 1 (i.e. hazard accumulates at the same rate for the two treatments). Red lines with a slope >45 degrees indicate a HR above one, and red lines with a slope <45 degrees indicate a HR below one.

OS cumulative hazard plots (Figure 2) suggest that in MARIPOSA, osimertinib initially has lower hazards until about 7 months. Between 7 and 16 months the treatment effect improves markedly in favour of amivantamab-lazertinib. After 16 months the treatment effect is still in favour of amivantamab-lazertinib, and even though not as marked as in the previous period, keeps steadily improving (i.e. treatment effect keeps increasing in favour of amivantamab-lazertinib vs. osimertinib), with the rate of increase getting faster after 35 months. For FLAURA2, osimertinib initially has lower hazards, but after 14 months hazard accumulates faster in the osimertinib cohort compared to osimertinib-chemotherapy, indicating improved efficacy of osimertinib-chemotherapy vs. osimertinib. However, unlike in MARIPOSA, after the treatment effect decreases (at 26 months), the red line becomes more parallel to the yellow line, indicating that the treatment effect of osimertinib-chemotherapy vs. osimertinib is decreasing, and the decrease is more marked after 35 months. The common cut-off points were selected as 7 months, 15 months (i.e. the mid-point between 14 and 16 months), 26 months, and 35 months.

Figure 2. Cumulative Hazard Plots, MARIPOSA and FLAURA2, OS

OS MARIPOSA	OS FLAURA2
[redacted]	[redacted]

Abbreviations: AMI+LAZ: amivantamab-lazertinib; MAR: MARIPOSA; OS: overall survival; OSI: osimertinib; OSI+CP: osimertinib-chemotherapy.

PFSINV cumulative hazard plots (Figure 3) suggests that in MARIPOSA, the hazard accumulates at around the same rate for both treatment arms in the beginning of follow up until about 7 months. Between 7 months and 24 months, the hazard accumulates faster in the osimertinib cohort compared to amivantamab-lazertinib cohort, and after 24 months, there is a slight increase in the speed at which hazard accumulates in the osimertinib cohort (i.e. slightly better treatment effect in favour of amivantamab-lazertinib). In FLAURA2, osimertinib-chemotherapy treatment effect is stable until about 19 months, and after 19 months there is a sharp turn towards the diagonal yellow line, indicating that osimertinib-chemotherapy treatment effect decreases sharply. The common cut-off points were selected as 7 months, 19 months, and 24 months.

Figure 3. Cumulative Hazard Plots, MARIPOSA and FLAURA2, PFSINV

PFSINV MARIPOSA	PFSINV FLAURA2
	

Abbreviations: AMI+LAZ: amivantamab-lazertinib; MAR: MARIPOSA; OSI: osimertinib; OSI+CP: osimertinib-chemotherapy; PFSINV: progression-free survival assessed by investigator.

1.3 Standard Parametric fits to FLAURA2 osimertinib-chemotherapy and osimertinib OS and PFSINV

Estimation of relative treatment effects with parametric NMA requires estimation of treatment effects in both trials through same parametric models. Supplementary material includes plots from the seven parametric models fit to OS and PFSINV from FLAURA2 osimertinib-chemotherapy and osimertinib arms, as well as MARIPOSA amivantamab-lazertinib and osimertinib arms for easier comparison of standard models across treatment arms. No standard parametric model has adequate fit to all four arms. Goodness of fit information for the models are provided in Table 3 for OS and Table 4 for PFSINV.

Table 3: Goodness of fit of Standard parametric models to FLAURA2 osimertinib-chemotherapy and osimertinib OS

	Osimertinib-chemotherapy				Osimertinib (FLAURA2)			
Distribution	AIC	BIC	AIC RANK	BIC RANK	AIC	BIC	AIC RANK	BIC RANK
Exponential	1524.04	1527.67	5	3	1727.56	1731.19	7	7
Weibull	1520.10	1527.36	3	2	1703.08	1710.34	2	2
Lognormal	1548.94	1556.20	7	7	1720.83	1728.09	6	6
Loglogistic	1527.75	1535.01	6	6	**1702.97**	**1710.22**	1	1
Gompertz	**1515.77**	**1523.03**	1	1	1711.09	1718.34	5	5
Gamma	1521.74	1529.00	4	4	1703.44	1710.70	3	3
Generalised gamma	1518.55	1529.44	2	5	1704.98	1715.86	4	4

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; OS: overall survival.

Table 4: Goodness of fit of Standard parametric models to FLAURA2 osimertinib-chemotherapy and osimertinib PFSINV

	Osimertinib-chemotherapy				Osimertinib (FLAURA2)			
Distribution	AIC	BIC	AIC RANK	BIC RANK	AIC	BIC	AIC RANK	BIC RANK
Exponential	1139.50	1143.10	6	5	1427.10	1430.70	7	4
Weibull	1130.30	1137.60	3	2	1421.10	1428.30	3	3
Lognormal	1154.90	1162.20	7	7	1425.30	1432.60	5	6
Loglogistic	1137.60	1144.90	5	6	**1419.30**	**1426.50**	1	1
Gompertz	**1123.40**	**1130.70**	1	1	1425.80	1433.10	6	7
Gamma	1132.70	1140.00	4	4	1420.10	1427.40	2	2
Generalised gamma	1126.70	1137.60	2	2	1421.40	1432.30	4	5

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; PFSINV: progression-free survival assessed by investigator.

2 Fractional polynomials (FP) – Parametric and Cox

2.1 Cox FP PFSINV Result Overview

Log-transformed PFSINV HRs from all the fitted models are shown in Figure 4 and Figure 5, and they span a wide range of trajectories (red horizontal zero line indicates no treatment effect. Trajectories below the zero-line favour amivantamab-lazertinib vs. osimertinib monotherapy in MARIPOSA in Figure 4 and trajectories below zero-line favour osimertinib-chemotherapy versus. osimertinib monotherapy in FLAURA2 in Figure 5. The relative effects of osimertinib-chemotherapy vs. amivantamab-lazertinib are presented in Figure 6 (trajectories above the zero-line favour amivantamab-lazertinib vs. osimertinib-chemotherapy). Figure 7 represents the osimertinib-chemotherapy PFSINV extrapolations obtained from applying 164 Cox FP models on amivantamab-lazertinib (Weibull) and osimertinib-chemotherapy base case extrapolation for PFS. Figure 8 represented the PFSINV Extrapolations for osimertinib-chemotherapy obtained by Cox FP [redacted] relative treatment effect estimate applied to amivantamab-lazertinib.

Figure 4. MARIPOSA amivantamab-lazertinib versus osimertinib monotherapy, time-dependent treatment effect on PFSINV with FP-based Cox models

Abbreviations: amilaz: amivantamab-lazertinib; FP: fractional polynomial; HR: hazard ratio; M1AMILAZ: MARIPOSA amivantamab-lazertinib; osi: osimertinib monotherapy.

Figure 5: FLAURA2 osimertinib-chemotherapy versus osimertinib monotherapy, time-dependent treatment effect on PFSINV with FP-based Cox models

Abbreviations: FP: fractional polynomial; F2OSICP: FLAURA2 osimertinib-chemotherapy; HR: hazard ratio; osi: osimertinib monotherapy; osicp: osimertinib-chemotherapy.

Figure 6: Osimertinib-chemotherapy versus amivantamab-lazertinib, time-dependent relative treatment effect on PFSINV with FP-based Cox models

Abbreviations: amilaz: amivantamab-lazertinib; FP: fractional polynomial; F2OSICP: FLAURA2 osimertinib-chemotherapy; HR: hazard ratio; M1AMILAZ: MARIPOSA amivantamab-lazertinib; NMA: network meta-analysis; osicp: osimertinib-chemotherapy.

Figure 7. Osimertinib-chemotherapy PFSINV extrapolations obtained from applying 164 Cox FP models on amivantamab-lazertinib Weibull and osimertinib-chemotherapy base case extrapolation (dark orange)

Abbreviations: amilaz: amivantamab-lazertinib; FP: fractional polynomial; HR: hazard ratio; OSICP: osimertinib-chemotherapy; PFSINV: progression-free survival assessed by investigator.

Figure 8. PFSINV Extrapolations for osimertinib-chemotherapy obtained by Cox FP [redacted] relative treatment effect estimate applied to amivantamab-lazertinib

Abbreviations: CP: chemotherapy; FP: fractional polynomial; KM : Kaplan-Meier; PFSINV: progression-free survival assessed by investigator.

2.2 Fractional polynomials (FP) – Parametric and Cox Model Assessment

The following provides a comprehensive description of all 164 PFS (Progression-Free Survival) and OS (Overall Survival) Cox FP models, as well as the 44 PFS and OS parametric FP models. The accompanying table offers a brief explanation of the observations across various settings.

FP models with lowest total AIC score across the two trials are highlighted in purple. For Cox FP models, these are the 3rd order FP with powers –2, -2, and –1 for OS, and the 3rd order FP with powers –2, -2, and -.05 for PFSINV. HR estimates in both trials go to extreme values near time 0 with both FPs. For parametric FP models, lowest AIC models are the 2nd order FP with powers 2 and 2 for OS and the 2nd order FP with powers 0.5 and 1 for PFSINV. PFSINV parametric FP with powers 0.5 and 1 implies that FLAURA2 osimertinib + chemotherapy PFSINV hazard increases above the FLAURA2 osimertinib PFSINV hazard. OS parametric FP with powers 2 and 2 for OS FP implies that osimertinib + chemotherapy OS decreases below that of osimertinib monotherapy.

Table 5. Summary of AIC values from Cox FP models, MARIPOSA and FLAURA2

AIC across models	Cox FP		Parametric FP			
	FLAURA2	MARIPOSA	FLAURA2 OSICP	FLAURA2 OSI	MARIPOSA AMILAZ	MARIPOSA OSI
OS						
min	3705.44	3333.57	372.01	486.84	481.78	567.43
max	3713.08	3341.97	389.05	514.04	495.73	599.54
range	7.64	8.40	17.05	27.20	13.96	32.11
PFSINV						
min	3314.05	4754.04	393.50	506.92	845.09	1059.14
max	3324.57	4761.54	413.59	522.01	852.92	1076.02
range	10.52	7.50	20.09	15.08	7.83	16.87

Abbreviations: AIC: Akaike information criterion; AMILAZ: amivantamab-lazertinib; FP: fractional polynomial; KM: Kaplan-Meier; OS: overall survival; OSI: osimertinib; OSICP: osimertinib-chemotherapy; PFSINV: progression-free survival assessed by investigator.

For each Cox FP model, time-dependent log HRs from MARIPOSA and FLAURA2, estimated through smoothed Schoenfeld residuals and the implied time-dependent relative treatment effects, were overlaid on the trial-specific treatment effect and relative treatment effect estimated through the Cox FP, for visual inspection of results (attachment 2, 'Cox_FPs_OS_PFSINV). Osimertinib-chemotherapy OS and PFSINV extrapolations obtained by applying the resulting time-dependent relative treatment effect on per-cycle hazard of amivantamab-lazertinib OS (unadjusted, Weibull) and PFSINV (unadjusted, gamma) was also plotted together with amivantamab-lazertinib and osimertinib, along with their undiscounted LYs to further asses the plausibility of results. For each parametric FP, six plots are provided in attachment 1 ('Parametric_FPs_OS_PFSINV): 1) FLAURA2 osimertinib-chemotherapy and osimertinib KM were overlaid with the FP model-estimated survival and MARIPOSA amivantamab-lazertinib and osimertinib KM were overlaid with the FP model-estimated survival, for visual assessment of goodness of fit of the FP model to all four arms, which is important for accurate estimation of time-dependent trial-specific treatment effects and the relative treatment effect. Hazards estimated with the FP for both arms of each trial were also plotted to assess plausibility of evolution of hazards. Fifth, the time-dependent log HRs from MARIPOSA and FLAURA2 estimated through smoothed Schoenfeld residuals and the implied time-dependent relative treatment effect were overlaid on the trial-specific treatment effect and relative treatment effect estimated through the parametric FP, for visual inspection of results. Finally, osimertinib-chemotherapy OS and PFSINV extrapolations obtained by applying the resulting time-dependent relative treatment effect on per-cycle hazard of amivantamab-lazertinib OS (unadjusted, Weibull)

and PFSINV (unadjusted, gamma) was also plotted together with the amivantamab-lazertinib and osimertinib, along with their undiscounted LYs to further asses the plausibility of results.

Plausibility was assessed based on reflecting the trends observed in the two trials and plausibility of extrapolated treatment effects and OS and PFSINV outcomes. Both among Cox and parametric FPs, options that yielded extreme hazard or hazard ratio values near time zero were rejected, this criterion is also in line with Royston et. al.,[1] who noted that the absence of extreme results near extreme values of zero is a model selection criterion. Extreme hazard or hazard ratio estimates near 0 yield survival curves that drop to zero very near time 0, as is the case in many of the FP options, plots from these FPs were also included to allow visual inspection. In addition, very rapidly increasing or decreasing hazards or hazard ratios in the extrapolated period, or hazards that led to lower osimertinib-chemotherapy OS or PFSINV compared to osimertinib monotherapy, were rejected. Parametric FPs that did not fit well to all four arms were also rejected.

Among the Cox FP models, 1st order FP with log transformation of time for PFSINV and 1st order FP with power 0.5 for OS gave the most plausible results. These have been highlighted in bold within the table. None of the parametric FPs provided good fit to all four arms.

A short description of each Cox FP and parametric FP is provided in Table 6 and Table 7, respectively.

Table 6. Summary of Cox FP models

FP name	Cox regression - PFSINV	Cox regression - OS
FP_-2_-2_-2	HR estimates for MARIPOSA and FLAURA2 are going to extreme values near time 0. F2 AIC: 3317.88 RANK: 115 - M AIC: 4754.12 RANK: 2 SUM AIC: 8072 RANK: 7	HR estimates for MARIPOSA and FLAURA2 are going to extreme values near time 0. F2 AIC: 3709.01 RANK: 78 - M AIC: 3334.13 RANK: 2 SUM AIC: 7043.15 RANK: 2
FP_-2_-2_-1	HR estimates for MARIPOSA and FLAURA2 are going to extreme values near time 0. F2 AIC: 3317.31 RANK: 102 - M AIC: 4754.04 RANK: 1 SUM AIC: 8071.35 RANK: 2	HR estimates for MARIPOSA and FLAURA2 are going to extreme values near time 0. F2 AIC: 3709.15 RANK: 100 - M AIC: 3333.57 RANK: 1 SUM AIC: 7042.72 RANK: 1
FP_-2_-2_-0.5	HR estimates for MARIPOSA and FLAURA2 are going to extreme values near time 0. F2 AIC: 3316.81 RANK: 83 - M AIC: 4754.52 RANK: 3 SUM AIC: 8071.32 RANK: 1	HR estimates for MARIPOSA and FLAURA2 are going to extreme values near time 0. F2 AIC: 3709.37 RANK: 128 - M AIC: 3334.24 RANK: 4 SUM AIC: 7043.61 RANK: 4
FP_-2_-2_log(t)	HR estimates for MARIPOSA and FLAURA2 are going to extreme values near time 0. FLAURA2 HR is increasing rapidly. F2 AIC: 3316.23 RANK: 49 - M AIC: 4755.62 RANK: 5 SUM AIC: 8071.85 RANK: 5	HR estimates for MARIPOSA and FLAURA2 are going to extreme values near time 0. F2 AIC: 3709.63 RANK: 148 - M AIC: 3335.6 RANK: 7 SUM AIC: 7045.23 RANK: 10
FP_-2_-2_0.5	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. F2 AIC: 3315.71 RANK: 20 - M AIC: 4757.01 RANK: 12 SUM AIC: 8072.72 RANK: 11	HR estimates for MARIPOSA and FLAURA2 are going to extreme values near time 0. F2 AIC: 3709.76 RANK: 156 - M AIC: 3337.26 RANK: 11 SUM AIC: 7047.02 RANK: 39
FP_-2_-2_1	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. MARIPOSA HR is decreasing rapidly. F2 AIC: 3315.35 RANK: 18 - M AIC: 4758.22 RANK: 33 SUM AIC: 8073.57 RANK: 18	HR estimates for MARIPOSA and FLAURA2 are going to extreme values near time 0. HR estimate for MARIPOSA go to zero. F2 AIC: 3709.72 RANK: 153 - M AIC: 3338.58 RANK: 21 SUM AIC: 7048.3 RANK: 58
FP_-2_-2_2	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. MARIPOSA HR is decreasing rapidly. F2 AIC: 3315.25 RANK: 15 - M AIC: 4759.76 RANK: 81 SUM AIC: 8075.01 RANK: 35	HR estimates for MARIPOSA and FLAURA2 are going to extreme values near time 0. HR estimate for MARIPOSA go to zero. F2 AIC: 3709.53 RANK: 142 - M AIC: 3339.87 RANK: 60 SUM AIC: 7049.4 RANK: 84
FP_-2_-2_3	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. MARIPOSA HR is decreasing rapidly. F2 AIC: 3315.75 RANK: 24 - M AIC: 4760.55 RANK: 154 SUM AIC: 8076.3 RANK: 62	HR estimates for MARIPOSA and FLAURA2 are going to extreme values near time 0. HR estimate for MARIPOSA go to zero. FLAURA2 HR increases rapidly F2 AIC: 3709.49 RANK: 136 - M AIC: 3340.32 RANK: 69 SUM AIC: 7049.81 RANK: 93

FP_-2_-1_-1	HR estimates for MARIPOSA and FLAURA2 are going to extreme values near time 0. F2 AIC: 3317 RANK: 90 - M AIC: 4754.66 RANK: 4 SUM AIC: 8071.66 RANK: 4	HR estimates for MARIPOSA and FLAURA2 are going to extreme values near time 0. F2 AIC: 3709.35 RANK: 126 - M AIC: 3334.16 RANK: 3 SUM AIC: 7043.51 RANK: 3
FP_-2_-1_-0.5	HR estimates for MARIPOSA and FLAURA2 are going to extreme values near time 0. F2 AIC: 3316.68 RANK: 71 - M AIC: 4755.65 RANK: 6 SUM AIC: 8072.33 RANK: 9	HR estimates for MARIPOSA and FLAURA2 are going to extreme values near time 0. F2 AIC: 3709.51 RANK: 139 - M AIC: 3335.29 RANK: 6 SUM AIC: 7044.8 RANK: 5
FP_-2_-1_log(t)	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. F2 AIC: 3316.32 RANK: 51 - M AIC: 4757.07 RANK: 14 SUM AIC: 8073.39 RANK: 16	HR estimates for FLAURA2 is going to extreme values near time 0. F2 AIC: 3709.59 RANK: 146 - M AIC: 3337.08 RANK: 10 SUM AIC: 7046.67 RANK: 29
FP_-2_-1_0.5	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. F2 AIC: 3315.98 RANK: 32 - M AIC: 4758.48 RANK: 44 SUM AIC: 8074.46 RANK: 28	HR estimates for FLAURA2 is going to extreme values near time 0. F2 AIC: 3709.52 RANK: 140 - M AIC: 3338.86 RANK: 24 SUM AIC: 7048.38 RANK: 61
FP_-2_-1_1	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. MARIPOSA HR is decreasing rapidly. F2 AIC: 3315.75 RANK: 23 - M AIC: 4759.57 RANK: 72 SUM AIC: 8075.32 RANK: 44	HR estimates for FLAURA2 is going to extreme values near time 0. MARIPOSA HR goes to zero. F2 AIC: 3709.36 RANK: 127 - M AIC: 3340.09 RANK: 66 SUM AIC: 7049.45 RANK: 85
FP_-2_-1_2	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. MARIPOSA HR is decreasing rapidly. F2 AIC: 3315.72 RANK: 21 - M AIC: 4760.82 RANK: 159 SUM AIC: 8076.54 RANK: 72	HR estimates for FLAURA2 is going to extreme values near time 0. MARIPOSA HR goes to zero. FLAURA2 HR is increasing rapidly. F2 AIC: 3709.11 RANK: 94 - M AIC: 3341.17 RANK: 126 SUM AIC: 7050.28 RANK: 122
FP_-2_-1_3	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. MARIPOSA HR is decreasing rapidly. F2 AIC: 3316.09 RANK: 43 - M AIC: 4761.43 RANK: 163 SUM AIC: 8077.52 RANK: 109	HR estimates for FLAURA2 is going to extreme values near time 0. MARIPOSA HR goes to zero. FLAURA2 HR is increasing rapidly. F2 AIC: 3709.13 RANK: 98 - M AIC: 3341.5 RANK: 152 SUM AIC: 7050.63 RANK: 147
FP_-2_-0.5_-0.5	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. F2 AIC: 3316.5 RANK: 58 - M AIC: 4756.83 RANK: 10 SUM AIC: 8073.33 RANK: 14	HR estimates for FLAURA2 is going to extreme values near time 0. F2 AIC: 3709.53 RANK: 141 - M AIC: 3336.72 RANK: 9 SUM AIC: 7046.24 RANK: 16

FP_-2_-0.5_log(t)	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. F2 AIC: 3316.26 RANK: 50 - M AIC: 4758.16 RANK: 29 SUM AIC: 8074.42 RANK: 27	HR estimates for FLAURA2 is going to extreme values near time 0. F2 AIC: 3709.42 RANK: 133 - M AIC: 3338.49 RANK: 16 SUM AIC: 7047.91 RANK: 52
FP_-2_-0.5_0.5	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. F2 AIC: 3316.04 RANK: 40 - M AIC: 4759.22 RANK: 64 SUM AIC: 8075.26 RANK: 42	HR estimates for FLAURA2 is going to extreme values near time 0. F2 AIC: 3709.19 RANK: 104 - M AIC: 3339.91 RANK: 61 SUM AIC: 7049.1 RANK: 75
FP_-2_-0.5_1	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. MARIPOSA HR is decreasing rapidly. F2 AIC: 3315.89 RANK: 26 - M AIC: 4759.9 RANK: 103 SUM AIC: 8075.79 RANK: 54	HR estimates for FLAURA2 is going to extreme values near time 0. MARIPOSA HR is decreasing rapidly. F2 AIC: 3708.94 RANK: 73 - M AIC: 3340.74 RANK: 89 SUM AIC: 7049.68 RANK: 89
FP_-2_-0.5_2	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. MARIPOSA HR is decreasing rapidly. F2 AIC: 3315.9 RANK: 27 - M AIC: 4760.55 RANK: 155 SUM AIC: 8076.45 RANK: 68	HR estimates for FLAURA2 is going to extreme values near time 0. MARIPOSA HR is decreasing rapidly. FLAURA2 HR is increasing rapidly. F2 AIC: 3708.69 RANK: 60 - M AIC: 3341.33 RANK: 145 SUM AIC: 7050.02 RANK: 101
FP_-2_-0.5_3	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. MARIPOSA HR is decreasing rapidly. F2 AIC: 3316.18 RANK: 46 - M AIC: 4760.82 RANK: 160 SUM AIC: 8077 RANK: 85	HR estimates for FLAURA2 is going to extreme values near time 0. MARIPOSA HR is decreasing rapidly. FLAURA2 HR is increasing rapidly. F2 AIC: 3708.81 RANK: 66 - M AIC: 3341.44 RANK: 148 SUM AIC: 7050.25 RANK: 119
FP_-2_log(t)_log(t)	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. F2 AIC: 3316.16 RANK: 44 - M AIC: 4759.03 RANK: 53 SUM AIC: 8075.18 RANK: 39	HR estimates for FLAURA2 is going to extreme values near time 0. F2 AIC: 3709.1 RANK: 92 - M AIC: 3339.76 RANK: 55 SUM AIC: 7048.86 RANK: 69
FP_-2_0.5_log(t)	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. F2 AIC: 3316.05 RANK: 42 - M AIC: 4759.48 RANK: 70 SUM AIC: 8075.52 RANK: 48	HR estimates for FLAURA2 is going to extreme values near time 0. FLAURA2 HR increases rapidly. F2 AIC: 3708.72 RANK: 63 - M AIC: 3340.46 RANK: 79 SUM AIC: 7049.18 RANK: 78
FP_-2_1_log(t)	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. F2 AIC: 3315.98 RANK: 31 - M AIC: 4759.65 RANK: 74 SUM AIC: 8075.63 RANK: 49	HR estimates for FLAURA2 is going to extreme values near time 0. FLAURA2 HR increases rapidly. F2 AIC: 3708.42 RANK: 53 - M AIC: 3340.72 RANK: 88 SUM AIC: 7049.14 RANK: 77

FP_-2_2_log(t)	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. F2 AIC: 3316.01 RANK: 34 - M AIC: 4759.72 RANK: 78 SUM AIC: 8075.73 RANK: 50	HR estimates for FLAURA2 is going to extreme values near time 0. MARIPOSA HR is decreasing rapidly. FLAURA2 HR is increasing rapidly. F2 AIC: 3708.3 RANK: 50 - M AIC: 3340.81 RANK: 94 SUM AIC: 7049.11 RANK: 76
FP_-2_3_log(t)	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. F2 AIC: 3316.17 RANK: 45 - M AIC: 4759.71 RANK: 77 SUM AIC: 8075.88 RANK: 57	HR estimates for FLAURA2 is going to extreme values near time 0. MARIPOSA HR is decreasing rapidly. FLAURA2 HR is increasing rapidly. F2 AIC: 3708.61 RANK: 57 - M AIC: 3340.77 RANK: 92 SUM AIC: 7049.38 RANK: 83
FP_-2_0.5_0.5	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. F2 AIC: 3316.03 RANK: 38 - M AIC: 4759.4 RANK: 67 SUM AIC: 8075.43 RANK: 46	HR estimates for FLAURA2 is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. F2 AIC: 3708.28 RANK: 49 - M AIC: 3340.51 RANK: 82 SUM AIC: 7048.78 RANK: 66
FP_-2_0.5_1	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. F2 AIC: 3316.02 RANK: 35 - M AIC: 4759.27 RANK: 66 SUM AIC: 8075.29 RANK: 43	HR estimates for FLAURA2 is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. F2 AIC: 3708.04 RANK: 42 - M AIC: 3340.45 RANK: 77 SUM AIC: 7048.49 RANK: 62
FP_-2_0.5_2	FLAURA2 HR is going to extreme values near time 0. FLAURA2 and MARIPOSA HR are increasing rapidly. F2 AIC: 3316.04 RANK: 39 - M AIC: 4759.16 RANK: 63 SUM AIC: 8075.19 RANK: 41	HR estimates for FLAURA2 is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. F2 AIC: 3708.19 RANK: 45 - M AIC: 3340.47 RANK: 80 SUM AIC: 7048.66 RANK: 63
FP_-2_0.5_3	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is decreasing rapidly. MARIPOSA HR is increasing rapidly. F2 AIC: 3316.04 RANK: 41 - M AIC: 4759.14 RANK: 61 SUM AIC: 8075.19 RANK: 40	HR estimates for FLAURA2 is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. F2 AIC: 3708.71 RANK: 62 - M AIC: 3340.52 RANK: 83 SUM AIC: 7049.23 RANK: 79
FP_-2_1_1	FLAURA2 HR is going to extreme values near time 0. FLAURA2 and MARIPOSA HR are increasing rapidly. F2 AIC: 3316.03 RANK: 37 - M AIC: 4759.07 RANK: 56 SUM AIC: 8075.1 RANK: 38	HR estimates for FLAURA2 is going to extreme values near time 0. MARIPOSA and FLAURA2 HR are increasing rapidly. F2 AIC: 3707.94 RANK: 41 - M AIC: 3340.37 RANK: 73 SUM AIC: 7048.3 RANK: 59
FP_-2_1_2	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is decreasing rapidly. MARIPOSA HR is increasing rapidly. F2 AIC: 3315.97 RANK: 30 - M AIC: 4759.03 RANK: 54 SUM AIC: 8075.01 RANK: 34	HR estimates for FLAURA2 is going to extreme values near time 0. MARIPOSA and FLAURA2 HR are increasing rapidly. F2 AIC: 3708.38 RANK: 52 - M AIC: 3340.58 RANK: 84 SUM AIC: 7048.96 RANK: 71

FP_-2_1_3	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is decreasing rapidly. MARIPOSA HR is increasing rapidly. F2 AIC: 3315.8 RANK: 25 - M AIC: 4759.12 RANK: 58 SUM AIC: 8074.92 RANK: 33	HR estimates for FLAURA2 is going to extreme values near time 0. MARIPOSA and FLAURA2 HR are increasing rapidly. F2 AIC: 3709.01 RANK: 77 - M AIC: 3340.75 RANK: 90 SUM AIC: 7049.76 RANK: 91
FP_-2_2_2	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is decreasing rapidly. MARIPOSA HR is increasing rapidly. F2 AIC: 3315.62 RANK: 19 - M AIC: 4759.26 RANK: 65 SUM AIC: 8074.88 RANK: 32	HR estimates for FLAURA2 is going to extreme values near time 0. MARIPOSA and FLAURA2 HR are increasing rapidly. F2 AIC: 3709.06 RANK: 81 - M AIC: 3341.07 RANK: 115 SUM AIC: 7050.13 RANK: 110
FP_-2_2_3	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is decreasing rapidly. MARIPOSA HR is increasing rapidly. F2 AIC: 3315.05 RANK: 12 - M AIC: 4759.51 RANK: 71 SUM AIC: 8074.56 RANK: 29	HR estimates for FLAURA2 is going to extreme values near time 0. MARIPOSA and FLAURA2 HR are increasing rapidly. F2 AIC: 3709.51 RANK: 138 - M AIC: 3341.29 RANK: 142 SUM AIC: 7050.8 RANK: 156
FP_-2_3_3	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is decreasing rapidly. MARIPOSA HR is increasing rapidly. F2 AIC: 3314.14 RANK: 3 - M AIC: 4759.85 RANK: 88 SUM AIC: 8073.99 RANK: 24	HR estimates for FLAURA2 is going to extreme values near time 0. MARIPOSA HR is increasing rapidly. FLAURA2 HR is decreasing rapidly. F2 AIC: 3709.55 RANK: 143 - M AIC: 3341.5 RANK: 151 SUM AIC: 7051.05 RANK: 160
FP_-1_-1_-1	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR increases rapidly. F2 AIC: 3316.93 RANK: 88 - M AIC: 4755.75 RANK: 7 SUM AIC: 8072.68 RANK: 10	HR estimates for FLAURA2 is going to extreme values near time 0. F2 AIC: 3709.6 RANK: 147 - M AIC: 3335.22 RANK: 5 SUM AIC: 7044.82 RANK: 6
FP_-1_-1_-0.5	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR increases rapidly F2 AIC: 3316.78 RANK: 76 - M AIC: 4756.91 RANK: 11 SUM AIC: 8073.69 RANK: 19	HR estimates for FLAURA2 is going to extreme values near time 0. F2 AIC: 3709.71 RANK: 152 - M AIC: 3336.65 RANK: 8 SUM AIC: 7046.36 RANK: 18
FP_-1_-1_log(t)	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR increases rapidly. F2 AIC: 3316.57 RANK: 61 - M AIC: 4758.29 RANK: 39 SUM AIC: 8074.86 RANK: 31	HR estimates for FLAURA2 is going to extreme values near time 0. F2 AIC: 3709.7 RANK: 151 - M AIC: 3338.49 RANK: 18 SUM AIC: 7048.19 RANK: 56
FP_-1_-1_0.5	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. F2 AIC: 3316.37 RANK: 52 - M AIC: 4759.47 RANK: 69 SUM AIC: 8075.84 RANK: 55	HR estimates for FLAURA2 is going to extreme values near time 0. F2 AIC: 3709.55 RANK: 144 - M AIC: 3340.06 RANK: 63 SUM AIC: 7049.61 RANK: 87

FP_-1_-1_1	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. MARIPOSA HR is decreasing rapidly. F2 AIC: 3316.23 RANK: 48 - M AIC: 4760.28 RANK: 147 SUM AIC: 8076.51 RANK: 70	HR estimates for FLAURA2 is going to extreme values near time 0. F2 AIC: 3709.35 RANK: 125 - M AIC: 3341.02 RANK: 105 SUM AIC: 7050.38 RANK: 130
FP_-1_-1_2	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. MARIPOSA HR is decreasing rapidly. F2 AIC: 3316.23 RANK: 47 - M AIC: 4761.14 RANK: 162 SUM AIC: 8077.37 RANK: 103	HR estimates for FLAURA2 is going to extreme values near time 0. MARIPOSA HR is decreasing rapidly. FLAURA2 HR is increasing rapidly. F2 AIC: 3709.12 RANK: 95 - M AIC: 3341.78 RANK: 162 SUM AIC: 7050.9 RANK: 158
FP_-1_-1_3	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. MARIPOSA HR is decreasing rapidly. F2 AIC: 3316.47 RANK: 56 - M AIC: 4761.54 RANK: 164 SUM AIC: 8078.01 RANK: 123	HR estimates for FLAURA2 is going to extreme values near time 0. MARIPOSA HR is decreasing rapidly. FLAURA2 HR is increasing rapidly. F2 AIC: 3709.19 RANK: 103 - M AIC: 3341.97 RANK: 164 SUM AIC: 7051.15 RANK: 161
FP_-1_-0.5_-0.5	FLAURA2 HR is going to extreme values near time 0. F2 AIC: 3316.74 RANK: 73 - M AIC: 4758.02 RANK: 24 SUM AIC: 8074.76 RANK: 30	HR estimates for FLAURA2 is going to extreme values near time 0. F2 AIC: 3709.74 RANK: 154 - M AIC: 3338.09 RANK: 15 SUM AIC: 7047.83 RANK: 51
FP_-1_-0.5_log(t)	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. F2 AIC: 3316.64 RANK: 64 - M AIC: 4759.13 RANK: 60 SUM AIC: 8075.77 RANK: 53	HR estimates for FLAURA2 is going to extreme values near time 0. F2 AIC: 3709.63 RANK: 149 - M AIC: 3339.65 RANK: 51 SUM AIC: 7049.28 RANK: 80
FP_-1_-0.5_0.5	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. MARIPOSA HR is decreasing rapidly. F2 AIC: 3316.54 RANK: 60 - M AIC: 4759.93 RANK: 110 SUM AIC: 8076.46 RANK: 69	HR estimates for FLAURA2 is going to extreme values near time 0. F2 AIC: 3709.41 RANK: 131 - M AIC: 3340.76 RANK: 91 SUM AIC: 7050.17 RANK: 114
FP_-1_-0.5_1	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. MARIPOSA HR is decreasing rapidly. F2 AIC: 3316.45 RANK: 54 - M AIC: 4760.4 RANK: 152 SUM AIC: 8076.86 RANK: 83	HR estimates for FLAURA2 is going to extreme values near time 0. F2 AIC: 3709.18 RANK: 102 - M AIC: 3341.35 RANK: 147 SUM AIC: 7050.53 RANK: 142
FP_-1_-0.5_2	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. MARIPOSA HR is decreasing rapidly. F2 AIC: 3316.45 RANK: 55 - M AIC: 4760.82 RANK: 158 SUM AIC: 8077.27 RANK: 93	HR estimates for FLAURA2 is going to extreme values near time 0. MARIPOSA HR is decreasing rapidly. FLAURA2 HR is increasing rapidly. F2 AIC: 3708.99 RANK: 75 - M AIC: 3341.71 RANK: 157 SUM AIC: 7050.7 RANK: 153

FP_-1_-0.5_3	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. MARIPOSA HR is decreasing rapidly. F2 AIC: 3316.6 RANK: 63 - M AIC: 4760.97 RANK: 161 SUM AIC: 8077.57 RANK: 112	HR estimates for FLAURA2 is going to extreme values near time 0. MARIPOSA HR is decreasing rapidly. FLAURA2 HR is increasing rapidly. F2 AIC: 3709.13 RANK: 96 - M AIC: 3341.73 RANK: 160 SUM AIC: 7050.86 RANK: 157
FP_-1_log(t)_log(t)	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. F2 AIC: 3316.67 RANK: 69 - M AIC: 4759.76 RANK: 83 SUM AIC: 8076.43 RANK: 66	HR estimates for FLAURA2 is going to extreme values near time 0. F2 AIC: 3709.42 RANK: 132 - M AIC: 3340.6 RANK: 85 SUM AIC: 7050.01 RANK: 100
FP_-1_0.5_log(t)	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. F2 AIC: 3316.66 RANK: 68 - M AIC: 4760.07 RANK: 129 SUM AIC: 8076.73 RANK: 78	HR estimates for FLAURA2 is going to extreme values near time 0. FLAURA2 HR increases rapidly. F2 AIC: 3709.13 RANK: 97 - M AIC: 3341.07 RANK: 116 SUM AIC: 7050.2 RANK: 116
FP_-1_1_log(t)	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. F2 AIC: 3316.65 RANK: 65 - M AIC: 4760.17 RANK: 138 SUM AIC: 8076.81 RANK: 80	HR estimates for FLAURA2 is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. F2 AIC: 3708.9 RANK: 72 - M AIC: 3341.23 RANK: 134 SUM AIC: 7050.13 RANK: 108
FP_-1_2_log(t)	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. F2 AIC: 3316.65 RANK: 66 - M AIC: 4760.19 RANK: 140 SUM AIC: 8076.84 RANK: 81	HR estimates for FLAURA2 is going to extreme values near time 0. MARIPOSA HR is decreasing rapidly. FLAURA2 HR is increasing rapidly. F2 AIC: 3708.81 RANK: 69 - M AIC: 3341.27 RANK: 140 SUM AIC: 7050.08 RANK: 104
FP_-1_3_log(t)	FLAURA2 HR is going to extreme values near time 0. FLAURA2 and MARIPOSA HR are increasing rapidly. F2 AIC: 3316.67 RANK: 70 - M AIC: 4760.18 RANK: 139 SUM AIC: 8076.85 RANK: 82	HR estimates for FLAURA2 is going to extreme values near time 0. MARIPOSA HR is decreasing rapidly. FLAURA2 HR is increasing rapidly. F2 AIC: 3709.07 RANK: 82 - M AIC: 3341.22 RANK: 129 SUM AIC: 7050.29 RANK: 123
FP_-1_0.5_0.5	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. F2 AIC: 3316.74 RANK: 74 - M AIC: 4759.98 RANK: 119 SUM AIC: 8076.72 RANK: 77	HR estimates for FLAURA2 is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. F2 AIC: 3708.83 RANK: 70 - M AIC: 3341.05 RANK: 111 SUM AIC: 7049.88 RANK: 94
FP_-1_0.5_1	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. F2 AIC: 3316.78 RANK: 79 - M AIC: 4759.87 RANK: 92 SUM AIC: 8076.64 RANK: 76	HR estimates for FLAURA2 is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. F2 AIC: 3708.65 RANK: 58 - M AIC: 3340.99 RANK: 102 SUM AIC: 7049.64 RANK: 88

FP_-1_0.5_2	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is decreasing rapidly. MARIPOSA HR is increasing rapidly. F2 AIC: 3316.77 RANK: 75 - M AIC: 4759.77 RANK: 84 SUM AIC: 8076.54 RANK: 71	HR estimates for FLAURA2 is going to extreme values near time 0. MARIPOSA and FLAURA2 are increasing rapidly. F2 AIC: 3708.74 RANK: 64 - M AIC: 3341.04 RANK: 107 SUM AIC: 7049.78 RANK: 92
FP_-1_0.5_3	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is decreasing rapidly. MARIPOSA HR is increasing rapidly. F2 AIC: 3316.65 RANK: 67 - M AIC: 4759.76 RANK: 82 SUM AIC: 8076.41 RANK: 65	HR estimates for FLAURA2 is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. F2 AIC: 3709.09 RANK: 89 - M AIC: 3341.08 RANK: 117 SUM AIC: 7050.17 RANK: 113
FP_-1_1_1	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is decreasing rapidly. MARIPOSA HR is increasing rapidly. F2 AIC: 3316.84 RANK: 86 - M AIC: 4759.7 RANK: 76 SUM AIC: 8076.54 RANK: 73	HR estimates for FLAURA2 is going to extreme values near time 0. MARIPOSA and FLAURA2 HR are increasing rapidly. F2 AIC: 3708.56 RANK: 56 - M AIC: 3340.95 RANK: 100 SUM AIC: 7049.51 RANK: 86
FP_-1_1_2	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is decreasing rapidly. MARIPOSA HR is increasing rapidly. F2 AIC: 3316.78 RANK: 77 - M AIC: 4759.68 RANK: 75 SUM AIC: 8076.45 RANK: 67	HR estimates for FLAURA2 is going to extreme values near time 0. MARIPOSA and FLAURA2 HR are increasing rapidly. F2 AIC: 3708.81 RANK: 68 - M AIC: 3341.17 RANK: 127 SUM AIC: 7049.98 RANK: 97
FP_-1_1_3	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is decreasing rapidly. MARIPOSA HR is increasing rapidly. F2 AIC: 3316.52 RANK: 59 - M AIC: 4759.74 RANK: 80 SUM AIC: 8076.26 RANK: 61	HR estimates for FLAURA2 is going to extreme values near time 0. MARIPOSA and FLAURA2 HR are increasing rapidly. F2 AIC: 3709.16 RANK: 101 - M AIC: 3341.32 RANK: 144 SUM AIC: 7050.48 RANK: 135
FP_-1_2_2	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is decreasing rapidly. MARIPOSA HR is increasing rapidly. F2 AIC: 3316.49 RANK: 57 - M AIC: 4759.86 RANK: 91 SUM AIC: 8076.34 RANK: 63	HR estimates for FLAURA2 is going to extreme values near time 0. MARIPOSA and FLAURA2 HR are increasing rapidly. F2 AIC: 3709.08 RANK: 86 - M AIC: 3341.6 RANK: 155 SUM AIC: 7050.68 RANK: 151
FP_-1_2_3	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is decreasing rapidly. MARIPOSA HR is increasing rapidly. F2 AIC: 3315.93 RANK: 28 - M AIC: 4760.06 RANK: 127 SUM AIC: 8075.99 RANK: 59	HR estimates for FLAURA2 is going to extreme values near time 0. MARIPOSA HR is increasing rapidly. FLAURA2 HR is decreasing rapidly. F2 AIC: 3709.14 RANK: 99 - M AIC: 3341.78 RANK: 161 SUM AIC: 7050.92 RANK: 159
FP_-1_3_3	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is decreasing rapidly. MARIPOSA HR is increasing rapidly. F2 AIC: 3315.13 RANK: 13 - M AIC: 4760.32 RANK: 148 SUM AIC: 8075.45 RANK: 47	HR estimates for FLAURA2 is going to extreme values near time 0. MARIPOSA and FLAURA2 HR are decreasing rapidly. F2 AIC: 3708.84 RANK: 71 - M AIC: 3341.92 RANK: 163 SUM AIC: 7050.76 RANK: 154

FP_-0.5_-0.5_-0.5	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is increasing above 1. F2 AIC: 3316.8 RANK: 81 - M AIC: 4758.93 RANK: 51 SUM AIC: 8075.73 RANK: 52	HR estimates for FLAURA2 is going to extreme values near time 0. F2 AIC: 3709.75 RANK: 155 - M AIC: 3339.31 RANK: 40 SUM AIC: 7049.07 RANK: 73
FP_-0.5_-0.5_log(t)	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is increasing above 1. F2 AIC: 3316.82 RANK: 85 - M AIC: 4759.72 RANK: 79 SUM AIC: 8076.54 RANK: 74	HR estimates for FLAURA2 is going to extreme values near time 0. F2 AIC: 3709.63 RANK: 150 - M AIC: 3340.46 RANK: 78 SUM AIC: 7050.09 RANK: 105
FP_-0.5_-0.5_0.5	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. F2 AIC: 3316.81 RANK: 82 - M AIC: 4760.21 RANK: 144 SUM AIC: 8077.01 RANK: 86	HR estimates for FLAURA2 is going to extreme values near time 0. FLAURA2 HR is increasing above 1. F2 AIC: 3709.41 RANK: 130 - M AIC: 3341.15 RANK: 124 SUM AIC: 7050.56 RANK: 145
FP_-0.5_-0.5_1	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. F2 AIC: 3316.78 RANK: 80 - M AIC: 4760.45 RANK: 153 SUM AIC: 8077.23 RANK: 91	HR estimates for FLAURA2 is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. F2 AIC: 3709.2 RANK: 106 - M AIC: 3341.46 RANK: 150 SUM AIC: 7050.66 RANK: 149
FP_-0.5_-0.5_2	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. F2 AIC: 3316.78 RANK: 78 - M AIC: 4760.61 RANK: 156 SUM AIC: 8077.39 RANK: 104	HR estimates for FLAURA2 is going to extreme values near time 0. MARIPOSA HR is decreasing rapidly. FLAURA2 HR is increasing rapidly. F2 AIC: 3709.07 RANK: 84 - M AIC: 3341.59 RANK: 154 SUM AIC: 7050.66 RANK: 150
FP_-0.5_-0.5_3	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. F2 AIC: 3316.82 RANK: 84 - M AIC: 4760.65 RANK: 157 SUM AIC: 8077.47 RANK: 108	HR estimates for FLAURA2 is going to extreme values near time 0. MARIPOSA HR is decreasing rapidly. FLAURA2 HR is increasing rapidly. F2 AIC: 3709.25 RANK: 113 - M AIC: 3341.55 RANK: 153 SUM AIC: 7050.8 RANK: 155
FP_-0.5_log(t)_log(t)	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. F2 AIC: 3316.96 RANK: 89 - M AIC: 4760.1 RANK: 133 SUM AIC: 8077.06 RANK: 87	HR estimates for FLAURA2 is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. F2 AIC: 3709.5 RANK: 137 - M AIC: 3341.02 RANK: 104 SUM AIC: 7050.51 RANK: 140
FP_-0.5_0.5_log(t)	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. F2 AIC: 3317.05 RANK: 92 - M AIC: 4760.23 RANK: 145 SUM AIC: 8077.28 RANK: 94	HR estimates for FLAURA2 is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. F2 AIC: 3709.28 RANK: 118 - M AIC: 3341.22 RANK: 130 SUM AIC: 7050.5 RANK: 138

FP_-0.5_1_log(t)	FLAURA2 HR is going to extreme values near time 0. F2 AIC: 3317.09 RANK: 93 - M AIC: 4760.23 RANK: 146 SUM AIC: 8077.32 RANK: 99	HR estimates for FLAURA2 is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. F2 AIC: 3709.11 RANK: 93 - M AIC: 3341.25 RANK: 138 SUM AIC: 7050.36 RANK: 127
FP_-0.5_2_log(t)	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is decreasing rapidly. MARIPOSA HR is increasing rapidly. F2 AIC: 3317.09 RANK: 94 - M AIC: 4760.19 RANK: 142 SUM AIC: 8077.28 RANK: 95	HR estimates for FLAURA2 is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. F2 AIC: 3709.08 RANK: 88 - M AIC: 3341.25 RANK: 137 SUM AIC: 7050.33 RANK: 126
FP_-0.5_3_log(t)	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is decreasing rapidly. MARIPOSA HR is increasing rapidly. F2 AIC: 3317.02 RANK: 91 - M AIC: 4760.17 RANK: 136 SUM AIC: 8077.19 RANK: 90	HR estimates for FLAURA2 is going to extreme values near time 0. MARIPOSA HR is decreasing rapidly. FLAURA2 HR is increasing rapidly. F2 AIC: 3709.29 RANK: 119 - M AIC: 3341.23 RANK: 132 SUM AIC: 7050.52 RANK: 141
FP_-0.5_0.5_0.5	FLAURA2 HR is going to extreme values near time 0. F2 AIC: 3317.22 RANK: 99 - M AIC: 4760.1 RANK: 132 SUM AIC: 8077.32 RANK: 100	HR estimates for FLAURA2 is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. F2 AIC: 3709.1 RANK: 91 - M AIC: 3341.1 RANK: 119 SUM AIC: 7050.2 RANK: 115
FP_-0.5_0.5_1	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is decreasing rapidly. MARIPOSA HR is increasing rapidly. F2 AIC: 3317.32 RANK: 103 - M AIC: 4759.99 RANK: 122 SUM AIC: 8077.31 RANK: 98	HR estimates for FLAURA2 is going to extreme values near time 0. MARIPOSA and FLAURA2 HR are increasing rapidly. F2 AIC: 3708.99 RANK: 76 - M AIC: 3341.04 RANK: 109 SUM AIC: 7050.03 RANK: 103
FP_-0.5_0.5_2	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is decreasing rapidly. MARIPOSA HR is increasing rapidly. F2 AIC: 3317.33 RANK: 104 - M AIC: 4759.93 RANK: 107 SUM AIC: 8077.25 RANK: 92	HR estimates for FLAURA2 is going to extreme values near time 0. MARIPOSA and FLAURA2 HR are increasing rapidly. F2 AIC: 3709.07 RANK: 83 - M AIC: 3341.15 RANK: 125 SUM AIC: 7050.22 RANK: 118
FP_-0.5_0.5_3	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is decreasing rapidly. MARIPOSA HR is increasing rapidly. F2 AIC: 3317.15 RANK: 97 - M AIC: 4759.94 RANK: 112 SUM AIC: 8077.08 RANK: 88	HR estimates for FLAURA2 is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. F2 AIC: 3709.28 RANK: 117 - M AIC: 3341.23 RANK: 133 SUM AIC: 7050.51 RANK: 139
FP_-0.5_1_1	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is decreasing rapidly. MARIPOSA HR is increasing rapidly. F2 AIC: 3317.45 RANK: 108 - M AIC: 4759.88 RANK: 96 SUM AIC: 8077.33 RANK: 102	HR estimates for FLAURA2 is going to extreme values near time 0. MARIPOSA and FLAURA2 HR are increasing rapidly. F2 AIC: 3708.95 RANK: 74 - M AIC: 3341.06 RANK: 114 SUM AIC: 7050.01 RANK: 99

FP_-0.5_1_2	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is decreasing rapidly. MARIPOSA HR is increasing rapidly. F2 AIC: 3317.43 RANK: 107 - M AIC: 4759.9 RANK: 104 SUM AIC: 8077.33 RANK: 101	HR estimates for FLAURA2 is going to extreme values near time 0. MARIPOSA and FLAURA2 HR are increasing rapidly. F2 AIC: 3709.08 RANK: 87 - M AIC: 3341.34 RANK: 146 SUM AIC: 7050.41 RANK: 132
FP_-0.5_1_3	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is decreasing rapidly. MARIPOSA HR is increasing rapidly. F2 AIC: 3317.13 RANK: 96 - M AIC: 4759.97 RANK: 118 SUM AIC: 8077.1 RANK: 89	HR estimates for FLAURA2 is going to extreme values near time 0. FLAURA2 and MARIPOSA HRs are increasing rapidly. F2 AIC: 3709.2 RANK: 105 - M AIC: 3341.46 RANK: 149 SUM AIC: 7050.65 RANK: 148
FP_-0.5_2_2	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is decreasing rapidly. MARIPOSA HR is increasing rapidly. F2 AIC: 3317.23 RANK: 101 - M AIC: 4760.06 RANK: 128 SUM AIC: 8077.29 RANK: 97	HR estimates for FLAURA2 is going to extreme values near time 0. MARIPOSA HR increases over time. F2 AIC: 3709.03 RANK: 79 - M AIC: 3341.66 RANK: 156 SUM AIC: 7050.69 RANK: 152
FP_-0.5_2_3	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is decreasing rapidly. MARIPOSA HR is increasing rapidly. F2 AIC: 3316.71 RANK: 72 - M AIC: 4760.19 RANK: 141 SUM AIC: 8076.9 RANK: 84	HR estimates for FLAURA2 is going to extreme values near time 0. MARIPOSA and FLAURA2 HR are decreasing rapidly. F2 AIC: 3708.79 RANK: 65 - M AIC: 3341.71 RANK: 158 SUM AIC: 7050.5 RANK: 137
FP_-0.5_3_3	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is decreasing rapidly. MARIPOSA HR is increasing rapidly. F2 AIC: 3316 RANK: 33 - M AIC: 4760.34 RANK: 149 SUM AIC: 8076.34 RANK: 64	HR estimates for FLAURA2 is going to extreme values near time 0. MARIPOSA and FLAURA2 HR are decreasing rapidly. F2 AIC: 3708.2 RANK: 46 - M AIC: 3341.73 RANK: 159 SUM AIC: 7049.93 RANK: 95
FP_log(t)_log(t)_log(t)	FLAURA2 HR is going to extreme values near time 0. F2 AIC: 3317.23 RANK: 100 - M AIC: 4760.2 RANK: 143 SUM AIC: 8077.42 RANK: 106	FLAURA2 HR is increasing rapidly. F2 AIC: 3709.44 RANK: 134 - M AIC: 3341.14 RANK: 121 SUM AIC: 7050.59 RANK: 146
FP_0.5_log(t)_log(t)	FLAURA2 HR is going to extreme values near time 0. F2 AIC: 3317.42 RANK: 106 - M AIC: 4760.12 RANK: 135 SUM AIC: 8077.54 RANK: 111	FLAURA2 HR is increasing rapidly. F2 AIC: 3709.31 RANK: 120 - M AIC: 3341.05 RANK: 112 SUM AIC: 7050.37 RANK: 128
FP_1_log(t)_log(t)	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is decreasing rapidly. F2 AIC: 3317.53 RANK: 110 - M AIC: 4760.04 RANK: 125 SUM AIC: 8077.57 RANK: 113	MARIPOSA and FLAURA2 HRs are increasing above 1. F2 AIC: 3709.21 RANK: 108 - M AIC: 3341 RANK: 103 SUM AIC: 7050.21 RANK: 117
FP_2_log(t)_log(t)	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is decreasing rapidly. MARIPOSA HR is increasing rapidly. F2 AIC: 3317.56 RANK: 111 - M AIC: 4759.98 RANK: 120 SUM AIC: 8077.54 RANK: 110	MARIPOSA and FLAURA2 HRs are increasing above 1. F2 AIC: 3709.24 RANK: 112 - M AIC: 3341.09 RANK: 118 SUM AIC: 7050.33 RANK: 125

FP_3_log(t)_log(t)	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is decreasing rapidly. MARIPOSA HR is increasing rapidly. F2 AIC: 3317.41 RANK: 105 - M AIC: 4759.98 RANK: 121 SUM AIC: 8077.39 RANK: 105	FLAURA2 HRs is increasing rapidly. F2 AIC: 3709.4 RANK: 129 - M AIC: 3341.14 RANK: 122 SUM AIC: 7050.54 RANK: 144
FP_0.5_0.5_log(t)	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is decreasing rapidly. F2 AIC: 3317.71 RANK: 112 - M AIC: 4759.95 RANK: 117 SUM AIC: 8077.66 RANK: 114	MARIPOSA and FLAURA2 HRs are increasing above 1. F2 AIC: 3709.26 RANK: 114 - M AIC: 3340.87 RANK: 95 SUM AIC: 7050.13 RANK: 111
FP_0.5_1_log(t)	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is decreasing rapidly. MARIPOSA HR is increasing rapidly. F2 AIC: 3317.9 RANK: 116 - M AIC: 4759.87 RANK: 93 SUM AIC: 8077.77 RANK: 116	MARIPOSA and FLAURA2 HRs are increasing above 1. F2 AIC: 3709.23 RANK: 111 - M AIC: 3340.9 RANK: 96 SUM AIC: 7050.13 RANK: 109
FP_0.5_2_log(t)	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is decreasing rapidly. MARIPOSA HR is increasing rapidly. F2 AIC: 3317.96 RANK: 118 - M AIC: 4759.89 RANK: 101 SUM AIC: 8077.86 RANK: 119	MARIPOSA and FLAURA2 HRs are increasing above 1. F2 AIC: 3709.28 RANK: 116 - M AIC: 3341.15 RANK: 123 SUM AIC: 7050.43 RANK: 133
FP_0.5_3_log(t)	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is decreasing rapidly. MARIPOSA HR is increasing rapidly. F2 AIC: 3317.74 RANK: 113 - M AIC: 4759.94 RANK: 115 SUM AIC: 8077.68 RANK: 115	FLAURA2 HR is increasing above 1. Resulting OS curve for OSICP is below that of OSI. F2 AIC: 3709.31 RANK: 121 - M AIC: 3341.22 RANK: 131 SUM AIC: 7050.54 RANK: 143
FP_1_1_log(t)	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is decreasing rapidly. MARIPOSA HR is increasing rapidly. F2 AIC: 3318.14 RANK: 122 - M AIC: 4759.85 RANK: 89 SUM AIC: 8077.99 RANK: 122	MARIPOSA and FLAURA2 HRs are both increasing above 1. F2 AIC: 3709.23 RANK: 110 - M AIC: 3341.04 RANK: 108 SUM AIC: 7050.27 RANK: 120
FP_1_2_log(t)	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is decreasing rapidly. MARIPOSA HR is increasing rapidly. F2 AIC: 3318.22 RANK: 124 - M AIC: 4759.94 RANK: 113 SUM AIC: 8078.16 RANK: 127	FLAURA2 and MARIPOSA HRs are both increasing above 1. F2 AIC: 3709.2 RANK: 107 - M AIC: 3341.28 RANK: 141 SUM AIC: 7050.48 RANK: 136
FP_1_3_log(t)	FLAURA2 HR is decreasing rapidly. MARIPOSA HR is increasing rapidly. F2 AIC: 3317.92 RANK: 117 - M AIC: 4760 RANK: 124 SUM AIC: 8077.92 RANK: 120	MARIPOSA and FLAURA2 HR are decreasing rapidly. F2 AIC: 3709.06 RANK: 80 - M AIC: 3341.25 RANK: 136 SUM AIC: 7050.31 RANK: 124

FP_2_2_log(t)	FLAURA2 HR is decreasing rapidly. MARIPOSA HR is increasing rapidly. F2 AIC: 3318.21 RANK: 123 - M AIC: 4760.05 RANK: 126 SUM AIC: 8078.25 RANK: 130	MARIPOSA and FLAURA2 HR are decreasing rapidly. F2 AIC: 3708.81 RANK: 67 - M AIC: 3341.21 RANK: 128 SUM AIC: 7050.02 RANK: 102
FP_2_3_log(t)	FLAURA2 HR is decreasing rapidly. MARIPOSA HR is increasing rapidly. F2 AIC: 3317.75 RANK: 114 - M AIC: 4760.09 RANK: 131 SUM AIC: 8077.84 RANK: 117	MARIPOSA and FLAURA2 HR are decreasing rapidly. F2 AIC: 3708.25 RANK: 48 - M AIC: 3341.04 RANK: 110 SUM AIC: 7049.3 RANK: 81
FP_3_3_log(t)	FLAURA2 HR is decreasing rapidly. MARIPOSA HR is increasing rapidly. F2 AIC: 3317.17 RANK: 98 - M AIC: 4760.12 RANK: 134 SUM AIC: 8077.29 RANK: 96	MARIPOSA and FLAURA2 HR are decreasing rapidly. F2 AIC: 3707.44 RANK: 21 - M AIC: 3340.91 RANK: 98 SUM AIC: 7048.35 RANK: 60
FP_0.5_0.5_0.5	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is decreasing rapidly. MARIPOSA HR is increasing rapidly. F2 AIC: 3318.14 RANK: 121 - M AIC: 4759.81 RANK: 86 SUM AIC: 8077.95 RANK: 121	MARIPOSA and FLAURA2 HRs are increasing rapidly. F2 AIC: 3709.32 RANK: 123 - M AIC: 3340.8 RANK: 93 SUM AIC: 7050.11 RANK: 106
FP_0.5_0.5_1	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is decreasing rapidly. MARIPOSA HR is increasing rapidly. F2 AIC: 3318.44 RANK: 128 - M AIC: 4759.81 RANK: 85 SUM AIC: 8078.25 RANK: 129	MARIPOSA and FLAURA2 HRs are increasing rapidly. F2 AIC: 3709.32 RANK: 124 - M AIC: 3340.95 RANK: 101 SUM AIC: 7050.27 RANK: 121
FP_0.5_0.5_2	FLAURA2 HR is decreasing rapidly. MARIPOSA HR is increasing rapidly. F2 AIC: 3318.58 RANK: 129 - M AIC: 4759.9 RANK: 102 SUM AIC: 8078.48 RANK: 134	MARIPOSA is decreasing, FLAURA2 HR is increasing then decreasing. The resulting osicp OS curve goes below osi mono. F2 AIC: 3709.27 RANK: 115 - M AIC: 3341.12 RANK: 120 SUM AIC: 7050.4 RANK: 131
FP_0.5_0.5_3	FLAURA2 HR is decreasing rapidly. MARIPOSA HR is increasing rapidly. F2 AIC: 3318.33 RANK: 125 - M AIC: 4759.95 RANK: 116 SUM AIC: 8078.28 RANK: 131	MARIPOSA and FLAURA2 HR are decreasing rapidly. F2 AIC: 3709.09 RANK: 90 - M AIC: 3341.03 RANK: 106 SUM AIC: 7050.12 RANK: 107
FP_0.5_1_1	FLAURA2 HR is decreasing rapidly. MARIPOSA HR is increasing rapidly. F2 AIC: 3318.82 RANK: 136 - M AIC: 4759.85 RANK: 87 SUM AIC: 8078.66 RANK: 138	MARIPOSA and FLAURA2 HRs are increasing. F2 AIC: 3709.31 RANK: 122 - M AIC: 3341.06 RANK: 113 SUM AIC: 7050.37 RANK: 129
FP_0.5_1_2	FLAURA2 HR is decreasing rapidly. MARIPOSA HR is increasing rapidly. F2 AIC: 3319.01 RANK: 138 - M AIC: 4759.92 RANK: 105 SUM AIC: 8078.93 RANK: 143	MARIPOSA and FLAURA2 HR are decreasing rapidly. F2 AIC: 3709.07 RANK: 85 - M AIC: 3340.91 RANK: 99 SUM AIC: 7049.99 RANK: 98

FP_0.5_1_3	FLAURA2 HR is decreasing rapidly. MARIPOSA HR is increasing rapidly. F2 AIC: 3318.7 RANK: 134 - M AIC: 4759.94 RANK: 114 SUM AIC: 8078.64 RANK: 137	MARIPOSA and FLAURA2 HR are decreasing rapidly. F2 AIC: 3708.65 RANK: 59 - M AIC: 3340.67 RANK: 87 SUM AIC: 7049.32 RANK: 82
FP_0.5_2_2	FLAURA2 HR is decreasing rapidly. MARIPOSA HR is increasing rapidly. F2 AIC: 3319.1 RANK: 139 - M AIC: 4759.93 RANK: 109 SUM AIC: 8079.03 RANK: 145	MARIPOSA and FLAURA2 HR are decreasing rapidly. F2 AIC: 3708.34 RANK: 51 - M AIC: 3340.36 RANK: 70 SUM AIC: 7048.7 RANK: 65
FP_0.5_2_3	FLAURA2 HR is decreasing rapidly. MARIPOSA HR is increasing rapidly. F2 AIC: 3318.65 RANK: 131 - M AIC: 4759.93 RANK: 108 SUM AIC: 8078.57 RANK: 136	MARIPOSA and FLAURA2 HR are decreasing rapidly. F2 AIC: 3707.57 RANK: 26 - M AIC: 3340.14 RANK: 68 SUM AIC: 7047.7 RANK: 50
FP_0.5_3_3	MARIPOSA and FLAURA2 HR are decreasing rapidly. F2 AIC: 3318.08 RANK: 120 - M AIC: 4759.93 RANK: 111 SUM AIC: 8078.01 RANK: 124	MARIPOSA and FLAURA2 HR are decreasing rapidly. F2 AIC: 3706.68 RANK: 9 - M AIC: 3340.1 RANK: 67 SUM AIC: 7046.78 RANK: 32
FP_1_1_1	FLAURA2 HR is decreasing rapidly. MARIPOSA HR is increasing rapidly. F2 AIC: 3319.29 RANK: 141 - M AIC: 4759.87 RANK: 94 SUM AIC: 8079.16 RANK: 147	MARIPOSA and FLAURA2 HR are decreasing rapidly. F2 AIC: 3709.22 RANK: 109 - M AIC: 3340.91 RANK: 97 SUM AIC: 7050.13 RANK: 112
FP_1_1_2	FLAURA2 HR is decreasing rapidly. MARIPOSA HR is increasing rapidly. F2 AIC: 3319.49 RANK: 143 - M AIC: 4759.88 RANK: 98 SUM AIC: 8079.37 RANK: 150	MARIPOSA and FLAURA2 HR are decreasing rapidly. F2 AIC: 3708.71 RANK: 61 - M AIC: 3340.36 RANK: 71 SUM AIC: 7049.07 RANK: 74
FP_1_1_3	FLAURA2 HR is decreasing rapidly. F2 AIC: 3319.12 RANK: 140 - M AIC: 4759.88 RANK: 97 SUM AIC: 8079.01 RANK: 144	MARIPOSA and FLAURA2 HR are decreasing rapidly. F2 AIC: 3708.05 RANK: 43 - M AIC: 3340.06 RANK: 64 SUM AIC: 7048.11 RANK: 54
FP_1_2_2	MARIPOSA and FLAURA2 HR are decreasing rapidly. F2 AIC: 3319.53 RANK: 144 - M AIC: 4759.85 RANK: 90 SUM AIC: 8079.38 RANK: 151	MARIPOSA and FLAURA2 HR are decreasing rapidly. F2 AIC: 3707.71 RANK: 34 - M AIC: 3339.64 RANK: 50 SUM AIC: 7047.35 RANK: 45
FP_1_2_3	MARIPOSA and FLAURA2 HR are decreasing rapidly. F2 AIC: 3319 RANK: 137 - M AIC: 4759.87 RANK: 95 SUM AIC: 8078.87 RANK: 141	MARIPOSA and FLAURA2 HR are decreasing rapidly. F2 AIC: 3706.84 RANK: 10 - M AIC: 3339.6 RANK: 49 SUM AIC: 7046.45 RANK: 19
FP_1_3_3	MARIPOSA and FLAURA2 HR are decreasing rapidly. F2 AIC: 3318.38 RANK: 127 - M AIC: 4759.92 RANK: 106 SUM AIC: 8078.3 RANK: 132	MARIPOSA and FLAURA2 HR are decreasing rapidly. F2 AIC: 3706.05 RANK: 6 - M AIC: 3339.85 RANK: 59 SUM AIC: 7045.9 RANK: 14
FP_2_2_2	MARIPOSA and FLAURA2 HR are decreasing rapidly. F2 AIC: 3319.36 RANK: 142 - M AIC: 4759.89 RANK: 99 SUM AIC: 8079.25 RANK: 148	MARIPOSA and FLAURA2 HR are decreasing rapidly. F2 AIC: 3706.51 RANK: 7 - M AIC: 3339.32 RANK: 41 SUM AIC: 7045.83 RANK: 12

FP_2_2_3	MARIPOSA and FLAURA2 HR are decreasing rapidly. F2 AIC: 3318.71 RANK: 135 - M AIC: 4760 RANK: 123 SUM AIC: 8078.71 RANK: 139	MARIPOSA and FLAURA2 HR are decreasing rapidly. F2 AIC: 3705.8 RANK: 5 - M AIC: 3339.78 RANK: 56 SUM AIC: 7045.59 RANK: 11
FP_2_3_3	MARIPOSA and FLAURA2 HR are decreasing rapidly. F2 AIC: 3318.05 RANK: 119 - M AIC: 4760.17 RANK: 137 SUM AIC: 8078.22 RANK: 128	MARIPOSA and FLAURA2 HR are decreasing rapidly. F2 AIC: 3705.44 RANK: 1 - M AIC: 3340.49 RANK: 81 SUM AIC: 7045.94 RANK: 15
FP_3_3_3	MARIPOSA and FLAURA2 HR are decreasing rapidly. F2 AIC: 3317.47 RANK: 109 - M AIC: 4760.38 RANK: 150 SUM AIC: 8077.85 RANK: 118	MARIPOSA and FLAURA2 HR are decreasing rapidly. F2 AIC: 3705.57 RANK: 2 - M AIC: 3341.32 RANK: 143 SUM AIC: 7046.89 RANK: 35
FP_-2_-2	FLAURA2 HR is going to extreme values near time 0. F2 AIC: 3316.02 RANK: 36 - M AIC: 4759.89 RANK: 100 SUM AIC: 8075.92 RANK: 58	HR estimates for FLAURA2 is going to extreme values near time 0. F2 AIC: 3707.76 RANK: 37 - M AIC: 3340.45 RANK: 76 SUM AIC: 7048.21 RANK: 57
FP_-2_-1	FLAURA2 HR is going to extreme values near time 0. F2 AIC: 3315.33 RANK: 16 - M AIC: 4760.4 RANK: 151 SUM AIC: 8075.73 RANK: 51	HR estimates for FLAURA2 is going to extreme values near time 0. F2 AIC: 3707.59 RANK: 29 - M AIC: 3341.26 RANK: 139 SUM AIC: 7048.85 RANK: 68
FP_-2_-0.5	FLAURA2 HR is going to extreme values near time 0. F2 AIC: 3314.81 RANK: 7 - M AIC: 4759.13 RANK: 59 SUM AIC: 8073.94 RANK: 23	HR estimates for FLAURA2 is going to extreme values near time 0. F2 AIC: 3707.53 RANK: 23 - M AIC: 3340.39 RANK: 75 SUM AIC: 7047.92 RANK: 53
FP_-2_log(t)	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. F2 AIC: 3314.32 RANK: 4 - M AIC: 4757.72 RANK: 17 SUM AIC: 8072.04 RANK: 8	HR estimates for FLAURA2 is going to extreme values near time 0. F2 AIC: 3707.64 RANK: 31 - M AIC: 3338.94 RANK: 25 SUM AIC: 7046.57 RANK: 23
FP_-2_0.5	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. F2 AIC: 3314.05 RANK: 1 - M AIC: 4757.48 RANK: 16 SUM AIC: 8071.53 RANK: 3	HR estimates for FLAURA2 is going to extreme values near time 0. F2 AIC: 3707.78 RANK: 39 - M AIC: 3338.52 RANK: 20 SUM AIC: 7046.29 RANK: 17
FP_-2_1	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. MARIPOSA HR is decreasing rapidly. F2 AIC: 3314.09 RANK: 2 - M AIC: 4757.9 RANK: 19 SUM AIC: 8071.99 RANK: 6	HR estimates for FLAURA2 is going to extreme values near time 0. MARIPOSA HR is decreasing rapidly. F2 AIC: 3707.79 RANK: 40 - M AIC: 3338.81 RANK: 23 SUM AIC: 7046.6 RANK: 24
FP_-2_2	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. MARIPOSA HR is decreasing rapidly. F2 AIC: 3314.99 RANK: 10 - M AIC: 4758.84 RANK: 50 SUM AIC: 8073.82 RANK: 21	HR estimates for FLAURA2 is going to extreme values near time 0. MARIPOSA HR is decreasing rapidly. FLAURA2 HR is increasing rapidly. F2 AIC: 3707.63 RANK: 30 - M AIC: 3339.37 RANK: 44 SUM AIC: 7047 RANK: 38

FP_-2_3	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. MARIPOSA HR is decreasing rapidly. F2 AIC: 3316.44 RANK: 53 - M AIC: 4759.43 RANK: 68 SUM AIC: 8075.87 RANK: 56	HR estimates for FLAURA2 is going to extreme values near time 0. MARIPOSA HR is decreasing rapidly. FLAURA2 HR is increasing rapidly. F2 AIC: 3707.58 RANK: 28 - M AIC: 3339.59 RANK: 48 SUM AIC: 7047.17 RANK: 44
FP_-1_-1	FLAURA2 HR is going to extreme values near time 0. F2 AIC: 3315.01 RANK: 11 - M AIC: 4760.08 RANK: 130 SUM AIC: 8075.09 RANK: 37	HR estimates for FLAURA2 is going to extreme values near time 0. F2 AIC: 3707.72 RANK: 35 - M AIC: 3341.24 RANK: 135 SUM AIC: 7048.96 RANK: 72
FP_-1_-0.5	FLAURA2 HR is going to extreme values near time 0. F2 AIC: 3314.78 RANK: 6 - M AIC: 4759.11 RANK: 57 SUM AIC: 8073.89 RANK: 22	HR estimates for FLAURA2 is going to extreme values near time 0. F2 AIC: 3707.74 RANK: 36 - M AIC: 3340.38 RANK: 74 SUM AIC: 7048.12 RANK: 55
FP_-1_log(t)	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. F2 AIC: 3314.67 RANK: 5 - M AIC: 4758.19 RANK: 30 SUM AIC: 8072.86 RANK: 12	HR estimates for FLAURA2 is going to extreme values near time 0. F2 AIC: 3707.7 RANK: 33 - M AIC: 3339.33 RANK: 42 SUM AIC: 7047.03 RANK: 40
FP_-1_0.5	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. F2 AIC: 3314.86 RANK: 9 - M AIC: 4758.07 RANK: 25 SUM AIC: 8072.92 RANK: 13	HR estimates for FLAURA2 is going to extreme values near time 0. F2 AIC: 3707.57 RANK: 27 - M AIC: 3339.09 RANK: 28 SUM AIC: 7046.66 RANK: 27
FP_-1_1	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. MARIPOSA HR is decreasing rapidly. F2 AIC: 3315.34 RANK: 17 - M AIC: 4758.41 RANK: 41 SUM AIC: 8073.75 RANK: 20	HR estimates for FLAURA2 is going to extreme values near time 0. FLAURA2 HR increases over time. F2 AIC: 3707.39 RANK: 19 - M AIC: 3339.36 RANK: 43 SUM AIC: 7046.75 RANK: 31
FP_-1_2	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. MARIPOSA HR is decreasing rapidly. F2 AIC: 3316.89 RANK: 87 - M AIC: 4759.15 RANK: 62 SUM AIC: 8076.04 RANK: 60	HR estimates for FLAURA2 is going to extreme values near time 0. FLAURA2 HR increases rapidly. MARIPOSA HR decreases rapidly. F2 AIC: 3707.15 RANK: 12 - M AIC: 3339.81 RANK: 57 SUM AIC: 7046.97 RANK: 37
FP_-1_3	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. MARIPOSA HR is decreasing rapidly. F2 AIC: 3318.69 RANK: 132 - M AIC: 4759.61 RANK: 73 SUM AIC: 8078.31 RANK: 133	HR estimates for FLAURA2 is going to extreme values near time 0. FLAURA2 HR increases over time. MARIPOSA HR decreases rapidly. F2 AIC: 3707.19 RANK: 13 - M AIC: 3339.97 RANK: 62 SUM AIC: 7047.16 RANK: 43
FP_-0.5_-0.5	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. F2 AIC: 3314.82 RANK: 8 - M AIC: 4758.66 RANK: 47 SUM AIC: 8073.49 RANK: 17	HR estimates for FLAURA2 is going to extreme values near time 0. F2 AIC: 3707.76 RANK: 38 - M AIC: 3339.84 RANK: 58 SUM AIC: 7047.6 RANK: 49

FP_-0.5_log(t)	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. F2 AIC: 3315.13 RANK: 14 - M AIC: 4758.24 RANK: 36 SUM AIC: 8073.37 RANK: 15	HR estimates for FLAURA2 is going to extreme values near time 0. FLAURA2 increases over time. F2 AIC: 3707.65 RANK: 32 - M AIC: 3339.25 RANK: 35 SUM AIC: 7046.9 RANK: 36
FP_-0.5_0.5	FLAURA2 HR is going to extreme values near time 0. FLAURA2 HR is increasing rapidly. F2 AIC: 3315.75 RANK: 22 - M AIC: 4758.25 RANK: 38 SUM AIC: 8074 RANK: 25	HR estimates for FLAURA2 is going to extreme values near time 0. FLAURA2 increases over time. F2 AIC: 3707.43 RANK: 20 - M AIC: 3339.24 RANK: 33 SUM AIC: 7046.66 RANK: 28
FP_-0.5_1	FLAURA2 HR is increasing rapidly. MARIPOSA HR is decreasing rapidly. F2 AIC: 3316.6 RANK: 62 - M AIC: 4758.47 RANK: 43 SUM AIC: 8075.06 RANK: 36	HR estimates for FLAURA2 is going to extreme values near time 0. FLAURA2 increases over time. F2 AIC: 3707.21 RANK: 14 - M AIC: 3339.47 RANK: 47 SUM AIC: 7046.67 RANK: 30
FP_-0.5_2	FLAURA2 HR is increasing rapidly. MARIPOSA HR is decreasing rapidly. F2 AIC: 3318.61 RANK: 130 - M AIC: 4758.82 RANK: 49 SUM AIC: 8077.43 RANK: 107	HR estimates for FLAURA2 is going to extreme values near time 0. FLAURA2 increases rapidly. MARIPOSA HR decreases rapidly. F2 AIC: 3707.08 RANK: 11 - M AIC: 3339.71 RANK: 53 SUM AIC: 7046.8 RANK: 33
FP_-0.5_3	FLAURA2 HR is increasing rapidly. MARIPOSA HR is decreasing rapidly. F2 AIC: 3320.65 RANK: 147 - M AIC: 4759 RANK: 52 SUM AIC: 8079.65 RANK: 152	HR estimates for FLAURA2 is going to extreme values near time 0. FLAURA2 increases rapidly. MARIPOSA HR decreases rapidly. F2 AIC: 3707.35 RANK: 18 - M AIC: 3339.73 RANK: 54 SUM AIC: 7047.08 RANK: 41
FP_log(t)_log(t)	FLAURA2 HR is increasing rapidly. F2 AIC: 3315.95 RANK: 29 - M AIC: 4758.2 RANK: 31 SUM AIC: 8074.15 RANK: 26	HR estimates for FLAURA2 is going to extreme values near time 0. FLAURA2 increases rapidly. F2 AIC: 3707.5 RANK: 22 - M AIC: 3339.14 RANK: 30 SUM AIC: 7046.64 RANK: 26
FP_0.5_log(t)	FLAURA2 HR is increasing rapidly. F2 AIC: 3317.1 RANK: 95 - M AIC: 4758.23 RANK: 34 SUM AIC: 8075.33 RANK: 45	FLAURA2 increases rapidly. F2 AIC: 3707.32 RANK: 16 - M AIC: 3339.22 RANK: 32 SUM AIC: 7046.54 RANK: 22
FP_1_log(t)	FLAURA2 HR is increasing rapidly. F2 AIC: 3318.37 RANK: 126 - M AIC: 4758.25 RANK: 37 SUM AIC: 8076.62 RANK: 75	FLAURA2 increases rapidly. F2 AIC: 3707.23 RANK: 15 - M AIC: 3339.29 RANK: 38 SUM AIC: 7046.51 RANK: 21
FP_2_log(t)	FLAURA2 HR is increasing rapidly. F2 AIC: 3320.67 RANK: 148 - M AIC: 4758.23 RANK: 35 SUM AIC: 8078.9 RANK: 142	FLAURA2 increases rapidly. F2 AIC: 3707.53 RANK: 24 - M AIC: 3339.3 RANK: 39 SUM AIC: 7046.83 RANK: 34
FP_3_log(t)	MARIPOSA and FLAURA2 HR are increasing rapidly. F2 AIC: 3322.55 RANK: 158 - M AIC: 4758.21 RANK: 32 SUM AIC: 8080.76 RANK: 158	FLAURA2 increases rapidly. MARIPOSA HR decreases rapidly. F2 AIC: 3708.24 RANK: 47 - M AIC: 3339.26 RANK: 36 SUM AIC: 7047.49 RANK: 47

FP_0.5_0.5	FLAURA2 HR is increasing rapidly. F2 AIC: 3318.7 RANK: 133 - M AIC: 4758.1 RANK: 27 SUM AIC: 8076.8 RANK: 79	FLAURA2 increases rapidly. F2 AIC: 3707.33 RANK: 17 - M AIC: 3339.12 RANK: 29 SUM AIC: 7046.46 RANK: 20
FP_0.5_1	FLAURA2 HR is increasing rapidly. F2 AIC: 3320.04 RANK: 146 - M AIC: 4757.99 RANK: 23 SUM AIC: 8078.03 RANK: 125	FLAURA2 increases rapidly. MARIPOSA HR increases. F2 AIC: 3707.53 RANK: 25 - M AIC: 3339.06 RANK: 27 SUM AIC: 7046.6 RANK: 25
FP_0.5_2	MARIPOSA and FLAURA2 HR are increasing rapidly. F2 AIC: 3321.92 RANK: 154 - M AIC: 4757.93 RANK: 20 SUM AIC: 8079.85 RANK: 153	FLAURA2 and MARIPOSA HR increase rapidly. F2 AIC: 3708.44 RANK: 54 - M AIC: 3339.15 RANK: 31 SUM AIC: 7047.59 RANK: 48
FP_0.5_3	MARIPOSA and FLAURA2 HR are increasing rapidly. F2 AIC: 3323.21 RANK: 162 - M AIC: 4757.95 RANK: 21 SUM AIC: 8081.16 RANK: 162	FLAURA2 and MARIPOSA HR increase rapidly. F2 AIC: 3709.56 RANK: 145 - M AIC: 3339.25 RANK: 34 SUM AIC: 7048.81 RANK: 67
FP_1_1	MARIPOSA and FLAURA2 HR are increasing rapidly. F2 AIC: 3321.16 RANK: 150 - M AIC: 4757.88 RANK: 18 SUM AIC: 8079.04 RANK: 146	FLAURA2 and MARIPOSA HR increase rapidly. F2 AIC: 3708.07 RANK: 44 - M AIC: 3339.06 RANK: 26 SUM AIC: 7047.13 RANK: 42
FP_1_2	MARIPOSA and FLAURA2 HR are increasing rapidly. F2 AIC: 3322.45 RANK: 157 - M AIC: 4757.95 RANK: 22 SUM AIC: 8080.4 RANK: 155	FLAURA2 and MARIPOSA HR increase rapidly. F2 AIC: 3709.47 RANK: 135 - M AIC: 3339.41 RANK: 46 SUM AIC: 7048.88 RANK: 70
FP_1_3	MARIPOSA and FLAURA2 HR are increasing rapidly. F2 AIC: 3323.15 RANK: 161 - M AIC: 4758.09 RANK: 26 SUM AIC: 8081.24 RANK: 163	FLAURA2 and MARIPOSA HR increase rapidly. F2 AIC: 3710.8 RANK: 158 - M AIC: 3339.65 RANK: 52 SUM AIC: 7050.45 RANK: 134
FP_2_2	MARIPOSA and FLAURA2 HR are increasing rapidly. F2 AIC: 3322.66 RANK: 159 - M AIC: 4758.32 RANK: 40 SUM AIC: 8080.98 RANK: 160	FLAURA2 and MARIPOSA HR increase rapidly. F2 AIC: 3711.3 RANK: 162 - M AIC: 3340.06 RANK: 65 SUM AIC: 7051.36 RANK: 162
FP_2_3	FLAURA2 HR is decreasing rapidly. MARIPOSA HR is increasing rapidly. F2 AIC: 3322.4 RANK: 156 - M AIC: 4758.63 RANK: 46 SUM AIC: 8081.03 RANK: 161	FLAURA2 and MARIPOSA HR increase rapidly. F2 AIC: 3712.44 RANK: 163 - M AIC: 3340.36 RANK: 72 SUM AIC: 7052.8 RANK: 163
FP_3_3	FLAURA2 HR is decreasing rapidly. MARIPOSA HR is increasing rapidly. F2 AIC: 3321.4 RANK: 152 - M AIC: 4759.04 RANK: 55 SUM AIC: 8080.44 RANK: 156	FLAURA2 and MARIPOSA HR increase rapidly. F2 AIC: 3713.08 RANK: 164 - M AIC: 3340.64 RANK: 86 SUM AIC: 7053.72 RANK: 164
FP_-2	FLAURA2 HR is going to extreme values near time 0. F2 AIC: 3319.56 RANK: 145 - M AIC: 4758.52 RANK: 45 SUM AIC: 8078.08 RANK: 126	HR estimates for FLAURA2 is going to extreme values near time 0. HR extrapolations do not go to extreme values, but they do not reflect the difference in the HR trend between the two trials. F2 AIC: 3705.8 RANK: 4 - M AIC: 3339.27 RANK: 37 SUM AIC: 7045.06 RANK: 7

FP_-1	FLAURA2 HR effect is consistently above that of MARIPOSA. This is inconsistent with how the HRs evolve over time in the two trials. F2 AIC: 3322.3 RANK: 155 - M AIC: 4758.44 RANK: 42 SUM AIC: 8080.74 RANK: 157	HR estimates for FLAURA2 is going to extreme values near time 0. HR extrapolations do not go to extreme values, but they do not reflect the difference in the HR trend between the two trials. F2 AIC: 3705.79 RANK: 3 - M AIC: 3339.4 RANK: 45 SUM AIC: 7045.19 RANK: 9
FP_-0.5	FLAURA2 HR effect is consistently above that of MARIPOSA. This is inconsistent with how the HRs evolve over time in the two trials. F2 AIC: 3324.4 RANK: 163 - M AIC: 4757.22 RANK: 15 SUM AIC: 8081.62 RANK: 164	FLAURA2 HR is extreme near time 0. HR extrapolations do not go to extreme values, but they do not reflect the difference in the HR trend between the two trials. F2 AIC: 3706.66 RANK: 8 - M AIC: 3338.49 RANK: 17 SUM AIC: 7045.15 RANK: 8
FP_log(t)	**MARIPOSA and FLAURA2 HRs cross, indicating better treatment effect for amilaz vs. osicp over time. F2 AIC: 3324.57 RANK: 164 - M AIC: 4756.25 RANK: 8 SUM AIC: 8080.82 RANK: 159**	HR extrapolations do not go to extreme values, but they do not reflect the difference in the HR trend between the two trials. F2 AIC: 3708.54 RANK: 55 - M AIC: 3337.34 RANK: 13 SUM AIC: 7045.87 RANK: 13
FP_0.5	MARIPOSA and FLAURA2 HRs cross, indicating better treatment effect for amilaz vs. osicp over time. However FLAURA2 HR is increasing fast, resulting in a lower PFSINV for osicp vs. osi mono. F2 AIC: 3322.93 RANK: 160 - M AIC: 4756.41 RANK: 9 SUM AIC: 8079.34 RANK: 149	**HR extrapolations do not go to extreme values, they reflect the trend observed in the data and provide clinically plausible LY estimates for osicp F2 AIC: 3710.15 RANK: 157 - M AIC: 3337.28 RANK: 12 SUM AIC: 7047.43 RANK: 46**
FP_1	MARIPOSA and FLAURA2 HRs cross, indicating better treatment effect for amilaz vs. osicp over time. However FLAURA2 HR is increasing fast, resulting in a lower PFSINV for osicp vs. osi mono. F2 AIC: 3321.53 RANK: 153 - M AIC: 4757.03 RANK: 13 SUM AIC: 8078.56 RANK: 135	HR extrapolations do not go to extreme values, they reflect the trend observed in the data and provide LY estimates that are close to the low clinical estimates. F2 AIC: 3710.92 RANK: 159 - M AIC: 3337.77 RANK: 14 SUM AIC: 7048.69 RANK: 64
FP_2	FLAURA2 HR is increasing rapidly. MARIPOSA HR is decreasing rapidly. F2 AIC: 3320.67 RANK: 149 - M AIC: 4758.13 RANK: 28 SUM AIC: 8078.8 RANK: 140	MARIPOSA HR decreases rapidly. F2 AIC: 3711.21 RANK: 161 - M AIC: 3338.5 RANK: 19 SUM AIC: 7049.72 RANK: 90
FP_3	FLAURA2 HR is increasing rapidly. MARIPOSA HR is decreasing rapidly. F2 AIC: 3321.24 RANK: 151 - M AIC: 4758.78 RANK: 48 SUM AIC: 8080.02 RANK: 154	FLAURA2 HR is increasing, MARIPOSA HR decreases rapidly. F2 AIC: 3711.19 RANK: 160 - M AIC: 3338.79 RANK: 22 SUM AIC: 7049.98 RANK: 96

Abbreviations: AIC: Akaike information criterion; F2OSI: FLAURA2 osimertinib monotherapy; F2OSICP: FLAURA2 osimertinib-chemotherapy; FP: fractional polynomial; HR: hazard ratio; MAMILAZ: MARIPOSA amivantamab-lazertinib; MOSI: MARIPOSA osimertinib monotherapy; OS: overall survival; OSICP: osimertinib-chemotherapy; PFSINV: progression-free survival assessed by investigator.

Table 7. Summary of Parametric FP models

FP name	Parametric FP PFSINV	Parametric FP OS
FP_-2_-2	MARIPOSA OSI hazard is extreme near time 0. F2OSICP AIC: 413.59 RANK: 44 - F2OSI AIC: 517.67 RANK: 28 MOSI AIC: 1067.64 RANK: 38 MAMILAZ AIC: 845.09 RANK: 1 SUM AIC: 2843.99 RANK: 43	FLAURA2 OSICP and OSI arm, and MARIPOSA OSI arm hazard is extreme near time 0. F2OSICP AIC: 389.05 RANK: 44 - F2OSI AIC: 510.47 RANK: 41 MOSI AIC: 598.31 RANK: 43 MAMILAZ AIC: 493.76 RANK: 44 SUM AIC: 1991.6 RANK: 43
FP_-2_-1	MARIPOSA OSI hazard is extreme near time 0. F2OSICP AIC: 411.47 RANK: 41 - F2OSI AIC: 517.45 RANK: 18 MOSI AIC: 1063.27 RANK: 29 MAMILAZ AIC: 846.29 RANK: 2 SUM AIC: 2838.48 RANK: 40	FLAURA2 OSICP and OSI arm, and MARIPOSA OSI arm hazard is extreme near time 0. F2OSICP AIC: 386.63 RANK: 40 - F2OSI AIC: 502.47 RANK: 35 MOSI AIC: 589.38 RANK: 41 MAMILAZ AIC: 493.3 RANK: 43 SUM AIC: 1971.78 RANK: 41
FP_-2_-0.5	MARIPOSA OSI hazard is extreme near time 0. F2OSICP AIC: 407.93 RANK: 38 - F2OSI AIC: 517.17 RANK: 11 MOSI AIC: 1061.36 RANK: 16 MAMILAZ AIC: 847.28 RANK: 5 SUM AIC: 2833.74 RANK: 34	FLAURA2 OSICP and OSI arm, and MARIPOSA OSI arm hazard is extreme near time 0. F2OSICP AIC: 382.7 RANK: 37 - F2OSI AIC: 497.51 RANK: 27 MOSI AIC: 579.57 RANK: 32 MAMILAZ AIC: 491.94 RANK: 38 SUM AIC: 1951.72 RANK: 34
FP_-2_log(t)	FP implies that FLAURA2 OSICP PFSINV decreases below FLAURA2 OSI PFSINV. F2OSICP AIC: 402.99 RANK: 35 - F2OSI AIC: 516.95 RANK: 9 MOSI AIC: 1061.74 RANK: 21 MAMILAZ AIC: 848.44 RANK: 11 SUM AIC: 2830.11 RANK: 28	FLAURA2 OSICP and OSI arm, and MARIPOSA OSI arm hazard is extreme near time 0. F2OSICP AIC: 377.71 RANK: 24 - F2OSI AIC: 495.51 RANK: 18 MOSI AIC: 571.93 RANK: 18 MAMILAZ AIC: 489.53 RANK: 28 SUM AIC: 1934.68 RANK: 25
FP_-2_0.5	FP implies that FLAURA2 OSICP PFSINV decreases below FLAURA2 OSI PFSINV. F2OSICP AIC: 398.95 RANK: 31 - F2OSI AIC: 516.86 RANK: 6 MOSI AIC: 1064.15 RANK: 31 MAMILAZ AIC: 849.44 RANK: 28 SUM AIC: 2829.39 RANK: 25	FLAURA2 OSICP and MARIPOSA OSI hazard is extreme near time 0, and FLAURA2 OSI hazard is close to 0 near time 0. F2OSICP AIC: 374.43 RANK: 11 - F2OSI AIC: 497.18 RANK: 25 MOSI AIC: 570.35 RANK: 11 MAMILAZ AIC: 487.59 RANK: 16 SUM AIC: 1929.55 RANK: 15
FP_-2_1	FP implies that FLAURA2 OSICP PFSINV decreases below FLAURA2 OSI PFSINV. F2OSICP AIC: 396.64 RANK: 26 - F2OSI AIC: 516.86 RANK: 7 MOSI AIC: 1067.03 RANK: 36 MAMILAZ AIC: 850.12 RANK: 36 SUM AIC: 2830.66 RANK: 29	FLAURA2 OSICP and MARIPOSA OSI hazard is extreme near time 0, and FLAURA2 OSI hazard is close to 0 near time 0. F2OSICP AIC: 373.51 RANK: 8 - F2OSI AIC: 500.67 RANK: 33 MOSI AIC: 572.76 RANK: 22 MAMILAZ AIC: 487.12 RANK: 12 SUM AIC: 1934.06 RANK: 24
FP_-2_2	FP implies that FLAURA2 OSICP PFSINV decreases below FLAURA2 OSI PFSINV. F2OSICP AIC: 395.22 RANK: 4 - F2OSI AIC: 516.91 RANK: 8 MOSI AIC: 1071.31 RANK: 40 MAMILAZ AIC: 850.81 RANK: 41 SUM AIC: 2834.25 RANK: 35	FLAURA2 OSICP hazard is extreme near time 0, and OSI hazard is close to 0 near time 0. F2OSICP AIC: 375.28 RANK: 14 - F2OSI AIC: 507.25 RANK: 39 MOSI AIC: 580.1 RANK: 35 MAMILAZ AIC: 488.82 RANK: 22 SUM AIC: 1951.45 RANK: 33
FP_-2_3	FP implies that FLAURA2 OSICP PFSINV decreases below FLAURA2 OSI PFSINV. F2OSICP AIC: 395.53 RANK: 16 - F2OSI AIC: 516.77 RANK: 5 MOSI AIC: 1073.54 RANK: 43 MAMILAZ AIC: 851.07 RANK: 44 SUM AIC: 2836.91 RANK: 39	FLAURA2 OSICP hazard is extreme near time 0, and OSI hazard is close to 0 near time 0. F2OSICP AIC: 378.1 RANK: 28 - F2OSI AIC: 511.16 RANK: 42 MOSI AIC: 586.06 RANK: 39 MAMILAZ AIC: 490.98 RANK: 34 SUM AIC: 1966.29 RANK: 39

FP_-1_-1	MARIPOSA OSI hazard is extreme near time 0. F2OSICP AIC: 408.71 RANK: 39 - F2OSI AIC: 517.51 RANK: 21 MOSI AIC: 1061.52 RANK: 18 MAMILAZ AIC: 847.02 RANK: 4 SUM AIC: 2834.76 RANK: 36	FLAURA2 OSICP and OSI arm and MARIPOSA OSI arm hazard is extreme near time 0. F2OSICP AIC: 382.87 RANK: 38 - F2OSI AIC: 497.43 RANK: 26 MOSI AIC: 579.99 RANK: 33 MAMILAZ AIC: 492.68 RANK: 39 SUM AIC: 1952.97 RANK: 35
FP_-1_-0.5	The relative treatment effect is extreme near time 0, causing the OSICP PFSINV to have a sudden drop at the beginning of follow-up. F2OSICP AIC: 405.41 RANK: 37 - F2OSI AIC: 517.45 RANK: 17 MOSI AIC: 1061.07 RANK: 14 MAMILAZ AIC: 847.78 RANK: 8 SUM AIC: 2831.71 RANK: 32	FLAURA2 OSICP and OSI arm and MARIPOSA OSI arm hazard is extreme near time 0. F2OSICP AIC: 379.05 RANK: 33 - F2OSI AIC: 495.25 RANK: 16 MOSI AIC: 573.32 RANK: 26 MAMILAZ AIC: 491.3 RANK: 36 SUM AIC: 1938.92 RANK: 27
FP_-1_log(t)	FP implies that FLAURA2 OSICP PFSINV decreases below FLAURA2 OSI PFSINV. F2OSICP AIC: 401.31 RANK: 33 - F2OSI AIC: 517.39 RANK: 16 MOSI AIC: 1061.7 RANK: 20 MAMILAZ AIC: 848.74 RANK: 13 SUM AIC: 2829.14 RANK: 24	FLAURA2 OSICP and MARIPOSA OSI arm hazard is extreme near time 0. F2OSICP AIC: 375.13 RANK: 12 - F2OSI AIC: 495.15 RANK: 14 MOSI AIC: 569.36 RANK: 4 MAMILAZ AIC: 489.02 RANK: 26 SUM AIC: 1928.65 RANK: 13
FP_-1_0.5	FP implies that FLAURA2 OSICP PFSINV decreases below FLAURA2 OSI PFSINV. F2OSICP AIC: 398.03 RANK: 29 - F2OSI AIC: 517.36 RANK: 15 MOSI AIC: 1063.15 RANK: 28 MAMILAZ AIC: 849.6 RANK: 31 SUM AIC: 2828.14 RANK: 20	FLAURA2 OSICP and MARIPOSA OSI arm hazard is extreme near time 0. FLAURA2 OSI hazard is close to 0 near time 0. F2OSICP AIC: 372.97 RANK: 5 - F2OSI AIC: 497.12 RANK: 24 MOSI AIC: 569.8 RANK: 8 MAMILAZ AIC: 487.27 RANK: 14 SUM AIC: 1927.17 RANK: 10
FP_-1_1	FP implies that FLAURA2 OSICP PFSINV decreases below FLAURA2 OSI PFSINV. F2OSICP AIC: 396.18 RANK: 25 - F2OSI AIC: 517.36 RANK: 14 MOSI AIC: 1064.71 RANK: 32 MAMILAZ AIC: 850.18 RANK: 37 SUM AIC: 2828.42 RANK: 22	FLAURA2 OSICP hazard is extreme near time 0 and FLAURA2 OSI hazard is close to 0 near time 0. F2OSICP AIC: 372.83 RANK: 4 - F2OSI AIC: 499.9 RANK: 31 MOSI AIC: 572.88 RANK: 23 MAMILAZ AIC: 486.99 RANK: 10 SUM AIC: 1932.6 RANK: 22
FP_-1_2	FP implies that FLAURA2 OSICP PFSINV decreases below FLAURA2 OSI PFSINV. F2OSICP AIC: 395.16 RANK: 3 - F2OSI AIC: 517.33 RANK: 13 MOSI AIC: 1066.86 RANK: 35 MAMILAZ AIC: 850.75 RANK: 40 SUM AIC: 2830.09 RANK: 27	FLAURA2 OSICP hazard is high near time 0 and FLAURA2 OSI hazard is close to 0 near time 0. FP implies FLAURA2 OSICP OS will decrease below FLAURA2 OSI. F2OSICP AIC: 375.48 RANK: 15 - F2OSI AIC: 504.38 RANK: 36 MOSI AIC: 580.06 RANK: 34 MAMILAZ AIC: 488.93 RANK: 23 SUM AIC: 1948.85 RANK: 31
FP_-1_3	FP implies that FLAURA2 OSICP PFSINV decreases below FLAURA2 OSI PFSINV. F2OSICP AIC: 395.6 RANK: 20 - F2OSI AIC: 517.18 RANK: 12 MOSI AIC: 1067.86 RANK: 39 MAMILAZ AIC: 850.94 RANK: 42 SUM AIC: 2831.58 RANK: 31	FLAURA2 OSICP hazard is extreme near time 0 and FLAURA2 OSI hazard is close to 0 near time 0. FP implies FLAURA2 OSICP OS will decrease below FLAURA2 OSI. F2OSICP AIC: 378.69 RANK: 32 - F2OSI AIC: 506.69 RANK: 37 MOSI AIC: 585.47 RANK: 38 MAMILAZ AIC: 491.22 RANK: 35 SUM AIC: 1962.06 RANK: 37

FP_-0.5_-0.5	FP implies that FLAURA2 OSICP PFSINV decreases below FLAURA2 OSI PFSINV. The relative treatment effect is extreme near time 0, causing the OSICP PFSINV to have a sudden drop at the beginning of follow-up. F2OSICP AIC: 402.68 RANK: 34 - F2OSI AIC: 517.5 RANK: 20 MOSI AIC: 1061.17 RANK: 15 MAMILAZ AIC: 848.34 RANK: 10 SUM AIC: 2829.69 RANK: 26	FLAURA2 OSICP hazard is extreme near time 0 and causes the OSICP curve to start with a sharp decrease very early on. MARIPOSA OSI hazard is extreme near time 0. F2OSICP AIC: 375.92 RANK: 18 - F2OSI AIC: 494.65 RANK: 12 MOSI AIC: 569.72 RANK: 7 MAMILAZ AIC: 489.93 RANK: 32 SUM AIC: 1930.23 RANK: 18
FP_-0.5_log(t)	FP implies that FLAURA2 OSICP PFSINV decreases below FLAURA2 OSI PFSINV. F2OSICP AIC: 399.45 RANK: 32 - F2OSI AIC: 517.52 RANK: 22 MOSI AIC: 1061.6 RANK: 19 MAMILAZ AIC: 848.94 RANK: 21 SUM AIC: 2827.51 RANK: 19	FLAURA2 OSICP and MARIPOSA OSI arm hazard is extreme near time 0 and causes the OSICP curve to start with a sharp decrease very early on. F2OSICP AIC: 373.18 RANK: 7 - F2OSI AIC: 495.29 RANK: 17 MOSI AIC: 568.44 RANK: 1 MAMILAZ AIC: 487.86 RANK: 19 SUM AIC: 1924.76 RANK: 6
FP_-0.5_0.5	FP implies that FLAURA2 OSICP PFSINV decreases below FLAURA2 OSI PFSINV. F2OSICP AIC: 397.01 RANK: 27 - F2OSI AIC: 517.52 RANK: 23 MOSI AIC: 1062.16 RANK: 23 MAMILAZ AIC: 849.27 RANK: 25 SUM AIC: 2825.96 RANK: 18	FLAURA2 OSICP hazard is extreme and MARIPOSA OSI arm hazard is very high near time 0, FLAURA2 OSI hazard is close to 0 near time 0, and causes the OSICP curve to start with a sharp decrease very early on. F2OSICP AIC: 372.21 RANK: 2 - F2OSI AIC: 496.85 RANK: 23 MOSI AIC: 570.15 RANK: 10 MAMILAZ AIC: 486.59 RANK: 7 SUM AIC: 1925.79 RANK: 7
FP_-0.5_1	FP implies that FLAURA2 OSICP PFSINV decreases below FLAURA2 OSI PFSINV. F2OSICP AIC: 395.75 RANK: 23 - F2OSI AIC: 517.52 RANK: 24 MOSI AIC: 1062.59 RANK: 24 MAMILAZ AIC: 849.4 RANK: 26 SUM AIC: 2825.26 RANK: 13	FLAURA2 OSICP hazard is extreme near time 0, FLAURA2 OSI hazard is close to 0 near time 0. FP implies that OSICP OS decreases below OSI OS. F2OSICP AIC: 372.99 RANK: 6 - F2OSI AIC: 498.46 RANK: 28 MOSI AIC: 573.25 RANK: 25 MAMILAZ AIC: 486.83 RANK: 8 SUM AIC: 1931.53 RANK: 21
FP_-0.5_2	FP implies that FLAURA2 OSICP PFSINV decreases below FLAURA2 OSI PFSINV. F2OSICP AIC: 395.24 RANK: 5 - F2OSI AIC: 517.53 RANK: 25 MOSI AIC: 1062.91 RANK: 26 MAMILAZ AIC: 849.47 RANK: 30 SUM AIC: 2825.14 RANK: 11	FLAURA2 OSICP hazard is very high near time 0, FLAURA2 OSI hazard is close to 0 near time 0. FP implies that OSICP OS decreases below OSI OS. F2OSICP AIC: 376.56 RANK: 21 - F2OSI AIC: 500.32 RANK: 32 MOSI AIC: 578.9 RANK: 31 MAMILAZ AIC: 489.39 RANK: 27 SUM AIC: 1945.17 RANK: 30
FP_-0.5_3	FP implies that FLAURA2 OSICP PFSINV decreases below FLAURA2 OSI PFSINV. F2OSICP AIC: 395.69 RANK: 22 - F2OSI AIC: 517.47 RANK: 19 MOSI AIC: 1062.85 RANK: 25 MAMILAZ AIC: 849.46 RANK: 29 SUM AIC: 2825.47 RANK: 14	FLAURA2 OSICP hazard is very high near time 0, FLAURA2 OSI hazard is close to 0 near time 0. FP implies that OSICP OS decreases below OSI OS. F2OSICP AIC: 379.99 RANK: 35 - F2OSI AIC: 500.82 RANK: 34 MOSI AIC: 582.51 RANK: 36 MAMILAZ AIC: 491.75 RANK: 37 SUM AIC: 1955.07 RANK: 36
FP_log(t)_log(t)	FP implies that FLAURA2 OSICP PFSINV decreases below FLAURA2 OSI PFSINV. F2OSICP AIC: 397.37 RANK: 28 - F2OSI AIC: 517.59 RANK: 26 MOSI AIC: 1061.36 RANK: 17 MAMILAZ AIC: 848.83 RANK: 16 SUM AIC: 2825.16 RANK: 12	FLAURA2 OSICP hazard is extreme near time 0. FP implies that OSICP OS decreases below OSI OS. F2OSICP AIC: 372.02 RANK: 1 - F2OSI AIC: 495.72 RANK: 19 MOSI AIC: 569.15 RANK: 2 MAMILAZ AIC: 486.4 RANK: 6 SUM AIC: 1923.29 RANK: 4

FP_0.5_log(t)	FP implies that FLAURA2 OSICP PFSINV decreases below FLAURA2 OSI PFSINV. F2OSICP AIC: 396.04 RANK: 24 - F2OSI AIC: 517.63 RANK: 27 MOSI AIC: 1060.99 RANK: 13 MAMILAZ AIC: 848.75 RANK: 14 SUM AIC: 2823.41 RANK: 9	FLAURA2 OSI hazard is close to 0 near time 0. FP implies that OSICP OS decreases below OSI OS. F2OSICP AIC: 372.6 RANK: 3 - F2OSI AIC: 496.02 RANK: 21 MOSI AIC: 571.16 RANK: 14 MAMILAZ AIC: 486.32 RANK: 5 SUM AIC: 1926.1 RANK: 8
FP_1_log(t)	FP implies that FLAURA2 OSICP PFSINV decreases below FLAURA2 OSI PFSINV. F2OSICP AIC: 395.52 RANK: 14 - F2OSI AIC: 517.68 RANK: 29 MOSI AIC: 1060.57 RANK: 10 MAMILAZ AIC: 848.76 RANK: 15 SUM AIC: 2822.53 RANK: 7	FP implies that OSICP OS decreases below OSI OS. F2OSICP AIC: 374.33 RANK: 10 - F2OSI AIC: 495.91 RANK: 20 MOSI AIC: 573.14 RANK: 24 MAMILAZ AIC: 487.38 RANK: 15 SUM AIC: 1930.75 RANK: 20
FP_2_log(t)	FP implies that FLAURA2 OSICP PFSINV decreases below FLAURA2 OSI PFSINV. F2OSICP AIC: 395.4 RANK: 10 - F2OSI AIC: 517.84 RANK: 31 MOSI AIC: 1059.92 RANK: 8 MAMILAZ AIC: 848.84 RANK: 17 SUM AIC: 2821.99 RANK: 2	FP implies that OSICP OS decreases below OSI OS. F2OSICP AIC: 378.04 RANK: 27 - F2OSI AIC: 494.96 RANK: 13 MOSI AIC: 575.43 RANK: 28 MAMILAZ AIC: 489.68 RANK: 30 SUM AIC: 1938.11 RANK: 26
FP_3_log(t)	FP implies that FLAURA2 OSICP PFSINV decreases below FLAURA2 OSI PFSINV. F2OSICP AIC: 395.56 RANK: 18 - F2OSI AIC: 518 RANK: 33 MOSI AIC: 1059.54 RANK: 5 MAMILAZ AIC: 848.91 RANK: 20 SUM AIC: 2822.01 RANK: 3	FP implies that OSICP OS decreases below OSI OS. F2OSICP AIC: 380.63 RANK: 36 - F2OSI AIC: 494.15 RANK: 10 MOSI AIC: 576.31 RANK: 29 MAMILAZ AIC: 490.97 RANK: 33 SUM AIC: 1942.07 RANK: 28
FP_0.5_0.5	FP implies that FLAURA2 OSICP PFSINV decreases below FLAURA2 OSI PFSINV. F2OSICP AIC: 395.64 RANK: 21 - F2OSI AIC: 517.74 RANK: 30 MOSI AIC: 1060.02 RANK: 9 MAMILAZ AIC: 848.74 RANK: 12 SUM AIC: 2822.14 RANK: 4	FP implies that OSICP OS decreases below OSI OS. F2OSICP AIC: 374.24 RANK: 9 - F2OSI AIC: 494.57 RANK: 11 MOSI AIC: 571.94 RANK: 19 MAMILAZ AIC: 487.14 RANK: 13 SUM AIC: 1927.89 RANK: 12
FP_0.5_1	FP implies that FLAURA2 OSICP PFSINV decreases below FLAURA2 OSI PFSINV. F2OSICP AIC: 395.55 RANK: 17 - F2OSI AIC: 517.9 RANK: 32 MOSI AIC: 1059.44 RANK: 4 MAMILAZ AIC: 848.9 RANK: 19 SUM AIC: 2821.79 RANK: 1	FP implies that OSICP OS decreases below OSI OS. F2OSICP AIC: 376.04 RANK: 19 - F2OSI AIC: 492.93 RANK: 8 MOSI AIC: 572.09 RANK: 20 MAMILAZ AIC: 488.04 RANK: 20 SUM AIC: 1929.1 RANK: 14
FP_0.5_2	FP implies that FLAURA2 OSICP PFSINV decreases below FLAURA2 OSI PFSINV. F2OSICP AIC: 395.47 RANK: 12 - F2OSI AIC: 518.36 RANK: 36 MOSI AIC: 1059.14 RANK: 1 MAMILAZ AIC: 849.2 RANK: 24 SUM AIC: 2822.18 RANK: 6	FP implies that OSICP OS decreases below OSI OS. F2OSICP AIC: 378.38 RANK: 30 - F2OSI AIC: 490.64 RANK: 6 MOSI AIC: 571.71 RANK: 17 MAMILAZ AIC: 488.95 RANK: 24 SUM AIC: 1929.67 RANK: 16
FP_0.5_3	FP implies that FLAURA2 OSICP PFSINV decreases below FLAURA2 OSI PFSINV. F2OSICP AIC: 395.33 RANK: 8 - F2OSI AIC: 518.83 RANK: 37 MOSI AIC: 1059.32 RANK: 3 MAMILAZ AIC: 849.42 RANK: 27 SUM AIC: 2822.9 RANK: 8	FP implies that OSICP OS decreases below OSI OS. F2OSICP AIC: 379.44 RANK: 34 - F2OSI AIC: 489.97 RANK: 4 MOSI AIC: 571.39 RANK: 16 MAMILAZ AIC: 488.96 RANK: 25 SUM AIC: 1929.76 RANK: 17

FP_1_1	FP implies that FLAURA2 OSICP PFSINV decreases below FLAURA2 OSI PFSINV. F2OSICP AIC: 395.6 RANK: 19 - F2OSI AIC: 518.21 RANK: 35 MOSI AIC: 1059.17 RANK: 2 MAMILAZ AIC: 849.19 RANK: 23 SUM AIC: 2822.17 RANK: 5	FP implies that OSICP OS decreases below OSI OS. F2OSICP AIC: 377.14 RANK: 23 - F2OSI AIC: 490.53 RANK: 5 MOSI AIC: 570.9 RANK: 13 MAMILAZ AIC: 488.26 RANK: 21 SUM AIC: 1926.82 RANK: 9
FP_1_2	FP implies that FLAURA2 OSICP PFSINV decreases below FLAURA2 OSI PFSINV. F2OSICP AIC: 395.48 RANK: 13 - F2OSI AIC: 519.05 RANK: 38 MOSI AIC: 1059.78 RANK: 7 MAMILAZ AIC: 849.66 RANK: 32 SUM AIC: 2823.97 RANK: 10	FP implies that OSICP OS decreases below OSI OS. F2OSICP AIC: 377.86 RANK: 26 - F2OSI AIC: 488.47 RANK: 1 MOSI AIC: 569.68 RANK: 6 MAMILAZ AIC: 487.73 RANK: 18 SUM AIC: 1923.73 RANK: 5
FP_1_3	FP implies that FLAURA2 OSICP PFSINV decreases below FLAURA2 OSI PFSINV. F2OSICP AIC: 395.25 RANK: 6 - F2OSI AIC: 519.79 RANK: 40 MOSI AIC: 1060.7 RANK: 11 MAMILAZ AIC: 849.96 RANK: 34 SUM AIC: 2825.7 RANK: 15	FP implies that OSICP OS decreases below OSI OS. F2OSICP AIC: 377.86 RANK: 25 - F2OSI AIC: 488.88 RANK: 3 MOSI AIC: 569.52 RANK: 5 MAMILAZ AIC: 486.9 RANK: 9 SUM AIC: 1923.16 RANK: 3
FP_2_2	FP implies that FLAURA2 OSICP PFSINV decreases below FLAURA2 OSI PFSINV. F2OSICP AIC: 395.46 RANK: 11 - F2OSI AIC: 520.48 RANK: 42 MOSI AIC: 1062.04 RANK: 22 MAMILAZ AIC: 850.3 RANK: 38 SUM AIC: 2828.27 RANK: 21	FP implies that OSICP OS decreases below OSI OS. F2OSICP AIC: 376.6 RANK: 22 - F2OSI AIC: 488.85 RANK: 2 MOSI AIC: 569.25 RANK: 3 MAMILAZ AIC: 485.47 RANK: 3 SUM AIC: 1920.17 RANK: 1
FP_2_3	FP implies that FLAURA2 OSICP PFSINV decreases below FLAURA2 OSI PFSINV. F2OSICP AIC: 395.37 RANK: 9 - F2OSI AIC: 521.39 RANK: 43 MOSI AIC: 1063.97 RANK: 30 MAMILAZ AIC: 850.65 RANK: 39 SUM AIC: 2831.39 RANK: 30	FP implies that FLAURA2 OS curves plateau 374. F2OSICP AIC: 375.85 RANK: 16 - F2OSI AIC: 491.71 RANK: 7 MOSI AIC: 570.36 RANK: 12 MAMILAZ AIC: 484.27 RANK: 2 SUM AIC: 1922.19 RANK: 2
FP_3_3	FP implies that FLAURA2 OSICP PFSINV decreases below FLAURA2 OSI PFSINV. F2OSICP AIC: 395.53 RANK: 15 - F2OSI AIC: 522.01 RANK: 44 MOSI AIC: 1066.43 RANK: 34 MAMILAZ AIC: 850.97 RANK: 43 SUM AIC: 2834.94 RANK: 37	FP implies that FLAURA2 OS curves plateau 373. F2OSICP AIC: 375.14 RANK: 13 - F2OSI AIC: 496.14 RANK: 22 MOSI AIC: 572.48 RANK: 21 MAMILAZ AIC: 483.53 RANK: 1 SUM AIC: 1927.3 RANK: 11
FP_-2	FLAURA2 OSI hazard is near time 0 near time 0. F2OSICP AIC: 412.18 RANK: 43 - F2OSI AIC: 515.68 RANK: 3 MOSI AIC: 1073.52 RANK: 42 MAMILAZ AIC: 850.1 RANK: 35 SUM AIC: 2851.48 RANK: 44	FLAURA2 OSICP hazard is extreme near time 0, FLAURA2 OSI hazard is close to 0 near time 0. F2OSICP AIC: 387.73 RANK: 41 - F2OSI AIC: 514.04 RANK: 44 MOSI AIC: 599.54 RANK: 44 MAMILAZ AIC: 492.74 RANK: 40 SUM AIC: 1994.05 RANK: 44

FP_-1	FP has very poor fit to FLAURA2 OSICP. The relative treatment effect is extreme near time 0, causing the OSICP PFSINV to have a sudden drop at the beginning of follow-up. F2OSICP AIC: 411.88 RANK: 42 - F2OSI AIC: 515.52 RANK: 1 MOSI AIC: 1066.42 RANK: 33 MAMILAZ AIC: 849.81 RANK: 33 SUM AIC: 2843.64 RANK: 42	The relative treatment effect of AMILAZ vs. OSICP is close to 0 near time 0. F2OSICP AIC: 388.85 RANK: 43 - F2OSI AIC: 506.72 RANK: 38 MOSI AIC: 596.73 RANK: 42 MAMILAZ AIC: 493.13 RANK: 42 SUM AIC: 1985.43 RANK: 42
FP_-0.5	FP has very poor fit to FLAURA2 OSICP. F2OSICP AIC: 409.22 RANK: 40 - F2OSI AIC: 515.53 RANK: 2 MOSI AIC: 1060.92 RANK: 12 MAMILAZ AIC: 847.6 RANK: 6 SUM AIC: 2833.26 RANK: 33	FP has very poor fit to the FLAURA2 OSICP arm. F2OSICP AIC: 388.83 RANK: 42 - F2OSI AIC: 498.86 RANK: 29 MOSI AIC: 587.48 RANK: 40 MAMILAZ AIC: 493 RANK: 41 SUM AIC: 1968.18 RANK: 40
FP_log(t)	FP has very poor fit to FLAURA2 OSICP. F2OSICP AIC: 403.15 RANK: 36 - F2OSI AIC: 516.03 RANK: 4 MOSI AIC: 1059.74 RANK: 6 MAMILAZ AIC: 846.94 RANK: 3 SUM AIC: 2825.86 RANK: 17	FP has poor fit to the FLAURA2 OSICP arm. F2OSICP AIC: 383.72 RANK: 39 - F2OSI AIC: 494.03 RANK: 9 MOSI AIC: 574.96 RANK: 27 MAMILAZ AIC: 489.68 RANK: 29 SUM AIC: 1942.39 RANK: 29
FP_0.5	FP implies that FLAURA2 OSICP PFSINV decreases below FLAURA2 OSI PFSINV. F2OSICP AIC: 398.05 RANK: 30 - F2OSI AIC: 517.04 RANK: 10 MOSI AIC: 1063.09 RANK: 27 MAMILAZ AIC: 847.6 RANK: 7 SUM AIC: 2825.79 RANK: 16	Among the parametric FPs, this FP has the best overall visual fit to all four curves. F2OSICP AIC: 378.24 RANK: 29 - F2OSI AIC: 495.24 RANK: 15 MOSI AIC: 570.1 RANK: 9 MAMILAZ AIC: 487.02 RANK: 11 SUM AIC: 1930.61 RANK: 19
FP_1	FP implies that FLAURA2 OSICP PFSINV decreases below FLAURA2 OSI PFSINV. F2OSICP AIC: 395.27 RANK: 7 - F2OSI AIC: 518.16 RANK: 34 MOSI AIC: 1067.27 RANK: 37 MAMILAZ AIC: 848.21 RANK: 9 SUM AIC: 2828.9 RANK: 23	FP implies that HRs in both trials go to zero over time. Resulting OSICP OS extrapolation decreases below that of OSI. F2OSICP AIC: 375.9 RANK: 17 - F2OSI AIC: 499.48 RANK: 30 MOSI AIC: 571.32 RANK: 15 MAMILAZ AIC: 486.26 RANK: 4 SUM AIC: 1932.96 RANK: 23
FP_2	FP implies that FLAURA2 OSICP PFSINV decreases below FLAURA2 OSI PFSINV. F2OSICP AIC: 393.5 RANK: 1 - F2OSI AIC: 519.6 RANK: 39 MOSI AIC: 1073.09 RANK: 41 MAMILAZ AIC: 848.87 RANK: 18 SUM AIC: 2835.06 RANK: 38	FP implies that OSICP OS decreases below OSI OS. F2OSICP AIC: 376.41 RANK: 20 - F2OSI AIC: 507.64 RANK: 40 MOSI AIC: 578.14 RANK: 30 MAMILAZ AIC: 487.72 RANK: 17 SUM AIC: 1949.9 RANK: 32
FP_3	FP implies that FLAURA2 OSICP PFSINV decreases below FLAURA2 OSI PFSINV. F2OSICP AIC: 393.69 RANK: 2 - F2OSI AIC: 520.02 RANK: 41 MOSI AIC: 1076.02 RANK: 44 MAMILAZ AIC: 849.11 RANK: 22 SUM AIC: 2838.84 RANK: 41	FP implies that OSICP OS decreases below OSI OS. F2OSICP AIC: 378.68 RANK: 31 - F2OSI AIC: 512.48 RANK: 43 MOSI AIC: 584.06 RANK: 37 MAMILAZ AIC: 489.77 RANK: 31 SUM AIC: 1964.99 RANK: 38

Abbreviations: AIC: Akaike information criterion; F2OSI: FLAURA2 osimertinib monotherapy; F2OSICP: FLAURA2 osimertinib-chemotherapy; FP: fractional polynomial; HR: hazard ratio; MAMILAZ: MARIPOSA amivantamab-lazertinib; MOSI: MARIPOSA osimertinib monotherapy; OS: overall survival; OSICP: osimertinib-chemotherapy; PFSINV: progression-free survival assessed by investigator.

3 Additional plots of survival outcomes of amivantamab-lazertinib and osimertinib matched to FLAURA2 population

3.1 Hazard plots

Smoothed KM and MAIC-weighted amivantamab-lazertinib cohort parametric hazard estimates are provided in the figures below.

Figure 9. Amivantamab-lazertinib OS, standard parametric and smoothed hazard, weighted to FLAURA2 population

Abbreviations: OS: overall survival.

Figure 10. Amivantamab-lazertinib OS, spline-based and smoothed hazard, weighted to FLAURA2 population

Abbreviations: OS: overall survival.

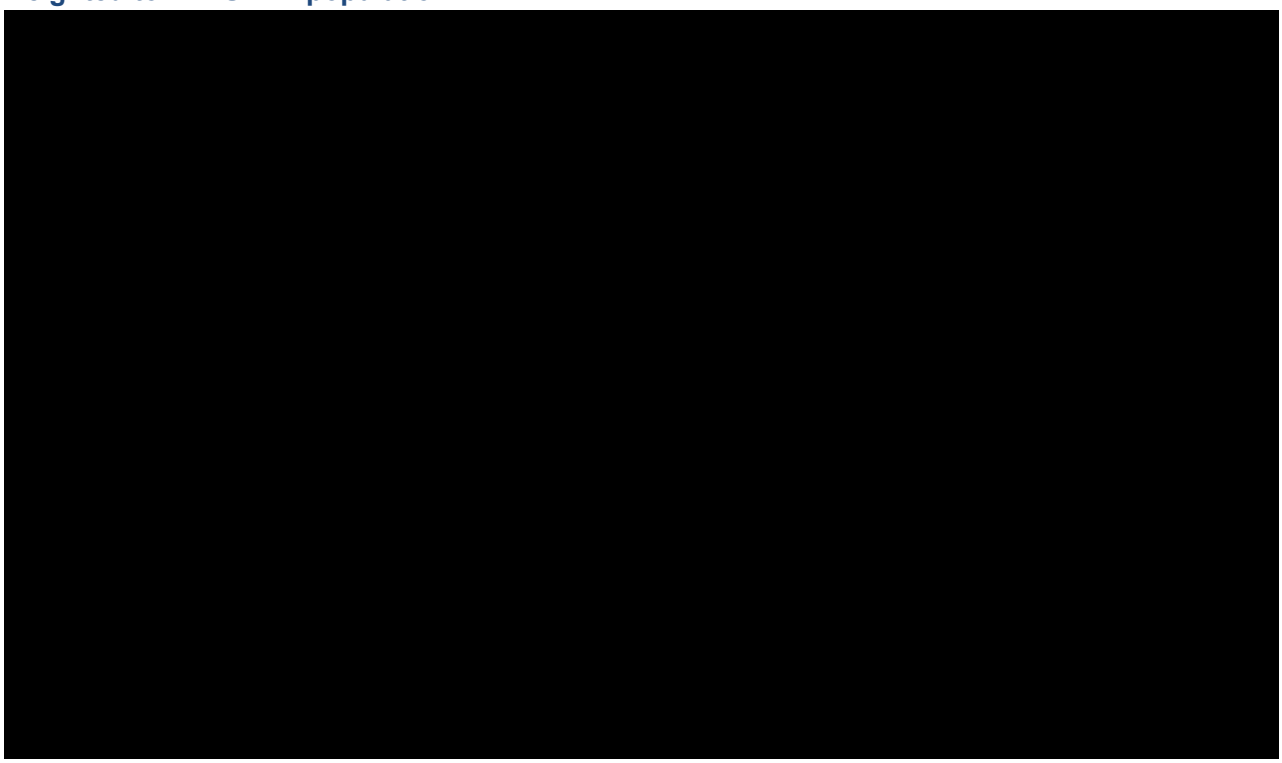
Figure 11. Osimertinib OS, standard parametric and smoothed hazard, weighted to FLAURA2 population

Abbreviations: OS: progression-free survival.

Figure 12. Osimertinib OS, spline-based and smoothed hazard, weighted to FLAURA2 population

Abbreviations: OS: progression-free survival.

Figure 13. Amivantamab-lazertinib PFS, standard parametric and smoothed hazard, weighted to FLAURA2 population



Abbreviations: PFS: progression-free survival.

Figure 14. Amivantamab-lazertinib PFS, spline-based and smoothed hazard, weighted to FLAURA2 population

Abbreviations: PFS: progression-free survival.

Figure 15. Osimertinib PFS, standard parametric and smoothed hazard, weighted to FLAURA2 population

Abbreviations: PFS: progression-free survival.

Figure 16. Osimertinib PFS, spline-based and smoothed hazard, weighted to FLAURA2 population

Abbreviations: PFS: progression-free survival.

Figure 17. Amivantamab TTD, standard parametric and smoothed hazard, weighted to FLAURA2 population

Abbreviations: TTD: time to treatment discontinuation.

Figure 18. Amivantamab TTD, spline-based and smoothed hazard, weighted to FLAURA2 population

Abbreviations: TTD: time to treatment discontinuation.

Figure 19. Lazertinib TTD, standard parametric and smoothed hazard, weighted to FLAURA2 population

Abbreviations: TTD: time to treatment discontinuation.

Figure 20. Lazertinib TTD, spline-based and smoothed hazard, weighted to FLAURA2 population

Abbreviations: TTD: time to treatment discontinuation.

Figure 21. Osimertinib TTD, standard parametric and smoothed hazard, weighted to FLAURA2 population

Abbreviations: TTD: time to treatment discontinuation.

Figure 22. Osimertinib TTD, spline-based and smoothed hazard, weighted to FLAURA2 population

Abbreviations: TTD: time to treatment discontinuation.

4 References

1. Royston P, Altman DG. Regression Using Fractional Polynomials of Continuous Covariates: Parsimonious Parametric Modelling. Journal of the Royal Statistical Society. Series C (Applied Statistics) 1994;43:429-467.

Clarification questions from the EAG in response to the additional analyses provided by the company in September 2025

a. Please provide the references for the fractional polynomial (FP) ITC based Cox regression described in 4.2.2.

The FP-NMA involved a 2-step approach:

1. Estimation of time-dependent treatment effects in the two trials separately, using FPs
2. Estimating the relative treatment effect between MARIPOSA and FLAURA2 based on the FPs estimated in part 1.

There is no specific reference for part 2 as this method follows assumptions made in part 1. The following references for part 1 are therefore the only references relevant to the FP ITC based Cox regression:

- Royston, Patrick, and Douglas G. Altman. “Regression Using Fractional Polynomials of Continuous Covariates: Parsimonious Parametric Modelling.” *Journal of the Royal Statistical Society. Series C (Applied Statistics)*, vol. 43, no. 3, 1994, pp. 429–67. *JSTOR*, https://doi.org/10.2307/2986270. (*already shared in reference pack*)
- Austin, P. C., Fang, J., & Lee, D. S. (2022). Using fractional polynomials and restricted cubic splines to model non-proportional hazards or time-varying covariate effects in the Cox regression model. *Statistics in medicine*, *41*(3), 612–624. https://doi.org/10.1002/sim.9259
- Therneau Terry, Crowson Cynthia, Atkinson Elizabeth, "Using Time Dependent Covariates and Time Dependent Coefficients in the Cox Model", R Survival Package Vignette, https://cran.r-project.org/web/packages/survival/vignettes/timedep.pdf

b. Please confirm if the plots presented in Attachment 2 (Cox_FPs_OS_PFSINV 2) are all related to this method?

Yes. The slide deck "Cox_FPs_OS_PFSINV.pptx" includes the Cox FP results. Parametric FP results are in the "Parametric_FPs_OS_PFSINV.pptx" slide deck. Both have been provided in our submission.

c. Please confirm if the data on rows 980 to 1475 of the ‘Data Storage’ sheets in the Excel model provide the first and second order FP-based Cox models giving a total of 44 models for each outcome (PFS and OS) and each trial (MARIPOSA and FLAURA-2).

Yes. The single order models are made up of two parameters and second order models made up of three. The 16 rows for the single order models therefore give eight curves. The 108 rows for the second order models therefore give 36 curves, totalling to 44 curves for each outcome and trial.

d. Please confirm that the 3rd order FP-based Cox models are not included in the Excel model and therefore not all 164 curves described in Section 4.2.2 are included in the

cost-effectiveness model. We are not requesting these to be added, but we just want to be clear if they are provided and hidden or not provided.

Confirming that 3rd order FP-based Cox models are not included in the Excel model and therefore not all 164 curves are included in the CE model.

e. Please confirm if the method described in Section 4.3.1 uses the Cope paper as the key reference. (Cope S, Chan K, Jansen JP. Multivariate network meta-analysis of survival function parameters. Research Synthesis Methods 2020;11: 443-456.) If not, please provide the references. Please confirm if the plots presented in Attachment 3 are all related to this method.

The Cope et al. (2020) paper is indeed the key reference for the method described in Section 4.3.1. However, the second step described by Cope at al. was modified to use a frequentist rather than Bayesian ITC. Consequently, it could be implemented directly in the model workbook, with indirect treatment effects estimated dynamically in response to user selection of survival distributions. We can confirm the plots in Attachment 3 are all related to this method.

f. Please confirm if the method in Section 4.3.2 uses the Jansen paper as the key reference. (Jansen, Jeroen P. "Network meta-analysis of survival data with fractional polynomials." BMC medical research methodology 11.1 (2011): 61) If not, please provide the references. Please confirm if the plots presented in Attachment 1 (Parametric_FPs_OS_PFSINV 2) are all related to this method.

Jensen et al., 2011 is the key reference for Section 4.3.2. An additional reference of interest is:

- Wiksten A, Hawkins N, Piepho HP, Gsteiger S. Nonproportional hazards in network meta-analysis: efficient strategies for model building and analysis. Value in Health. 2020 Jul 1;23(7):918-27. https://doi.org/10.1016/j.jval.2020.03.010

The plots presented in Attachment 1 are related to the Jensen et al., 2011 method.

g. Please provide a plot showing the KM data for TTD before and after adjusting for the matching to the FLAURA-2 population (i.e. equivalent to Figure 17 for OS and Figure 18 for PFS).

Figure 1. TTD KM data for amivantamab, lazertinib and osimertinib before and after adjusting for the matching to FLAURA2 population.

h. In the last row of Table 19 it is stated that the incidence of AEs for the osimertinib-chemotherapy arm has been informed by the updated FLAURA-2 DCO, but it is then stated on page 62 that the model has not been updated to reflect the updated AE data. The EAG believe the data in the model have not been amended and therefore the statement of page 62 is correct. Please clarify if the statement in Table 19 is therefore incorrect.

The data in the model has not been amended and therefore the statement on page 62 is correct. The rationale is due to the updated FLAURA2 DCO only reporting rounded integers for a smaller subset of AEs than the prior DCO. Given the similarity in incidence between the presented AEs in the prior and updated safety data between each DCO, we determined the more accurate approach would be to remain with the prior safety data.

i. The EAG believes there to be an error in the 'Scenario Analysis' sheet affecting the scenarios involving population adjustment (labelled scenarios 4 and 5 in Table 28; results in Table 27 are not affected by these scenarios). The EAG believes cell K11 should be 'opt_HR_PFS_adj' instead of 'opt_HR_PFS_adj_apply_limit' and cell L11 should be 'opt_HR_TTD_adj' instead of 'opt_HR_TTD_adj_apply_limit'. The EAG believes this means that the population adjustment is only occurring for the OS outcome in these two scenarios for the set of results presented in Table 28. The EAG has extracted what it believes are the correct results for these scenarios (see Table 1). Can the company please confirm if the results in Table 1 are correct. If not, can the company provide corrected results for these scenarios or explain why the original results are correct.

Thank you for the suggested changes to the model - we can confirm they are accurate, and therefore we agree with the proposed adjustments. Table 1 has the correct results.

Table 1: Extract from company's Table 28: Scenario analysis results for amivantamab-lazertinib versus osimertinib-chemotherapy (updated model; deterministic) [PAS prices] with EAG correction

Scenario		At amivantamab and lazertinib PAS prices		
		Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Base case		[redacted]	[redacted]	-987,103.32
4	Population adjustment	[redacted]	[redacted]	-440,623.99
5	Population adjustment with time limit	[redacted]	[redacted]	-511,869.27

Abbreviations: ICER: incremental cost-effectiveness ratio; incr: incremental; PAS: patient access scheme; QALYs: quality-adjusted life years; PF HSUV: progression-free health state utility value

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256].
A Single Technology Appraisal
3rd Addendum: EAG critique of the company's additional evidence

Produced by	Sheffield Centre for Health and Related Research (SCHARR), The University of Sheffield
Authors	Sarah Davis, Senior Research Fellow, SCHARR, University of Sheffield, Sheffield, UK Munira Essat, Senior Research Fellow, SCHARR, University of Sheffield, Sheffield, UK Sarah Ren, Research Associate, SCHARR, University of Sheffield, Sheffield, UK Sunhong Kwon, Research Associate, SCHARR, University of Sheffield, Sheffield, UK Emily Pulsford, Research Assistant, SCHARR, University of Sheffield, Sheffield, UK
Correspondence Author	Sarah Davis, Senior Research Fellow, SCHARR, University of Sheffield, Sheffield, UK
Date completed	29th October 2025

Source of funding: This report was commissioned by the NIHR Evidence Synthesis Programme as project number NIHR171848.

Declared competing interests of the authors

None of the other authors have any conflicts of interest to declare.

Rider on responsibility for report addendum

The views expressed in this report addendum are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

This addendum to the EAG report should be referenced as follows:

Davis S., Essat M., Ren S., Kwon S., Pulsford E. Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]. A Single Technology Appraisal – 3rd Addendum: EAG critique of the company's additional evidence. Sheffield Centre for Health and Related Research (SCHARR), 2025.

Contributions of authors

Sarah Davis was project lead. Munira Essat critiqued the clinical effectiveness evidence reported within the company's response to the draft guidance and Sarah Ren critiqued the statistical aspects. Sarah Davis critiqued the updated health economic analysis submitted by the company and undertook additional exploratory analyses.

1 Introduction

In August 2025, NICE held a second appraisal committee meeting (ACM2) to consider the responses to the draft guidance on amivantamab with lazertinib (ami-laz) for untreated epidermal growth factor receptor (EGFR) mutation-positive advanced non-small-cell lung cancer (NSCLC). Following ACM2, the NICE committee requested that the company provide additional analyses to support their decision making,[1] which we summarise briefly here as follows:

1. Both osimertinib with chemotherapy (osi-chemo) and osimertinib monotherapy (osi-mono) should be considered as relevant comparators in the decision problem and modelling assumptions should reflect this
2. For the indirect treatment comparison (ITC) of overall survival (OS) and progression free survival (PFS), alternative approaches using time-varying hazards and population adjustment should be explored, with the following approaches suggested:
    a. Parametric curves fitted to the data
    b. Fractional polynomials if parametric curve fits are inappropriate
    c. Population adjustment methods such as an anchored matching-adjusted indirect comparison (MAIC) to adjust the MARIPOSA trial population before fitting curves to each arm
    d. Time-varying hazards and population adjustment using multi-level network meta-regression could be explored
3. An ITC of adverse events (AE)
4. An ITC of time to treatment discontinuation (TTD)
5. An exploration of different progression-free (PF) utility values taking into account the findings from the ITC of AE and considering the time period over which any AEs may apply. For progressed disease (PD) the committee preferred the utility value from TA1060, but requested exploration of differences in subsequent treatments between arms.
6. Adjustment of the subsequent treatments for the osi-chemo arm modelled to reflect the committee's preferred assumptions which were:
    a. Second-line treatment to comprise of 50% platinum-based chemotherapy and 50% docetaxel
    b. Third-line treatment to comprise of best supportive care only
    c. Subsequent treatment initiation to align with discontinuation of osimertinib for patients treated with osi-chemo
    d. EAG's assumptions for the administration costs of subsequent treatments
    e. Scenarios analyses exploring the proportion using nintedanib with docetaxel and the proportion using atezolizumab with bevacizumab, carboplatin and paclitaxel (ABCP) as a third line treatment

The committee's request noted the availability of an updated data cut-off (DCO) from the FLAURA2 trial and the potential for these data to be used to inform the OS, PFS and TTD outcomes. As the above text provides only a brief summary the committee's request for additional analyses, please also refer to the exact wording of the request which will be available within the committee papers.[1]

In its response to the request from the NICE committee, the company provided some additional evidence including an updated cost-effectiveness analysis.[2] This third addendum to the EAG report provides a critique of the company's additional evidence (referred to hereafter as the CAE), and should be read in conjunction with the main EAG report and the previous two addendums.

Section 2 of this addendum focuses on describing any newly available primary evidence including the updated data from the final analysis of the FLAURA2 trial, and additional data presented by the company from the COCOON and PALOMA-3 studies. The EAG notes that Section 3 of the CAE presents evidence which it describes as providing a plausible explanation for the durable response of ami-laz and a clinical rationale for an expected long-term benefit in OS favouring ami-laz over osi-chemo. The evidence presented includes a discussion of resistance mechanisms, quality of response and immune mediate effects. The EAG considers that these additional outcomes fall outside of the scope and has therefore not critiqued this part of the CAE. The CAE then provides a discussion of the comparative adverse events profiles for ami-laz versus osi-chemo and discusses how these may impact outcomes through limiting the duration of first-line treatment (specifically pemetrexed in FLAURA2) or affecting the fitness of patient to receive subsequent treatments. The EAG has not critiqued this additional evidence on the basis that any impact of AEs on TTD or subsequent treatments, should already be captured within the outcomes reported in the MARIPOSA and FLAURA2 trials. Given the limited time available to prepare this addendum, the EAG has therefore focused on the sections of the CAE which directly address the committee's request and which directly inform the cost effectiveness analysis.

Sections 3.1 to 3.8 of this addendum describe and critique the company' response to the request for alternative methods to be explored for the ITCs of PFS, OS and TTD (requests 2 and 4). Section 3.9 of this addendum addresses the ITC for AEs (request 3). Sections 4.1 describes and critiques the updated cost-effectiveness analysis provided by the company (requests 5 and 6), which is followed by the company's updated cost-effectiveness results in Section 4.2. Section 5.1 presents the methods for the EAG's additional analyses, followed by the results for these analyses in Section 5.2. Section 6 provides the EAG's conclusions on the company's additional evidence and a discussion of the remaining uncertainties.

2 Summary of additional primary data included in the CAE

2.1 FLAURA2 final analysis

The company provided updated data (DCO 12th June 2025) from the FLAURA2 trial for osimertinib with pemetrexed and platinum-based chemotherapy (osi-chemo) and osimertinib monotherapy (osi-mono). These data were presented at the International Association for the Study of Lung Cancer (IASLC) 2025 World Conference on Lung Cancer (WCLC)[3] on 7th September 2025.

2.1.1 OS

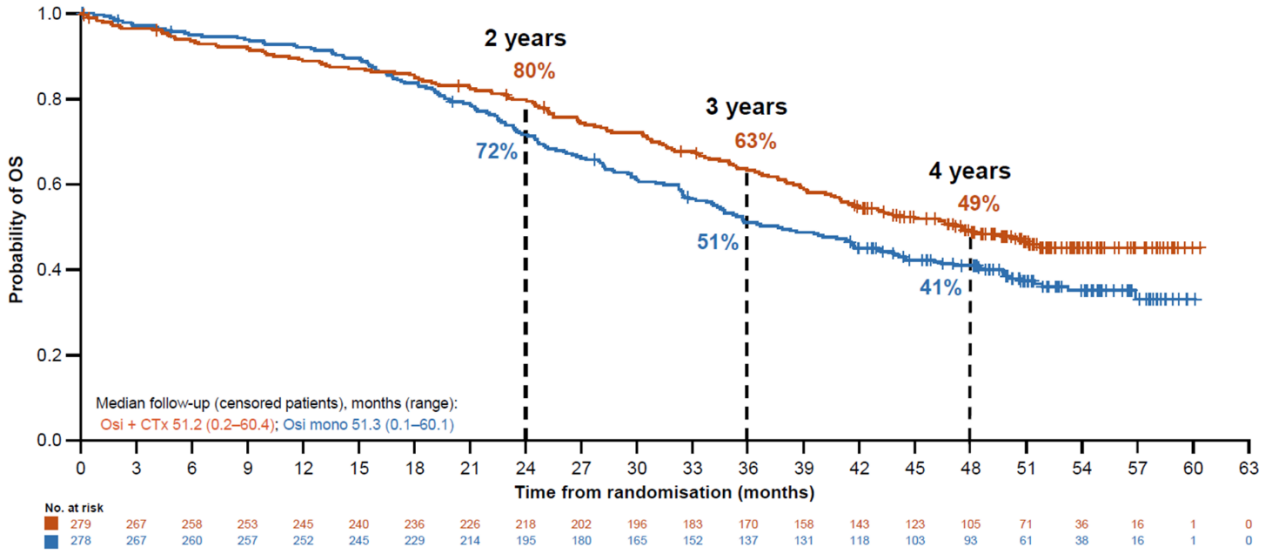
Osi-chemo demonstrated a statistically significant improvement in OS compared with osi-mono (47.5 months vs 37.6 months) hazard ratio [HR] = 0.77 at the final analysis (DCO: 12 June 2025), with a median follow-up of 51.2 months. Table 1 presents the updated OS data from the final analysis alongside the previous data from the 8 January 2024 DCO. The corresponding Kaplan–Meier (KM) curve for the latest DCO (12 June 2025) is shown in Figure 1.

Table 1 FLAURA2 OS results based on 8th January 2024 and 12th June 2025 DCOs (reproduced from CAE, Table 2)

	DCO: 12th June 2025[3]		**DCO: 8th January 2024[4]**	
	Osi-chemo (N=279)	**Osi-mono (N=278)**	**Osi-chemo (N=279)**	**Osi-mono (N=278)**
Event, n (%)	144 (51.6)	171 (61.5)	100 (35.8)	126 (45.3)
mOS, months (95% CI)	47.5 (41.0, NC)	37.6 (33.2, 43.2)	NR (38.0, NC)	36.7 (33.2, NC)
HR (95% CI)	0.77 (0.61, 0.96)		0.75 (0.57, 0.97)	
p-value	0.0202		0.0280	

Abbreviations: CI: confidence interval; DCO: data cut-off; HR: hazard ratio; mOS: median overall survival; NC: not calculable; NR: not reported; OS: overall survival.
Source: Planchard *et al.* (2025);[3] Valdiviezo *et al.* (2024).[4]

Figure 1 KM plot of OS, 12th June 2025 DCO; FAS (reproduced from CAE, Figure 1)



Abbreviations: FAS: full analysis set; KM: Kaplan-Meier; OS: overall survival.
Source: Adapted from Planchard *et al.* (2025).[3]

The company stated that although osi-chemo demonstrates a statistically significant improvement in OS versus osi-mono at the final OS analysis (DCO: 12th June 2025) of FLAURA2 trial, the increasing HR and narrowing of the curves around 39 months, implies an uncertainty around the long-term durability of survival benefit.

2.1.2 PFS and TTD

The company noted that in the update there was no new information on PFS or TTD, therefore the company did not include any updated data on these outcomes.

2.1.3 AEs

A summary of AE data from FLAURA2 (DCOs: 12 June 2025 and 3 April 2023) and the MARIPOSA trial is presented in Table 2.

No new safety signals were reported in the final analysis of FLAURA2, and the AE profiles between the two DCOs (12 June 2025 and 3 April 2023) were comparable. A higher proportion of patients in the osi-chemo arm experienced Grade ≥3 and serious AEs (SAEs) compared to those in the osi-mono arm (70% vs 34% and 46% vs 27%, respectively). AEs leading to discontinuation of osimertinib occurred in 12% of patients in the osi-chemo arm versus 7% in the osi-mono arm.[3] AEs leading to death were reported in 8% of patients receiving osi–chemo, compared with 4% for osi-mono.[3]

In EAG report Addendum 2 (Tables 12 and 13), the EAG presented AE data from the MARIPOSA trial and from FLAURA2 (DCO: 3 April 2023). Comparing AE data from MARIPOSA with the updated FLAURA2 data (DCO: 12 June 2025) shows that the incidence of serious AEs was higher in the ami-laz arm of MARIPOSA than in the osi-chemo arm of FLAURA2 (55% vs 46%), and the proportion of patients experiencing Grade ≥3 AEs was also higher (80% vs 70%).

However, the company explored an adjusted comparison of the AEs of ami-laz compared with osi-chemo and osi-mono and looked at the relative proportion of Grade ≥3 AEs and SAEs in osi-chemo compared to ami-laz (see Table 3). This suggested that overall, osi-chemo has a higher relative incidence of Grade ≥3 AEs and SAEs compared to ami-laz. Furthermore, the company indicated that the incidence of AEs over time was comparable across both trials, with most events taking place in the first 4 months of treatment.[15,21]

Table 2 Summary of AEs observed in FLAURA2 and MARIPOSA (adapted from CAE, Table 3 and EAG Addendum 2, Table 12)

	FLAURA2				MARIPOSA	
	12th June 2025 DCO		3 April 2023 DCO		4th December 2024 DCO	
AE any cause, n (%)	**Osi-chemo (N=276)**	**Osi-mono (N=275)**	**Osi-chemo (N=276)**	**Osi-mono (N=275)**	**Ami-laz (N=421)**	**Osi-mono (N=428)**
Any grade	276 (100)	269 (98)	276 (100%)	268 (97%)	421 (100.0)	426 (>99.5)
Grade ≥3	193 (70)	94 (34)	176 (64)	75 (27)	337 (80.0)	224 (52)
Serious	126 (46)	75 (27)	104 (38)	53 (19)	233 (55)	177 (41)
AE leading to death	22 (8)	10 (4)	18 (7)	8 (3)	37 (9)	34 (8)
AEs leading to discontinuation of any study agent	NR	NR	NR	NR	[redacted]	[redacted]
AEs leading to discontinuation of osimertinib	34 (12)	20 (7)	30 (11)	17 (6)	NA	[redacted]
AEs leading to discontinuation of pemetrexed	137 (50)	NA	NR	NA	NA	NA
AEs leading to discontinuation of platinum chemotherapy	46 (17)	NA	NR	NA	NA	NA

AEs leading to dose reduction of any study agent	NR	NR	27 (10)	8 (3)	[redacted]	[redacted]
AEs leading to dose interruption of any study agent[c]	NR	NR	120 (43)	52 (19)	[redacted]	[redacted]
AEs leading to discontinuation of osimertinib	34 (12)	20 (7)	NR	NR	NA	NR
AEs leading to discontinuation of pemetrexed	137 (50)	NA	NR	NA	NA	NA
AEs leading to discontinuation of platinum chemotherapy	46 (17)	NA	NR	NA	NA	NA

[c] Excludes infusion related reactions.
Abbreviations: AE: adverse event; DCO: data cut off; NA: not applicable; NR; not reported; SAS: safety analysis set
Source: Planchard *et al.* (2025);[3] Planchard *et al.* (2023).;[5] *Yang et al.* (2025)[6]

Table 3 Relative proportion of Grade ≥3 AEs and SAEs in the MARIPOSA and FLAURA2 trials (reproduced from CAE, Table 11)

	MARIPOSA		FLAURA2	
	AMI-LAZ	**OSI**	**OSI-CT**	**OSI**
Median follow-up, months	38		51	
Grade ≥3 AEs, %	80	52	70	34
% difference, intervention versus comparator arm	+54		+106	
SAEs, %	55	41	46	27
% difference, intervention versus comparator arm	+34		+70	

Abbreviations: AE: adverse event; AMI-LAZ: amivantamab-lazertinib; OSI: osimertinib; OSI-CT: osimertinib-chemotherapy; SAE: serious adverse event.

Grade ≥3 AEs data from the FLAURA2 trial were consistent across the two DCO points: 3rd April 2023 and 12th June 2025 (see Table 4). However, when compared with data from the MARIPOSA trial, the AE profiles appear to differ between the two treatment regimens. As previously noted by the EAG in EAG report, Addendum 2, Section 3.3, ami-laz was associated with higher rates of Grade ≥3 AEs such as rash, paronychia, infusion-related reactions (IRRs) and deep-vein thrombosis (DVT). In contrast, osi-chemo was associated with higher rates of Grade ≥3 anaemia, neutropenia and thrombocytopenia. Due to the difference in the leading mechanism of action (MOA) for toxicities between the two treatment

arms, as well as influences by various trial-level factors such as follow-up intensity and data cut-off timing, a comparison of specific AE data between the two regimens becomes difficult, hence, caution should be applied. The risk difference of AEs of any grade in MARIPOSA versus FLAURA2 is presented in Figure 2 and the risk difference or Grade ⩾3 AEs in MARIPOSA versus FLAURA2 in Figure 3.

The comparison of the osi-mono arm in FLAURA2 and MARIPOSA trial showed that although the types of AE in the osi-mono arm in both trials were broadly similar (rash, diarrhoea, dry skin, pneumonitis), the rates of Grade ≥3 events, SAE and treatment discontinuations differed markedly, indicating that the population in the MARIPOSA study were more prone to having a SAE or Grade ≥3 AEs recorded. Further details are provided in Addendum 2, Section 3.3, Table 12 and Table 13.

Table 4 Grade ≥3 AEs based on FLAURA2 and MARIPOSA trial (adapted CAE, Table 4)

Adverse events (%)	**FLAURA2**				**MARIPOSA[6]**	
	Osi-chemo (N=276) DCO: 12th June 2025[3]	**Osi-mono (N=275) DCO: 12th June 2025[3]**	**Osi-chemo (N=276) DCO: 3rd April 2023[5]**	**Osi-mono (N=275) DCO: 3rd April 2023[5]**	**Ami-laz (N=421)**	**Osi-mono (N=428)**
Anaemia	20	1	20	<1	5	2
Diarrhoea	3	<1	3	<1	2	1
Nausea	1	0	1	0	1	<1
Decreased appetite	3	1	3	1	1	2
Constipation	<1	0	<1	0	0	0
Rash	1	0	<1	0	17	1
Fatigue	3	<1	3	<1	1	1
Vomiting	1	<1	1	0	NR	NR
COVID-19	1	0	1	0	2	2
Stomatitis	<1	<1	1	<1	1	<1
Paronychia	1	<1	1	<1	12	<1
Neutropenia	14	1	14	1	NR	NR
Neutrophil count decreased	12	1	11	1	NR	NR
ALT increased	2	1	1	<1	7	2
Thrombocytopenia	7	1	7	1	1	1
IRR	0	0	0	0	6	0
Pulmonary embolism	NR	NR	NR	NR	9	3
Dermatitis acneiform	NR	NR	NR	NR	9	0

Deep-vein thrombosis	NR	NR	NR	NR	3	<1

Abbreviations: AE: adverse event; ALT: alanine transaminase; DCO: data cut off.
Source: Planchard *et al.* (2025);[3] Planchard *et al.* (2023).;[5] *Yang et al.* (2025)[6]

Figure 2 Risk difference for AEs of any grade in MARIPOSA versus FLAURA2 (reproduced from CAE, Figure 20)

Based on MARIPOSA FA and FLAURA2 FA
Abbreviations: AE: adverse event; ALT: alanine transaminase.

Figure 3 Risk difference for Grade ≥3 AEs in MARIPOSA versus FLAURA2 (reprroduced from CAE, Figure 21)

Based on MARIPOSA FA and FLAURA2 FA
Abbreviations: AE: adverse event; ALT: alanine transaminase.

2.2 COCOON Interim Analysis

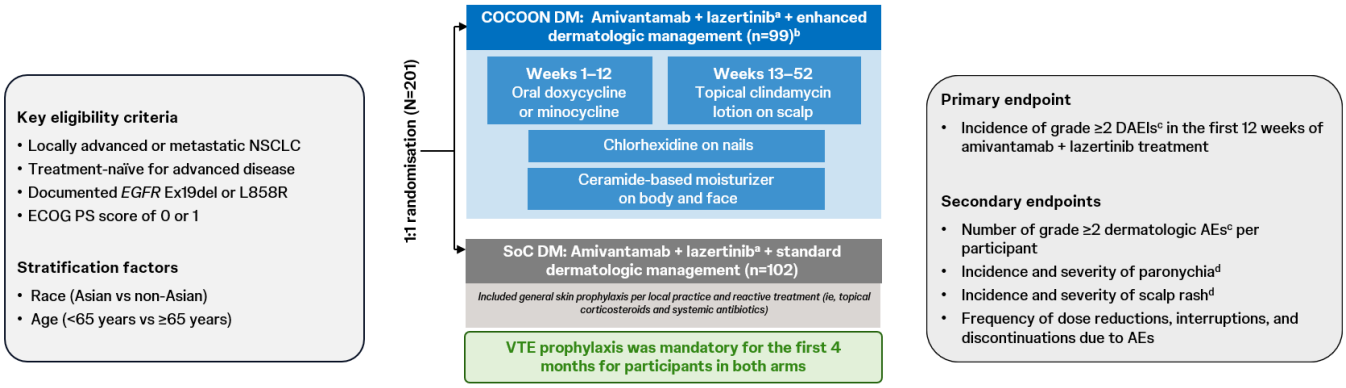
To address the higher incidence of dermatologic AEs, such as rash, observed with ami-laz arm compared to osi-mono arm in the MARIPOSA trial, the company provided supporting evidence from the COCOON trial (NCT06120140), which evaluated the effectiveness of enhanced dermatologic management strategies in reducing the burden of dermatologic toxicity.

The COCOON trial (NCT06120140) is a Phase 2, open-label, multicentre trial designed to assess the impact of enhanced dermatologic management (COCOON DM) versus standard of care dermatologic management (SoC DM) on the incidence and severity of dermatological AEs among patients with common EGFR-mutated (cEGFRm) advanced or metastatic NSCLC receiving first line intravenous (IV) amivantamab in combination with lazertinib.

The population in MARIPOSA and COCOON are similar, as both included patients with cEGFRm (Exon 19 deletion or L858R) NSCLC, receiving first-line treatment with amivantamab in combination with lazertinib and included patients who are treatment-naïve, with advanced or metastatic disease. However, it should be noted that the COCOON trial is smaller in size (n=199).

In the COCOON trial patients were randomised (1:1) to COCOON DM (N=99) or SoC DM (N=100). All patients, regardless of arm, received general skincare recommendations, including avoiding exposure to sunlight, wearing protective clothing (including a hat and sunglasses), using broad spectrum sunscreen (SPF>30), and avoiding alcohol-based topical agents, and patients could receive reactive treatment upon occurrence of skin toxicity as per local practice.[7] Patients in the COCOON DM arm received prophylactic antibiotics (twice-daily oral doxycycline or minocycline 100 mg during weeks 1–12; once-daily topical clindamycin 1% lotion on the scalp before bedtime starting at week 13 and onward), once-daily chlorhexidine 4% to wash the fingernails and toenails, and a ceramide-based moisturiser on the body and face at least once daily for skin moisturisation for the duration of the study. Patients in the SoC DM arm were managed according to local clinical practice, and there was no standard preventive regimen. The COCOON study design is presented in Figure 4.[7]

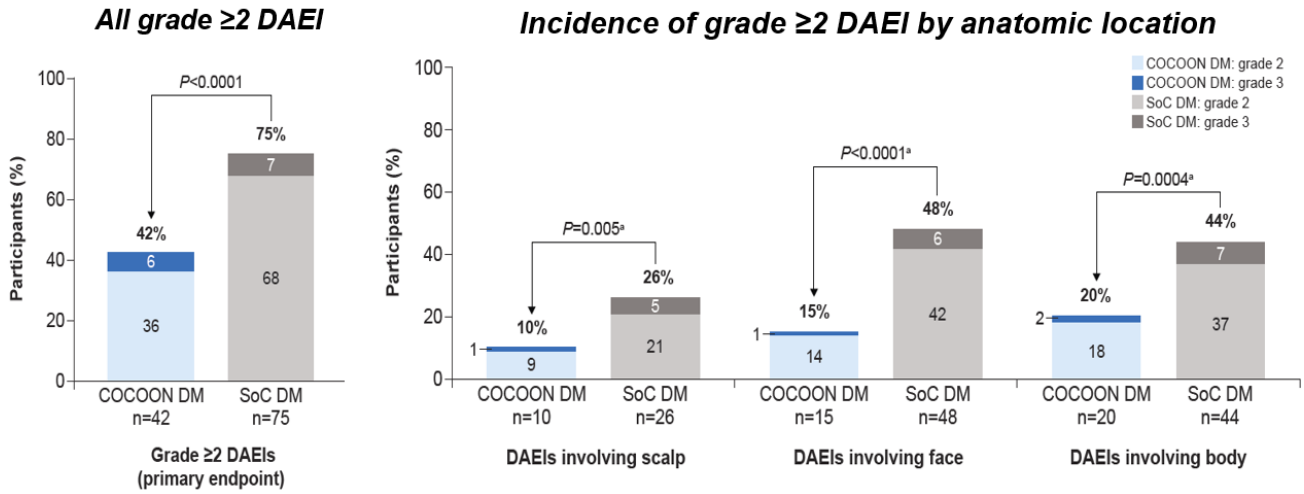
Figure 4 COCOON study design (reproduced from CAE, Figure 28)



Footnotes: [a]IV amivantamab was administered at 1050 mg (1400 mg if ≥80 kg) once weekly for 4 weeks and every 2 weeks thereafter; lazertinib was orally administered daily at 240 mg. [b]Prophylactic antibiotics: oral doxycycline or minocycline 100 mg BID; topical clindamycin lotion 1% on scalp QD before bedtime. Paronychia prophylaxis: chlorhexidine 4% on the fingernails and toenails QD. Skin moisturization: La Roche Posay Lipikar AP+M moisturiser on the body and face at least QD. [c]DAEIs include rash, dermatitis acneiform, pruritus, skin fissures, acne, folliculitis, erythema, eczema, maculopapular rash, skin exfoliation, skin lesion, skin irritation, dermatitis, rash erythematous, rash macular, rash papular, rash pruritic, rash pustular, dermatitis contact, dermatitis exfoliative generalised, drug eruption, dyshidrotic eczema, eczema asteatotic, and paronychia. [d]AE severity per NCI CTCAE v5.0.
Abbreviations: AE: adverse event; BID: twice daily; CTCAE: Common Terminology Criteria for Adverse Events; DAEI: dermatologic adverse event of interest; DM: dermatologic management; ECOG: European Cooperative Oncology Group; EGFR: epidermal growth factor receptor; Ex19del: exon 19 deletion; IV: intravenous; L858R: exon 21 L858R substitution; NCI: National Cancer Institute; NSCLC: non-small cell lung cancer; QD: once a day; SoC: standard of care; VTE: venous thromboembolism.
Source: Adapted from Cho *et al.* (2025)[8]

The primary endpoint in the COCOON trial, is the incidence of Grade**2 dermatologic AEs of interest (DAEI). The primary endpoint was evaluated at the pre-planned interim analysis after 12 weeks of study follow-up (see Figure 5). During the first 12 weeks of treatment with ami-laz, the incidence of Grade *2 DAEI was significantly lower for patients treated with COCOON DM compared to those treated with SoC DM (42% versus 75% respectively; odds ratio [OR]: 0.24 [95% CI, 0.13–0.45]; P<0.0001).[7] Reductions in the incidence of Grade ≥2 DAEIs by anatomic location were also observed (see Figure 5).[7]

Figure 5 Results from COCOON, pre-planned 12-week interim analysis (reproduced from CS, Figure 29)



Footnotes: [a]Nominal *P* value
Abbreviation: CI: confidence interval; DAEI: dermatologic adverse event of interest; DM: dermatologic management; OR: odds ratio; SoC: standard of care.
Source: Cho *et al.* (2025)[7]

The company stated that the COCOON DM prophylactic regimen is widely available in routine clinical practice therefore patients in UK clinical practice would be treated with ami-laz with COCOON DM for cEGFRm advanced or metastatic NSCLC, and would therefore be expected to experience fewer DAEI compared to those in MARIPOSA, with incidence rates more similar to those observed in COCOON. Furthermore, the company stated that the use of COCOON DM over SoC DM did not have any material impact on the antitumour effect, the objective response rate was ami-laz (82% [95% CI, 73–89] versus 75% [95% CI, 65–83], respectively, at a median follow-up of 7.1 months. The number of participants who had a partial response was 79 (82%) in the COCOON DM arm versus 74 (74%) in the SoC DM arm; the number of participants who had stable disease was 10 (10%) in the COCOON DM arm versus 17 (17%) in the SoC DM arm. As the median duration of follow-up was 7.1 months, the median PFS and median duration of response were not reached in both treatment arms.[7, 8]

2.3 PALOMA-3

The CAE also summarised AE outcomes from the PALOMA-3 study. The majority of these data were previously presented and discussed in EAG report Addendum 2 (Section 2.4.1.6) based on outcomes reported by Leighl *et al.*[9] These data are therefore not discussed further in this addendum as they have been previously critiqued by the EAG. The data on hypoalbuminemia and peripheral oedema, appeared to be updated as they are redacted, but these data were very similar to the data presented previously by the EAG based on the publication by Leighl *et al*.[9] Some additional information was also presented on AEs having a ≥5% difference between arms. This showed substantial differences in myalgia (16% vs 6%), weight loss ([redacted]% versus [redacted]%) and hypotension ([redacted]% versus [redacted]%) for subcutaneous (SC) versus IV formulations. The company concludes that, *"the treatment-related adverse event (TRAE)*

profile of SC amivantamab-lazertinib is largely comparable to IV amivantamab-lazertinib, except for a reduction in rates of IRRs and VTE with the SC formulation where the profile is more favourable for SC administration."

3 Indirect treatment comparisons

3.1 Anchored MAIC for PFS, OS and TTD

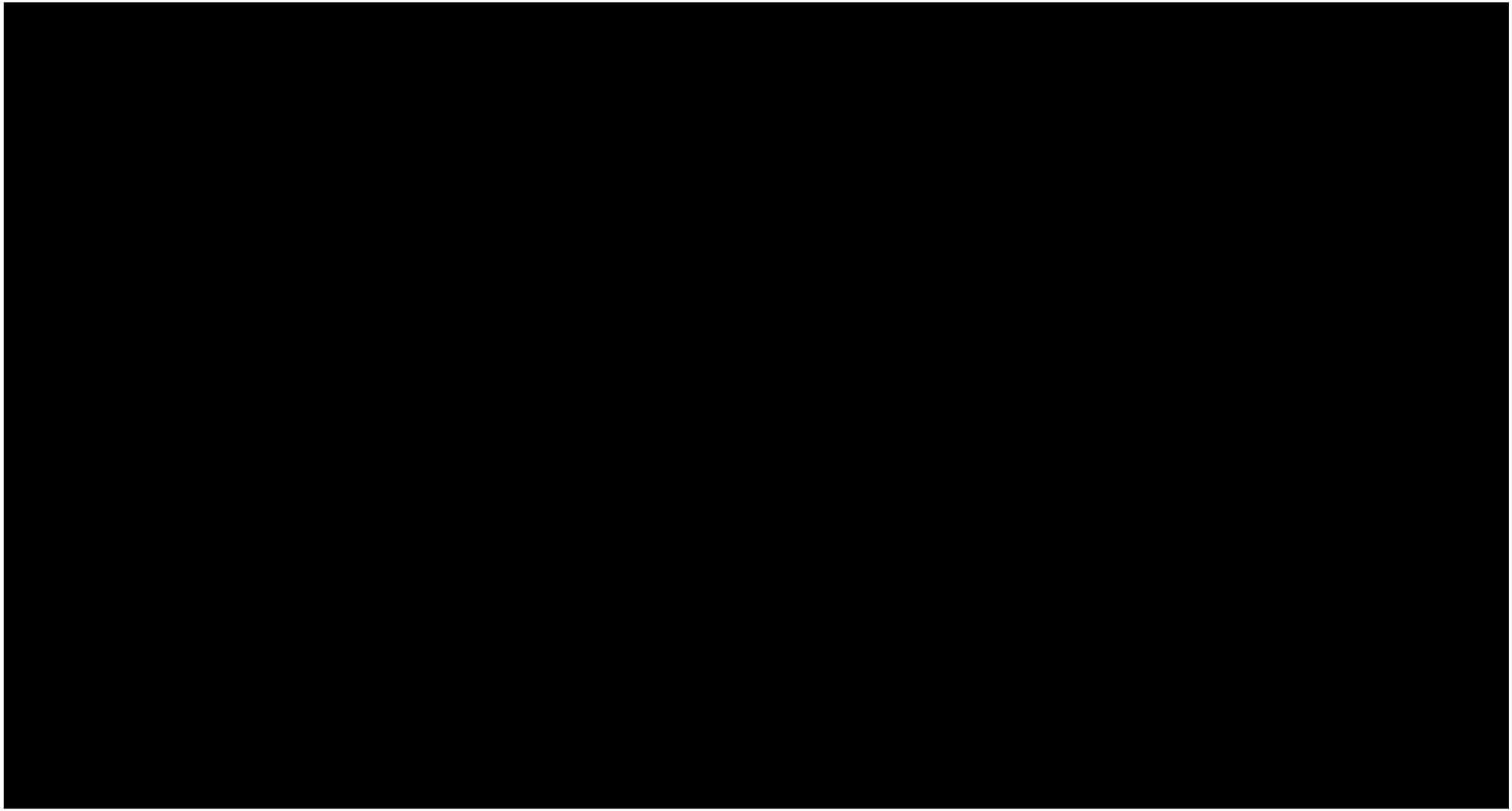
The company has conducted a MAIC analysis to match the MARIPOSA patients to the FLAURA2 population on the following baseline characteristics: ECOG, exon 19 deletion, L858 mutation, liver metastases, bone and locomotor system metastases, age, race, sex, smoking status and histologic tumour type. The baseline characteristics before and after matching are presented in Table 5. The effect sample size after matching is 693. The adjusted and unadjusted KM curves for OS, PFS and TTD are presented in Figure 6, Figure 7 and Figure 8. , respectively, with adjusted curves being close to unadjusted curves. The matching had a limited impact on the HR, with OS HR of [redacted] after matching, compared to 0.75 (95% CI: 0.61 to 0.92) before matching, and PFS INV HR of [redacted], compared to [redacted] before matching. The company stated that the anchored MAIC was not considered as a scenario due to the lack of treatment effect modification by differences in measured baseline characteristics.

Based on the evidence presented by the company, the EAG notes that the anchored MAIC appears to have appropriately adjusted for the population differences. The EAG also considers a scenario analysis based on a constant HR estimated using the anchored MAIC to be inappropriate due to the violation of proportional hazard assumption.

Table 5. Baseline characteristics before and after matching MARIPOSA patients to the FLAURA2 population (reproduced from CAE, Table 10)

Baseline characteristic	FLAURA2	MARIPOSA, before matching	MARIPOSA, after matching
ECOG 0 (%)	37	34	[redacted]
ECOG 1–2 (%)	63	66	[redacted]
Exon 19 deletion (%)	62	60	[redacted]
L858 mutation (%)	38	40	[redacted]
Liver metastases (%)	19	16	[redacted]
Bone and locomotor system metastases (%)	49	46	[redacted]
Age, median	61.5	63	[redacted]
Race: Asian (%)	63	59	[redacted]
Race: white (%)	28	38	[redacted]
Race: other (%)	9	3	[redacted]
Sex: male (%)	38	39	[redacted]
Current or former smoker (%)	33	31	[redacted]
Histologic type: adenocarcinoma (%)	99	97	[redacted]
Histologic type: other (%)	1	3	[redacted]

Figure 6. Ami-laz and osi-mono OS before and after matching to FLAURA2 population (reproduced from CAE, Figure 17)



Abbreviations: OS: overall survival.

Figure 7. Ami-laz and osi-mono PFS before and after matching to FLAURA2 population (reproduced from CAE, Figure 18)

Abbreviations: PFS: progression free survival.

Figure 8. TTD KM data for amivantamab, lazertinib and osimertinib before and after adjusting for the matching to FLAURA2 population (reproduced from Figure 1 of the company's response to clarification questions on the CAE)

3.2 Unanchored MAIC for PFS, OS and TTD

An unanchored MAIC approach was selected in the company's base case analysis. In this approach, patients from the MARIPOSA trial were reweighted using weights obtained in the anchored MAIC. Then standard parametric models and spline models were fitted to the reweighted MARIPOSA data to inform the long-term extrapolation for ami-laz and osi-mono. For osi-chemo, survival models were fitted directly to FLAURA2 data to inform long term extrapolation (see section 4.1.1 for a discussion of the choice of curves fitted to the updated FLAURA2 data). This approach allows all three interventions to be modelled in the FLAURA2 population and it was used in the company's base case for their updated economic analysis.

The EAG notes that although the unanchored MAIC adjusts for population differences between MARIPOSA and FLAURA2, this approach is not protected by randomisation. The EAG also notes that although unanchored MAIC allows for long-term extrapolation to support cost-effectiveness comparisons, it does not provide an estimate of relative clinical effectiveness.

3.3 Population adjustment methods presented at ACM2 for PFS, OS and TTD

At ACM2, the company explored using the HR between the osi-mono arms in the two trials as a reference to adjust for population differences. In the CAE following ACM2, the company presented results using this previous approach as scenario 4 in their economic analysis. The company also presented results using this approach but with a time limit for the adjustment (47 months for OS, 33 months for PFS and TTD) as scenario 5 in their economic analysis.

3.4 Naïve comparison presented at ACM2 for PFS, OS and TTD

At ACM2, the EAG preferred not to incorporate the population adjustment described in Section 3.3 and instead preferred a naïve comparison obtained by fitting survival models to both arms of the MARIPOSA trial and the osi-chemo arm of the FLAURA 2 trial directly. This was because the EAG considered that the population adjustment lacked face validity because the adjustment went one way for PFS and the other way for OS. This approach, which was the EAG's preferred approach at ACM2, has been presented as scenario analysis 3 in the company's updated economic analysis.

3.5 Parametric ITC for PFS, OS and TTD

The company has also explored a parametric ITC approach,[10] which requires fitting the same distributions to data from MARIPOSA and FLAURA2. The company stated that there was no common distribution that would adequately model outcomes in all four arms of MARIPOSA and FLAURA2, especially in the case of OS and TTD. Regardless of that, the company has attempted to reparametrize exponential, Weibull, gamma and log-normal as special cases of generalised gamma models. Parametric ITC for PFS is feasible with reparameterization. For OS, the company stated that it was not possible to

conduct a parametric ITC without selecting a distribution with inadequate fit for the osi-chemo arm of FLAURA-2. For TTD, the company had to select an alternative standard parametric fit (Weibull) for the osimertinib component of the osi-chemo arm. The treatment effect of osi-chemo was estimated using parametric ITC and then applied to osi-mono to inform the long-term extrapolations of osi-chemo. The curve choices selected for this comparison are shown Table 6 and the extrapolations for osi-chemo are shown in Figure 9. This approach was applied as scenario analysis 7 in the company's updated economic analysis. The company also presented, as scenario 9 in the economic model, an analysis in which the parametric ITC approach was applied for PFS, but the base case approach was applied for TTD and OS, meaning that the reweighted data were used to reflect the FLAURA2 population.

Fitting the same parametric distributions to data from both MARIPOSA and FLAURA2 makes the use of parametric ITC approach challenging. The EAG is content with the distributions selected in company's scenario analysis 7. The EAG notes that using Weibull distributions for both OS and TTD data from MARIPOSA and FLAURA2 may have provided less adequate fit compared to the models used in the company's base case but considered the long-term extrapolations to be still plausible. The EAG has presented an additional scenario analysis (ASA) using the parametric ITC applied to the EAG's preferred base case (see Section 5.1.5).

Table 6. Standard parametric curves explored in scenario analyses (modified from Table 25)

Endpoint	Treatment	Curve Choice	Rationale
PFS	Ami-laz	Gamma	Maintains the accepted curve.
	Osi-mono	Gamma	Maintains the accepted curve.
	Osi-chemo	Weibull	Maintains the accepted curve.
OS	Ami-laz	Weibull	Maintains the accepted curve.
	Osi-mono	Weibull	Maintains the accepted curve.
	Osi-chemo	Weibull	Does not fit the shape of the KM curve, provides unrealistically high survival based on clinical validation, but is the least unfavourable fitting of the available options.
TTD	Amivantamab	Spline, normal scale, 2 knots	Maintains the accepted curve.
	Lazertinib	Spline, hazard scale, 1 knot*	Maintains the accepted curve.

	Osi-mono	Weibull	Previously presented by the Company as the most appropriate parametric curve.
	Osimertinib component of osi-chemo	Weibull	Does not fit the shape of the KM curve and is higher than earlier company base case but is the least unfavourable of the available options.
	Chemotherapy component of osim-chemo	Exponential	EAG preferred curve.

Abbreviations: EAG: External Assessment Group; OS: overall survival; PFS: progression-free survival; TTD: time-to-treatment discontinuation. Splines can be used for amivantamab and lazertinib TTD since the reference treatment for osimertinib-chemotherapy is osimertinib monotherapy. *The EAG has modified a typo for the distribution used here.

Figure 9. Long-term OS, PFS and TTD projections of osimertinib-chemotherapy from parametric ITC with distributions selected for scenario analysis (reproduced from Figure 42)

Abbreviations: ITC: indirect treatment comparison; PFS: progression-free survival; OS: overall survival; TTD: time to discontinuation.

3.6 Fractional polynomial ITC using parametric models for PFS and OS

Fractional polynomial (FP) ITC with parametric models was also used to allow for flexible modelling of outcomes. In this analysis, FPs were used to model log hazard function of each arm.[11, 12] Specifically, the company fitted 44 FPs to all four treatment arms of MARIPOSA and FLAURA2, including 8 first order FPs and 36 second order FPs. Then a time-dependent treatment effect of ami-laz versus osi-chemo was estimated using differences of the FP parameters. The long-term extrapolation of osi-chemo was informed by applying the HR obtained to the ami-laz extrapolation (Weibull for unadjusted OS and gamma for unadjusted PFS). The company stated that parametric FPs were not included in the health economic model as they either estimated extreme hazards or provided inadequate fit.

The EAG agrees with the company that the time-dependent HR of ami-laz versus osi-chemo was not properly estimated using parametric FPs and the results from parametric FPs were uncertain.

3.7 Piecewise Cox regression models for PFS and OS

To relax the constant HR assumption of the standard Cox regression model, the company explored using a piecewise Cox regression model for ITC.[13] Using this method, the trial period was divided into several shorter intervals, and a separate constant HR was estimated for each interval using the piecewise Cox regression model. Interval-specific HRs were obtained for ami-laz versus osi-mono and osi-chemo versus osi-mono separately using data from MARIPOSA and FLAURA2. Then the HRs of ami-laz versus osi-chemo were obtained for each interval, which were then applied to the ami-laz extrapolation to obtain the osi-chemo extrapolation. Results were presented for a four-interval model as well as a five-interval model and the company concluded that the osi-chemo extrapolations are sensitive to the time cutoff point selection. OS extrapolations for osi-chemo using piecewise Cox regression model are presented below in Figure 10.

The EAG notes that the osi-chemo extrapolation beyond the trial follow up period relies on the HR obtained for the last interval. The HR of osi-chemo versus ami-laz was estimated to be [redacted] for >26 months in the 4-interval model and [redacted] for >35 months in the five-interval model. Applying such HRs would assume that osi-chemo has a higher hazard than ami-laz from 26 months and 35 months onward, respectively, corresponding to a larger survival benefit for ami-laz. The EAG considered that the piecewise Cox regression models did not appear to fit the data well in years 1-2 and the EAG were concerned that the assumption of a fixed HR in the long term lacked face validity. The approach was presented as scenario analysis 6 in the company's updated economic analysis.

Figure 10. OS Extrapolations for osi-chemo obtained by applying piecewise Cox model HRs to ami-laz (reproduced from CAE, Figure 8)

Abbreviations: HR: hazard ratio; KM: Kaplan-Meier; OS: overall survival; CP: chemotherapy; pw: piecewise.

3.8 Fractional polynomial ITC using Cox regression for PFS and OS

A Cox regression model[14] with time-dependent treatment effect modelled by fractional polynomials[15] was explored in this analysis. A total of 164 FP-based Cox models of orders 1, 2, and 3 with powers -2, -1, -0.5, 0, 0.5, 1, 2 and 3 were fitted to MARIPOSA and FLAURA2 separately to capture the complex shape of the treatment effect. The relative treatment effect of ami-laz versus osi-chemo was estimated by taking the difference of the parameters fitted to MARIPOSA and FLAURA2. The smoothed plot for log HR is presented in Figure 11. The estimated log HR of osi-chemo versus ami-laz is presented in Figure 12 for OS and Figure 13 for PFS for all the fitted models.

A [redacted] polynomial with power [redacted] was selected for estimating OS HR and first order polynomial with power 0 (i.e. log transformation of time) was selected for estimating PFS HR. The estimated HR of osi-chemo versus ami-laz has a monotonically increasing trend, suggesting that the hazard of osi-chemo is continuously increasing compared to osi-chemo, as presented in Figure 14 for OS and Figure 15 for PFS. The long-term extrapolations of osi-chemo, presented in Figure 16 for OS and Figure 17 for PFS, were informed by applying the estimated HR to ami-laz (Weibull for unadjusted OS and gamma for unadjusted PFS). This approached was presented as scenario analysis 8 in the company's updated economic analysis.

The EAG notes that the smoothed log HR plots for ami-laz versus osi and osi-chemo versus osi have similar change patterns with decreasing tails. The log HR plot for ami-laz versus osi-mono started to decline earlier than the plot for osi-chemo versus osi-mono at the tail of the curve, potentially leading

to the survival gain for ami-laz compared to osi-chemo. This appears to have been translated into a monastically increasing tail for the estimated log HR of osi-chemo versus ami-laz using fractional polynomials. In practice, a HR that favours ami-laz increasingly over time without bound is unlikely to be clinical plausible. Therefore, the EAG explored a modified scenario by assuming the HR of osi-chemo versus ami-laz stabilised after 38 months (median follow-up from MARIPOSA), providing a more plausible ITC scenario. For OS, this resulted in the HR stabilising at [redacted], whereas for PFS, this resulted in the HR stabilising at [redacted] This EAG exploratory analyses is provided in Section 5. The EAG notes one limitation of this approach is that the modelled HR of ami-laz versus osi-chemo shows a different trend to the smoothed time-dependent HR.

Figure 11: Time-dependent treatment effect for OS in MARIPOSA and updated FLAURA2 (reproduced CAE, from Figure 7)

Abbreviations: AMILAZ: amivantamab-lazertinib; F2: FLAURA2; HR: hazard ratio; M: MARIPOSA; OS: overall survival; OSI: osimertinib; OSICP: osimertinib-chemotherapy.

Figure 12. Osi-chemo versus ami-laz , time-dependent relative treatment effect on OS with FP-based Cox models (reproduced CAE, from Figure 11)

Abbreviations: amilaz: amivantamab-lazertinib; FP: fractional polynomial; F2OSICP: FLAURA2 osimertinib-chemotherapy; HR: hazard ratio; M1AMILAZ: MARIPOSA amivantamab-lazertinib; NMA: network meta-analysis; osicp: osimertinib-chemotherapy

Figure 13. Osi-chemo versus ami-laz , time-dependent relative treatment effect on PFSINV with FP-based Cox models (reproduced from CAE, Appendix Figure 6)

Abbreviations: amilaz: ami-laz ; FP: fractional polynomial; F2OSICP: FLAURA2 osimertinib-chemotherapy; HR: hazard ratio; M1AMILAZ: MARIPOSA amivantamab-lazertinib; NMA: network meta-analysis; osicp: osimertinib-chemotherapy

Figure 14. OS HR estimated using Cox FP [power [redacted] (reproduced from CAE, Attachment 2 page 57)

Figure 15. PFS HR estimated using Cox FP [[redacted]] (reproduced from CAE, Attachment 2 page 2)

Figure 16. OS Extrapolations for osi-chemo obtained by Cox FP [power [redacted] relative treatment effect estimate applied to ami-laz (reproduced, CAE from Figure 12)

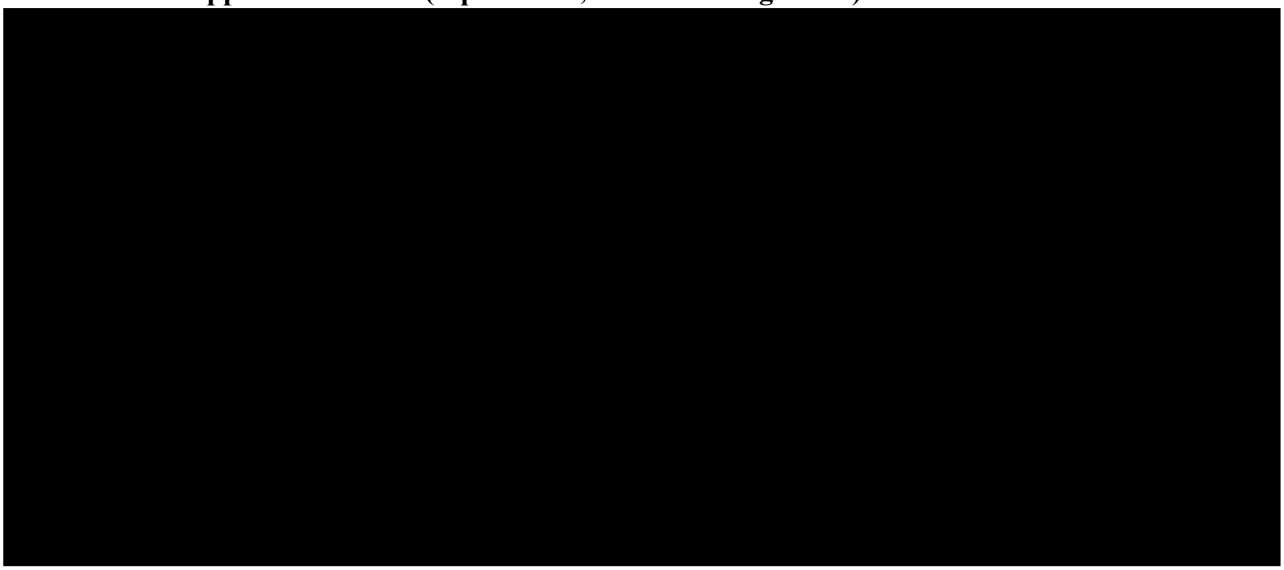


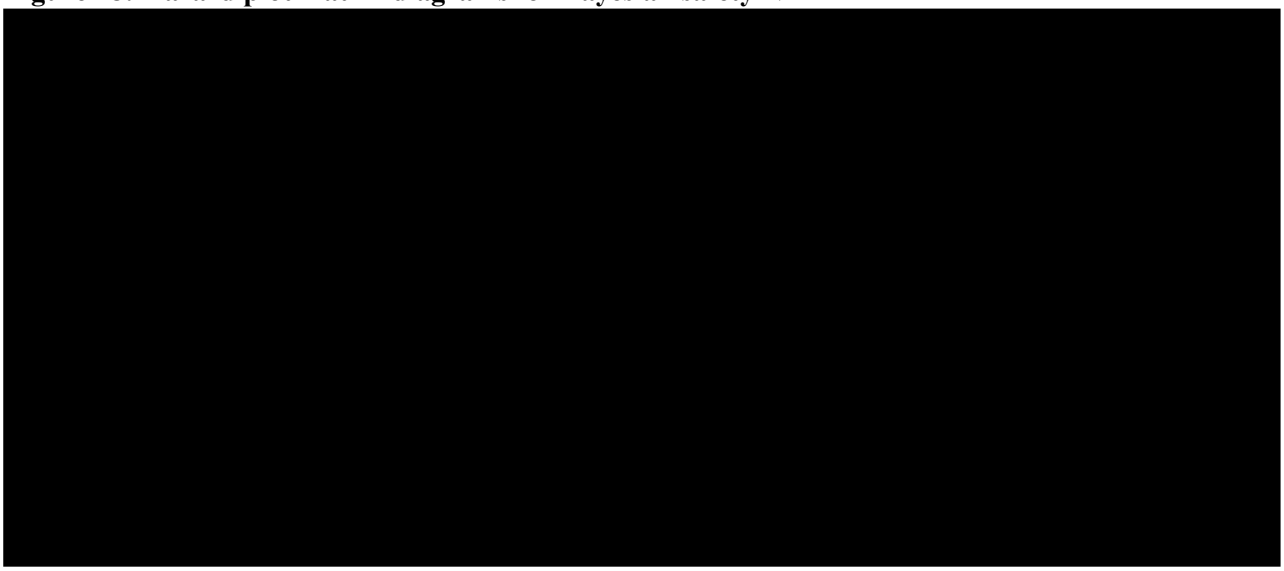
Figure 17. PFSINV Extrapolations for osi-chemo obtained by Cox FP [redacted])] relative treatment effect estimate applied to ami-laz (reproduced from CAE, Appendix Figure 8)

3.9 ITC of adverse events

A Bayesian NMA was used to compare the safety profile of ami-laz and osi-chemo, with results presented in Figure 18. The odds ratio (OR) of ami-laz versus osi-chemo was estimated to be [redacted] forGrade≥3 AEs and [redacted] for SAEs. An anchored MAIC was also conducted to adjust for the population differences between MARIPOSA and FLAURA2. A summary of MAIC results for Grade ≥3 AEs and SAEs is presented in Figure 19 and Figure 20 with different sets of covariates adjusted. The similarity between the adjusted and

unadjusted ORs suggests that the adjustment had a limited impact on the results. The EAG considers both ITC analysis to be appropriate.

Figure 18: Hazard plot matrix diagrams for Bayesian safety NMA



Abbreviations: AE: adverse event; AMI+LAZ: amivantamab-lazertinib; DC: data cut; FE: fixed effect; NMA: network meta analysis; OSI: osimertinib; OSI-CP: osimertinib-chemotherapy; SAE: serious adverse event.

Figure 18: MAIC results for Grade ≥3 AEs

Abbreviations: AE: adverse event; AMI+LAZ: amivantamab-lazertinib; OR: odds ratio; OSI: osimertinib; OSI+CP: osimertinib-chemotherapy.

Figure 19: MAIC results for SAEs

Abbreviations: AE: adverse event; AMI+LAZ: amivantamab-lazertinib; OR: odds ratio; OSI: osimertinib; OSI+CP: osimertinib-chemotherapy.

3.10 Summary of the ITC methods

A summary of all ITC methods is presented in Table 7. The EAG considers the use of an unanchored MAIC to be appropriate for the base case analysis, as it allows for population adjustment and accommodates a time-varying HR, but notes that the unanchored MAIC does not provide an estimate of the relative treatment effect for ami-laz versus osi-chemo. The anchored MAIC is protected by randomization, but it relies on a constant HR for indirect treatment comparison. The four ITC methods that allow for time-varying hazard ratios, including parametric ITC, fractional polynomial ITC using parametric models, piecewise Cox regression models and fractional polynomial ITC using Cox regression, do not adjust for the population differences between MARIPOSA and FLAURA2. The piecewise Cox regression method is sensitive to the choice of cutoff points and the results lack face validity. When using the fractional polynomial approach to model the hazard function of each arm with the so called parametric fractional polynomial ITC method, they either provide extreme estimates to the hazard function or inadequate fit to the survival curve.

Overall, the EAG did not consider that any of the alternative ITC methods explored by the company were preferable to the approach used in the company's updated base case but it has presented the parametric ITC approach and the fractional polynomial ITC using Cox regression approach in its scenario analysis. Requiring the same parametric distributions across MARIPOSA and FLAURA2 makes the use of parametric ITC approach challenging. The EAG is content with the distributions selected in company's scenario analysis 7 and has kept the same options in its ASA (see Section 5.1.5). Fractional polynomial ITC using Cox regression provides a better estimate of the hazard ratio of ami-

laz versus osi-chemo, compared to the parametric fractional polynomial ITC method and piecewise Cox regression models. The EAG modified the fractional polynomial ITC using Cox regression approach in a scenario analysis to provide a more plausible ITC scenario (See Section 5.1.5). The EAG notes one limitation of this approach is that the modelled HR of ami-laz versus osi-chemo shows a different trend to the smoothed time-dependent HR.

Table 7. Summary of the ITC methods

Methods	Outcomes	Adjust for population differences?	Allow for a time-varying hazard ratio?	Use a common comparator for ITC?
Anchored MAIC	PFS, OS, TTD	Y	N	Y
Unanchored MAIC	PFS, OS, TTD	Y	Y	N
Population adjustment methods presented at ACM2	PFS, OS, TTD	Y	N	N
Naive comparison presented at ACM2	PFS, OS, TTD	N	Y	N
Parametric ITC	PFS, OS, TTD	N	Y	Y
Fractional polynomial ITC using parametric models	PFS, OS	N	Y	Y
Piecewise Cox regression models	PFS, OS	N	Y	Y
Fractional polynomial ITC using Cox regression	PFS, OS	N	Y	Y

4 Updated economic analysis provided by the company

4.1 Methods of the company's updated cost-effectiveness analysis

4.1.1 Updated FLAURA2 data

More mature data from FLAURA2 are now available (DCO: 12th June 2025) for OS but not for PFS and TTD. These updated data were used to inform the unanchored MAIC in which the osi-chemo arm is modelled based on the FLAURA2 data. After digitalising the published KM curve and reconstructing pseudo-IPD, the company fitted standard parametric and spline models to inform the osi-chemo extrapolation. Two-knot hazard spline model was selected as the base case based on visual inspection, Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), clinical plausibility, expert clinical validation and the results from TA1060.

After checking the AIC/BIC, visual fit, hazard plots and clinical plausibility, the EAG notes that two-knot odds and two-knot normal spline models are also plausible alternatives. The AIC/BIC of two-knot odds and two-knot normal spline models are within one-point difference to that of the two-knot hazard spline model. The long-term extrapolations from two-knot odds and two-knot normal spline models are higher than that of the two-knot hazard spline model. The hazard plots of two-knot odds and two-knot normal spline models have a decreasing tail, similar to the tail of the smoothed hazard plot, while the hazard plot from the two-knot hazard model has an increasing tail. Due to the uncertainty in the tail of the smoothed hazard plot, the EAG considers two-knot hazard, odds and normal spline models all to be plausible. The osi-chemo extrapolation in the company's base case was modelled using a two-knot hazard spline model with the unanchored MAIC approach. The EAG has explored an alternative scenario using a two-knot normal spline model to model OS for osi-chemo and this is further described in Section 5.1.4.

For TTD of osimertinib component of osi-chemo, the EAG notes that the company has maintained its preference of using the average of the gamma and the Gompertz curves fitted to the TTD data from FLAURA2. There have been no new TTD data to inform this extrapolation and the company's choice is consistent with their preference at ACM2. The company did however note that the updated DCO from FLAURA2 indicated higher treatment exposure to osimertinib in the osi-chemo arm versus the osi-mono arm (30.5 months versus 21.2 months). It considered that this data supported its choice of TTD curve for osi-mono. It also stated that clinical validation of the modelling supported a TTD curve for the osimertinib component of osi-chemo that remains higher than the PFS for osi-chemo and higher than the TTD curve for osi-mono. Although the EAG has maintained the company's choice in its base case, the EAG has explored an alternative extrapolation in a scenario analysis, using its preferred approach at ACM2. This is further discussed in Section 5.1.4.

Figure 20. Long-term OS projections of osi-chemo (reproduced, CAE from Figure 30)

Abbreviations: CP: chemotherapy; KM: Kaplan-Meier; OS: overall survival; OSI: osimertinib.

Table 8. AIC and BIC of osi-chemo OS (reproduced CAE, from Table 15)

Distribution	AIC	BIC	AIC Rank	BIC Rank
Exponential	1524.04	1527.67	14	5
Weibull	1520.10	1527.36	12	4
Lognormal	1548.94	1556.20	16	16
Loglogistic	1527.75	1535.01	15	15
Gompertz	1515.77	1523.03	5	1
Gamma	1521.74	1529.00	13	6
Generalised gamma	1518.55	1529.44	10	7
1-knot hazard scale	1515.70	1526.59	4	2
2-knot, hazard scale	**1517.78**	**1532.31**	**8**	**13**
3-knot, hazard scale	1514.13	1532.29	3	12
1-knot, odds scale	1516.42	1527.31	6	3
2-knot, odds scale	**1517.55**	**1532.08**	**7**	**11**
3-knot, odds scale	1513.83	1531.99	2	10
1-knot, normal scale	1518.94	1529.84	11	8
2-knot, normal scale	**1518.31**	**1532.83**	**9**	**14**
3-knot, normal scale	1513.36	1531.51	1	9

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; OS: overall survival.

Figure 21. Osi-chemo OS standard parametric and smoothed hazard plots (reproduced from CAE, Figure 31)

Abbreviations: OS: overall survival.

Figure 22. Osi-chemo OS spline and smoothed hazard plots (reproduced from CAE, Figure 32)

Abbreviations: OS: overall survival.

4.1.2 Reweighted MARIPOSA population

The MARIPOSA population was reweighted to match the FLAURA2 population to account for the population differences. The reweighted data were used to inform the company's base case using the unanchored MAIC. The company has fitted new survival curves to the reweighted data for OS, PFS and TTD for ami-laz and osi-mono. The same distributions were selected for extrapolation of the reweighted data. However, the model selection process was not described in the report.

After checking the AIC/BIC included in the economic model, the visual fit of the curves, the hazard plots presented in the appendix, and clinical plausibility, the EAG considers using the same distributions to be appropriate. As the two populations have similar baseline characteristics, the adjusted and unadjusted KM curves are closely aligned, with comparable follow-up durations and only small reductions in sample size. Therefore, it is reasonable that the same distribution remains the best fit.

However, the EAG has explored the sensitivity of the cost-effectiveness results to an alternative extrapolation for the osi-mono arm in it additional analyses, and this is further described in Section 5.1.4.

4.1.3 Summary of the curves for OS, PFS and TTD

Summary of the selected base case curve choices for OS, PFS and TTD used in the company's base case are presented in Table 9, Table 10 and Table 11, respectively. Summary of the selected base case extrapolations for OS, PFS and TTD are presented in Figure 24, Figure 25 and Figure 26, respectively.

Table 9: Selected base case extrapolations for OS in the updated model (adapted, CAE from Table 16)

	Selected base case extrapolation	Rationale
Ami-laz	Weibull	Aligned with Committee preference and no change when assessed within the unanchored MAIC
Osi-mono	Weibull	Aligned with Committee preference and no change when assessed within the unanchored MAIC
Osi-chemo	Two-knot hazard	Selected by the company based on the updated FLAURA2 data

Abbreviations: OS: overall survival; MAIC – matching-adjusted indirect comparison.

Figure 23: Long-term OS projections of ami-laz, osi-mono and osi-chemo selected for the base case in the updated model (reproduced from CAE, Figure 33)

Abbreviations: OS: overall survival; KM: Kaplan-Meier curve.

Table 10: Selected base case extrapolations for PFS in the updated model (reproduced from CAE, Table 17)

	Selected base case extrapolation	Rationale
Ami-laz	Gamma	Preferred by the EAG as part of the initial DGD response
Osi-mono	Gamma	Preferred by the EAG as part of the initial DGD response
Osi-chemo	Weibull	Preferred by the EAG as part of the initial DGD response

Abbreviations: PFS: progression-free survival.

Figure 24: Long-term PFS projections of ami-laz , osi-mono and osi-chemo selected for the base case (reproduced from CAE, Figure 34)

Abbreviations: PFS: progression-free survival.

Table 11: Selected base case extrapolations for TTD in the updated model (reproduced from CAE, Table 18)

	Selected base case extrapolation	Rationale
Amivantamab	2-knot Normal	Committee preference
Lazertinib	1-knot Hazard	Committee preference
Osi-mono	1-knot Normal	Committee preference
Osimertinib component of osi-chemo	Average of Gompertz and Gamma	Best fit to longer-term expectations, and aligns to PFS, OS, and the other accepted TTD curves
Chemotherapy component of osi-chemo	Exponential	EAG preference

Figure 26: Long-term TTD projections of ami-laz , osi-mono and osi-chemo selected for the base case (reproduced from CAE, Figure 35)

Abbreviations: TTD: time to discontinuation

4.1.4 Utilities

The company has updated the utility value applied in the progressed-disease (PD) state to match the value applied in TA1060, which the committee preferred. In its base case analysis, the company prefers to apply the treatment-specific utility values for the progression-free (PF) state from MARIPOSA for the ami-laz and osi-mono arms. The company also prefers to assume that the PF utility value from MARIPOSA can be applied to the osi-chemo arm of the model, although it claims that this approach is conservative for the following reasons:

a) the ITC for adverse events (see Section 3.10) shows a more favourable profile for ami-laz versus osi-chemo
b) the incidence of grade ≥3 AEs and SAEs may have been underestimated in FLAURA2 due to their lower incidence in the osi-mono arm compared with the osi-mono arm of MARIPOSA, meaning that the pooled utility value from FLAURA2 is higher than it would be if AEs were accurately captured.
c) the use of SC amivantamab would reduce time spent in a clinical setting and would result in an improved AE profile versus IV amivantamab, both of which have the potential to improve utilities for patients receiving ami-laz in clinical practice versus those observed in MARIPOSA.
d) enhanced dermatological management has the potential to reduce dermatological AEs resulting in improved utilities for patients reiving ami-laz versus those observed in MARIPOSA (see Section 2.2)
e) there is no publicly available evidence that supports an improved utility for patients stopping the chemotherapy element of the osi-chemo treatment combination.

The EAG accepts that it is plausible that osi-chemo may have lower utility for reason (a), although it notes that the ITC for AEs did not identify a statistically significant difference in favour of ami-laz, therefore the hypothesis of similar AEs cannot be rejected. The EAG also accepts that reasons (c) and (d) provide a plausible rationale for expecting higher utilities for ami-laz in clinical practice than were recorded in MARIPOSA, however, the size of any utility gain is unclear, meaning that all that can be said is that the company's analysis may be conservative.

The EAG does not follow the company's logic in reason (b). The company describes *"the pooled osimertinib monotherapy and osimertinib-chemotherapy PF HSUV [health state utility value] from FLAURA2*" as being 0.794. It then goes on to argue that this value is likely to be artificially inflated if AEs were not adequately captured in FLAURA2, therefore the true pooled utility values from FLAURA2 would be expected to be lower. It then makes a comparison against the pooled utility value from MARIPOSA to try to infer a comparison between osi-chemo and ami-laz on the basis that both pooled estimates contain the treatment of interest pooled with osi-mono. However, the EAG notes that in the committee papers for TA1060 (EAG report, p67), the PF utility value of 0.794 is described as being based on mapping outcomes from EORTC-QLQ-C30 to EQ-5D-3L using data from the original FLAURA study, which compared osi-mono to a standard EGFR- tyrosine kinase inhibitor (gefitinib or erlotinib). The values obtained from the FLAURA2 study in the committee papers for TA1060 are all redacted, and the EAG could not corroborate this value of 0.794 as having been based on outcomes from FLAURA2. This means that the company cannot infer anything from comparing the value 0.794 to the pooled utility from MARIPOSA. Furthermore, it is unclear whether differences in the AEs between the FLAURA2 and MARIPOSA osi-mono arms are based on differences in AE reporting or differences in the propensity of the recruited population to experience AEs.

In a scenario analysis, the company explored the impact of changing the PF utility for ami-laz to 0.794. This had the effect of also increasing the utility for osi-mono as this was calculated by applying the difference between ami-laz and osi-chemo from MARIPOSA to the ami-laz PF utility ([redacted]=0.794+[redacted]). However, the osi-chemo value remained unchanged at [redacted]. The application of this scenario does not match the company's description of this scenario analysis (CAE, Section 6.3), where they state that the osi-mono utility for PF remained at [redacted].

Whilst the EAG can see that the company's scenario analysis provides a situation this is consistent with its position that ami-laz has the potential to have higher utility than osi-chemo, whilst maintaining the difference in utility from osi-mono observed in MARIPOSA, the EAG does not follow the company's logic for applying the value of 0.794 for ami-laz. It also believes that the company has implemented this scenario analysis differently from it intended approach as it states that the value of [redacted] has been applied for osi-mono, but [redacted] has been implemented. The EAG has therefore provided a corrected version of this scenario analysis within the scenario analyses applied to the company's base case

(Scenario 2b in Table 14 and Table 15). However, it does not consider that the alternative value applied for ami-laz has any particular evidential basis given that it was obtained FLAURA and not FLAURA2 and is therefore more likely to be predictive of the PF utility for osi-mono than ami-laz.

The EAG notes that the company has not explored the potential for utilities to improve in patients having osi-chemo when the chemotherapy element of the combination treatment is discontinued, as suggested by the committee.

The EAG prefers to use the treatment-dependent PF utility estimates from MARIPOSA in its base case, which is consistent with its approach at ACM2 and the company's updated base case. It also accepts the company's update to include PD utility from TA1060 as being consistent with the committee's stated preference. The EAG agrees that applying the same utility values for ami-laz and osi-chemo may be conservative. However the EAG considers that the magnitude of any difference is uncertain, and the redaction of estimates from FLAURA2 within TA1060, make it difficult to identify values that could be explored in scenario analyses.

Table 12 Summary of the utilities applied by the company and EAG prior to ACM1 and those explored in the company's updated economic analysis

	Source	**PF: ami-laz**	**PF: osi-mono**	**PF: osi-chemo**	**PD: all treatments**
Company's updated base case	Treatment specific PF utility values for ami-laz and osi-mono from MARIPOSA; osi-chemo set equal to ami-laz; and value from TA1060 for PD	[redacted]	[redacted]	[redacted]	0.678
Company's scenario 1 - as described	As for base case but with ami-laz PF utility set to value from TA1060	0.794	[redacted]	[redacted]	0.678
Company's scenario 1 - as implemented	As for base case but with ami-laz PF utility set to value from TA1060 and osi-mono value set relative to ami-laz.	0.794	[redacted]	[redacted]	0.678

4.1.5 Subsequent treatments

The company has updated the mix of subsequent treatments applied in the model in response to the committee's request. It has assumed that at second-line, 50% of patient receive platinum-based chemotherapy and 50% receive non-platinum-based chemotherapy. This is applied equally across all three treatment arms, such that treatments received at second-line are not dependent on whether the patient received chemotherapy first-line. However, the EAG does not believe that the committee's request should be interpreted as applying to patients who did not receive chemotherapy within their first-line treatment. This was firstly because it interpreted the committee's as applying only to patients having osi-chemo as first-line treatment, and secondly because the company and EAG were previously aligned on second and third-line treatments in patients having either ami-laz or osi-mono as first-line treatment. Therefore, in the EAG's preferred base case (see section 5.1.2.) it continued to assume that 100% of second-line treatment would be platinum-based chemotherapy for patients having either ami-laz or osi-mono as first-line treatment, as this assumption was consistent across the company and EAG models considered at ACM2.

In addition, the company has assumed that all patients receive best supportive care at third-line, which they state is in-line with the committee's preferences. However, again, the EAG does not believe that the committee's preference was for this assumption to apply to patients having ami-laz or osi-mono as first-line treatment, as these patients still have the option of non-platinum-based chemotherapy available after receiving platinum-based chemotherapy second-line. In both the company and the EAG's preferred base case models at ACM2, the proportion receiving BSC in third-line was based on the MARIPOSA-2 trial for patients having either ami-laz or osi-mono first-line. Therefore, in the EAG's preferred base case (see Section 5.1.2) it continued to apply these data for the ami-laz and osi-mono arms and only applied the assumption of 100% receiving BSC for the osi-chemo arm. This was consistent with the EAG's preference at ACM2.

The EAG notes that the committee requested that the second-line treatment for patients having first-line osi-chemo should be docetaxel and requested that company should explore the proportion of patients receiving nintedanib with docetaxel. The EAG notes that the company was not explicit about the proportion of patients receiving nintedanib alongside docetaxel in its response to clarification (question 42 of the clarification questions pertaining to the original company submission). However the EAG believes from examining the company's model that 50% are assumed to receive nintedanib because the drug cost per week is £6.32 for docetaxel, £501.92 for nintedanib, but only £257.28 (=6.32+0.5*501.92) for the combination. The EAG's clinical advisors stated previously that nintedanib would be offered alongside docetaxel where patients were fit enough to receive it. Therefore, the EAG has kept has the company's assumption of 50% nintedanib usage alongside docetaxel in its base case, but has explored the impact of reducing this to 0% and increasing it to 100% in scenario analyses (see Section 5.1.7).

The committee also requested that the company explore the proportion of third-line usage of atezolizumab with bevacizumab, carboplatin and paclitaxel (ABCP) in a scenario analysis. However the company has not provided any scenarios exploring this. The EAG has therefore addressed this in its ASAs (see Section 5.1.8).

The company incorporated the EAG's preferred assumption to align the timing of subsequent treatments for the osi-chemo arm to the TTD for the chemotherapy element of osi-chemo, as requested by the committee. The company also incorporated the EAG's preferred assumptions at ACM2 for administration costs for subsequent treatments, as requested by the committee. The EAG was satisfied with the company's implementation of these changes as the company maintained the EAG's previous methods.

4.1.6 Other changes to the model which align with EAG preferences at ACM2

The company made several changes to its base case which aligned with the EAG's base case at ACM2. These included:

- incorporating the EAG's corrections to the company's model, with the exception of the choice of TTD curve for the osimertinib component of osi-chemo which the company did not consider to be an error
- setting the mean age to 68.5 to reflect the mean age in the Systemic Anti-Cancer Therapy Dataset cohort as quoted in the DGD
- using the outpatient cost for administration of a simple chemotherapy (SB12Z) to reflect administration costs for subcutaneous amivantamab
- selecting the gamma model to extrapolate PFS for ami-laz and osi-mono instead of the generalised gamma model

4.2 Results of the company's updated analysis

The results presented in this addendum for the company's updated base case, sensitivity and scenario analyses incorporate an updated patient access scheme discount for amivantamab ([redacted]) which was shared with the EAG on 28th of October 2025. For this reason, the results presented here differ from those provided in the CAE.

4.2.1 Company's updated base case

The results for the company's updated base case are provided in Table 13 for both the deterministic analysis and the probabilistic analysis. It should be noted that these results incorporate the PAS discounts for amivantamab and lazertinib but use list prices for comparator first-line treatments and subsequent line treatments. The EAG notes that there is a -23% difference between the incremental

QALYs for ami-laz versus osi-chemo when comparing the probabilistic results to the deterministic results. This appears to be driven by the fact that the QALYs in the osi-chemo arm are higher in the probabilistic analysis, and the incremental QALY gains for ami-laz versus osi-chemo are small, meaning that small differences in absolute gains for individual treatments translate into large percentage changes in incremental QALY gains.

Table 13: Company's updated base case with PAS prices for amivantamab and lazertinib and list prices for comparator drugs

Option	Absolute outcomes by treatment arm			Incremental outcomes for ami-laz versus comparator			ICER (£/QALY)
	LYGs*	QALYs	Costs (£)	LYGs	QALYs	Costs (£)	
Company's updated base case using list price for comparators - deterministic							
Ami-laz	5.10	[redacted]	[redacted]				
Osi-mono	3.77	[redacted]	[redacted]	1.33	[redacted]	[redacted]	Ami-laz dominates
Osi-chemo	4.75	[redacted]	[redacted]	0.35	[redacted]	[redacted]	Ami-laz dominates
Company's updated base case using list price for comparators – probabilistic							
Ami-laz	5.14	[redacted]	[redacted]				
Osi	3.79	[redacted]	[redacted]	1.35	[redacted]	[redacted]	Ami-laz dominates
Osi-chemo	4.86	[redacted]	[redacted]	0.28	[redacted]	[redacted]	Ami-laz dominates

4.2.2 Company's updated sensitivity analyses

The company's deterministic sensitivity analyses, presented in the form of tornado plots, are provided in Figure 27 and Figure 28 for the comparisons against osi-mono and osi-chemo respectively. It can be seen that the cost-effectiveness estimates are most sensitive to uncertainty in the parameters specified in the models used to extrapolate OS and TTD.

Figure 25: DSA tornado diagram for ami-laz versus osi-mono (updated model; at amivantamab and lazertinib PAS prices; generated by the EAG)

Abbreviations: DSA: deterministic sensitivity analysis; INMB: incremental net monetary benefit; OS: overall survival; TTD: time to treatment discontinuation or death.

Figure 26 DSA tornado diagram for ami-laz versus osi-chemo (updated model; at amivantamab and lazertinib PAS prices; generated by the EAG) ***Abbreviations:*** *DSA: deterministic sensitivity analysis; INMB: incremental net monetary benefit; OS: overall survival; TTD: time to treatment discontinuation or death.*

4.2.3 Company's updated scenario analyses

The company's scenario analyses for the comparison against osi-mono and osi-chemo are presented in Table 14 and Table 15 respectively. For scenarios 4 and 5 which involved the application of the population adjustment, the EAG identified an error in the company's implementation of the scenario analysis, which was corrected by the EAG. The EAG was able to verify the error and the corrected results with the company during a clarification request, and therefore the corrected results are presented in Table 15. For scenario 2, the EAG had identified that the company had not implemented its scenario analysis as described (see Section 4.1.4). Therefore, the EAG amended the scenario analysis tables such that scenario 2a presents the analysis as implemented and scenario 2b presents the analysis as described. It can be seen that ami-laz has greater QALY gains and lower costs in comparison to both osi-mono and osi-chemo across all of the scenarios presented by the company.

For the comparison against osi-mono, scenarios 4 to 8 provide identical results to the naïve comparison, because the different ITC methods only affect the comparison against osi-chemo. In the comparison against osi-mono, the QALY gain in the naïve comparison is increased ([redacted]) versus the company's base case ([redacted]) but cost savings are marginally decreased. The scenario using alternative utility values has limited impact.

For the comparison against osi-chemo, the QALY gains across the scenarios presented range from [redacted] to [redacted]* with the piecewise HR ITC providing the greatest QALY gains ([redacted]) and the largest absolute difference from the company's base case ([redacted]). There is less variation in the incremental costs, with only the scenario using the standard parametric ITC having a substantial impact. This is likely to be because the TTD extrapolation for the osimertinib component of osi-chemo is taking a Weibull functional form which does not fit the TTD for osi-chemo data well.

Table 14 Scenario analysis results for ami-laz versus osi-mono (updated model; deterministic; PAS prices for amivantamab and lazertinib)

Scenario		At amivantamab and lazertinib PAS prices		
		Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Base case		[redacted]	[redacted]	-142,662
Model characteristics				
1	Mean age informed by MARIPOSA trial (62.3 years)	[redacted]	[redacted]	-141,660
Utility				
2a	Three treatment-specific PF HSUVs (ami-laz : [redacted]; osi-mono: [redacted] osi-chemo: [redacted])	[redacted]	[redacted]	-140,262
2b	Three treatment-specific PF HSUVs (ami-laz : [redacted]; osi-mono: [redacted], osi-chemo: [redacted])	[redacted]	[redacted]	-132,042
Comparative effectiveness analyses				
3	Naïve comparison	[redacted]	[redacted]	-121,124

Scenario		At amivantamab and lazertinib PAS prices		
		Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
4	Population adjustment	[redacted]	[redacted]	-121,124
5	Population adjustment with time limit	[redacted]	[redacted]	-121,124
6	Piecewise hazard ratio indirect treatment comparison	[redacted]	[redacted]	-121,124
7	Standard parametric indirect treatment comparison	[redacted]	[redacted]	-104,050
8	Fractional polynomial indirect treatment comparison	[redacted]	[redacted]	-121,124
9	FLAURA2 population and PFS standard parametric indirect treatment comparison	[redacted]	[redacted]	-142,662

Abbreviations: ICER: incremental cost-effectiveness ratio; incr: incremental; PAS: patient access scheme; QALYs: quality-adjusted life years; PF HSUV: progression-free health state utility value

Table 15 Scenario analysis results for ami-laz versus osi-chemo (updated model; deterministic; PAS prices for amivantamab and lazertinib)

Scenario		At amivantamab and lazertinib PAS prices		
		Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Base case		[redacted]	[redacted]	-1,023,509
Model Characteristics				
1	Mean age informed by MARIPOSA trial (62.3 years)	[redacted]	[redacted]	-1,008,631
Utility				
2a	Three treatment-specific PF HSUVs (ami-laz : [redacted]; osi-mono: [redacted] osi-chemo: [redacted])	[redacted]	[redacted]	-737,147
2b	Three treatment-specific PF HSUVs (ami-laz : [redacted]; osi-mono: [redacted] osi-chemo: [redacted])	[redacted]	[redacted]	-737,147
Comparative effectiveness analyses				
3	Naïve comparison	[redacted]	[redacted]	-697,798
4	Population adjustment	[redacted]	[redacted]	-458,555
5	Population adjustment with time limit	[redacted]	[redacted]	-532,204
6	Piecewise hazard ratio indirect treatment comparison	[redacted]	[redacted]	-258,320
7	Standard parametric indirect treatment comparison	[redacted]	[redacted]	-1,131,260
8	Fractional polynomial indirect treatment comparison	[redacted]	[redacted]	-383,844
9	FLAURA2 population and PFS standard parametric indirect treatment comparison	[redacted]	[redacted]	-1,201,930

Abbreviations: ICER: incremental cost-effectiveness ratio; incr: incremental; PAS: patient access scheme; QALYs: quality-adjusted life years; PF HSUV: progression-free health state utility value

5 EAG's additional analyses

5.1 Methods of the EAG's additional analyses

5.1.1 Update to latest eMIT drug costs

The company had incorporated the prices for generic drugs updated in August 2025 into their base case analysis, to match prices in the EAG's model at ACM2, but had not updated these to reflect price changes since August 2025. The EAG used the information provided in the NICE price tracker to apply prices updated to October 2025. The EAG also noticed that some of the drugs used for concomitant treatments and enoxaparin for prophylaxis of venous thromboembolism (VTE) had not been included in the price tracker form. The EAG therefore obtained the latest eMIT prices for these drugs and where these were not available, the NHS Drug Tariff price was used. The updated prices for generic drugs applied in the model are provided in Table 16.

Table 16: The source for the prices used in the confidential appendix where the price differs from that used in the company's model

Treatment	Price in company's analysis	Source for price in company's model	Price used in the confidential appendix	Source for price used in the confidential appendix
Prices obtained from the NICE price tracker form				
Dexamethasone IV 10mg (pack of 1)	25.17	eMIT 4/08/25	27.50	eMIT 16/10/25
Paracetamol oral 500mg (pack of 100)	0.66	eMIT 4/08/25	0.73	eMIT 16/10/25
Carboplatin IV 450mg (pack of 1)	22.92	eMIT 4/08/25	22.92	eMIT 16/10/25
Cisplatin IV 100 mg (pack of 1)	43.86	eMIT 4/08/25	43.86	eMIT 16/10/25
Docetaxel IV 80mg (pack of 1)	9.48	eMIT 4/08/25	9.48	eMIT 16/10/25
Paclitaxel IV 300mg (pack of 1)	18.75	eMIT 4/08/25	23.23	eMIT 16/10/25
Additional prices updated by the EAG				
Enoxaparin 40 mg (pack of 10)	22.70	BNF 2024 (Arovi)	30.27	NHS Drug Tariff 24/10/25

Treatment	Price in company's analysis	Source for price in company's model	Price used in the confidential appendix	Source for price used in the confidential appendix
Carboplatin IV 600mg (pack of 1)	19.75	eMIT 2024	21.85	eMIT 24/10/25
Vitamin B12 IM (hydroxocobalamin) 1 mg (pack of 5)	11.03	eMIT 2024	8.96	eMIT 24/10/25
Folic acid 5 mg (pack of 28)	0.24	eMIT 2024	0.24	eMIT 24/10/25
Dexamethasone PO 4 mg (pack of 50)	35.97	eMIT 2024	39.60	eMIT 24/10/25
Famotidine PO 20 mg (pack of 28)	16.91	BNF 2025	2.49	NHS Drug Tariff 24/10/25

BNF – British National Formulary; CAA – Commercial access arrangement; MPSC – Medicines Procurement and Supply Chain; PAS – Patient Access Scheme

5.1.2 Returning second-line and third-line subsequent treatments to values used at ACM2

As discussed in Section 4.1.5, the EAG considered that het company had misinterpreted the committee's request to amend second-line and third-line treatments for the osi-chemo arm by applying the requested changes to all three arms equally. The EAG therefore restored the assumptions that were common across the EAG and company's model at ACM2 for the ami-laz and osi-mono arms.

5.1.3 EAG's preferred base case analysis

The EAG prefers the approach used in the company's base case to the alternative ITC methods presented by the company in its scenario analyses. However, the EAG has explored using an alternative ITC method in a scenario analysis (see Section 5.1.5).

The EAG has maintained the company's choice of curves for extrapolating OS, PFS and TTD. However, it has explored three alternative curve choices in scenario analyses (see Section 5.1.4).

Therefore, the only changes incorporated in the EAG's preferred base case were to restore the subsequent treatments for the osi-mono and ami-laz arms to their previous values (Section 5.1.2) and to incorporate the updated prices for generic drugs (Section 5.1.1).

5.1.4 Alternative curves in scenario analyses

For the extrapolation of OS for osi-mono, the EAG explored using a gamma model as an alternative extrapolation (ASA1). This provides a 10-year survival for osi-mono of 6.7%, versus the prediction of 3.9% provided by the company's choice of Weibull. The 10-year prediction of OS for osi-mono by the company's clinical experts was 5%. Therefore, the company's base case and the EAG's scenario analysis provide estimates falling either side of this prediction, allowing uncertainty in the long-term OS prediction to be explored.

For the extrapolation of OS for osi-chemo, the EAG explored using a two-knot normal spline model for alternative extrapolation (ASA2). It can be seen in Figure 29 that this provides a more favourable long-term extrapolation for osi-chemo (12.3% versus 8.4% 10-year survival) which reflects a long-term survival for osi-chemo that is similar to the long-term Weibull extrapolation of ami-laz (12.7%).

For TTD of osimertinib component of osi-chemo, the EAG explored using a capped Gompertz model, which was its preferred approach at ACM2 (ASA3). It can be seen in Figure 30, that this provides an extrapolation that better matches the TTD KM data around year 2, compared to the company's preferred approach of using the average of the Gompertz and the gamma extrapolations, but also remains above the PFS extrapolation for osi-chemo due to the capping. The average of the Gompertz and the gamma extrapolations for TTD have a bigger gap to osi-chemo PFS compared to the gap for the capped Gomperz extrapolation.

Figure 27 Comparison of long-term OS extrapolations for the EAG's scenario analyses compared to the company's base case

Figure 28 Comparison of long-term extrapolations of TTD for osimertinib component of osi-chemo for the company's base case and the EAG's scenario analysis, with TTD for osi-mono and PFS for osi-chemo for reference

.

5.1.5 Alternative ITC method in scenario analysis

The EAG modified the analysis using fractional polynomial ITC with Cox regression as this analysis assumes the hazard associated with ami-laz decreases continuously relative to osi-chemo. A hazard ratio that increasingly favours ami-laz over time is unlikely to be plausible. With the updated FLAURA2 OS data, the smoothed log HR of osi-chemo versus osi starts to exhibit a decreasing tail, similar to the tail of ami-laz versus osi. The HR is more likely to stabilize after some time. Therefore, the EAG explored

a modified scenario by assuming the HR of osi-chemo versus ami-laz stabilised after 38 months (median follow-up from MARIPOSA), providing a more plausible ITC scenario. For OS, this resulted in the HR stabilising at [redacted], whereas for PFS, this resulted in the HR stabilising at [redacted] This is presented as ASA4.*

The EAG has also presented the results when using the parametric ITC in an additional scenario analysis (ASA5). The EAG is content with the distributions selected in company's scenario analysis 7 (as described in Section 3.5) and has kept the same options in its scenario analysis.

5.1.6 Scenario analysis using alternative utility values

Although the EAG does not follow the company's rationale for the specific utility values applied for ami-laz in the company's scenario analysis where ami-laz has a higher PF utility than osi-chemo, the EAG accepts that it is possible that there is a utility difference in favour of ami-laz versus osi-chemo. It therefore presents the corrected version of the company's scenario analysis applied to the EAG's base case (ASA6) to explore the sensitivity of the cost-effectiveness results to the uncertainty regarding whether ami-laz has the same PF utility as osi-chemo.

5.1.7 Varying the proportion of patients receiving nintedanib alongside docetaxel

The committee requested that the company explore the proportion of patients receiving nintedanib with docetaxel, but the company did not provide any analyses in response to this request (see Section 4.1.5). The EAG has therefore conducted additional scenario analyses on this in which it varied the proportion of patients receiving nintedanib alongside docetaxel from 50% down to 0% (ASA7) and from 50% up to 100% (ASA8).

5.1.8 Incorporating ABCP as a third-line treatment.

The committee also requested that the company explore the proportion of third-line usage of atezolizumab with bevacizumab, carboplatin and paclitaxel (ABCP) in a scenario analysis, but the company did not provide any analyses in response to this request (see Section 4.1.5). The EAG has conducted a scenario analysis (ASA9) in which 6% of patients progressing on second-line treatment are assumed to have ABCP. The value of 6% was based on the committee papers for TA1050. In the osi-chemo arm, this achieved by assuming that 6% of third-line patients received active treatment instead of BSC, and 100% of this active treatment is ABCP. In the other two arms, this was achieved by having the same absolute proportion receiving ABCP as in the osi-chemo arm, but redistributing the remaining patients having active treatment across platinum and non-platinum based therapy according to their previous ratio ([redacted]).

5.2 Results of the EAG's additional analyses

Ami-laz dominates both osi-mono and osi-chemo in all of the EAG exploratory analyses presented in Table 17. However, the EAG notes that these results do not included the confidential prices for drugs other than amivantamab and lazertinib. Results including these discounts can be found in the confidential appendix. These exploratory analyses do however, indicate the sensitivity of the model results to the various data sources, assumptions and ITC approaches. For example, neither of the pair-wise comparison are particularly sensitive to the two changes incorporated in the EAG's updated base case. Furthermore, the incremental costs are not particularly sensitive to the assumptions regarding usage of nintedanib or ABCP for either comparison (ASAs 7 to 9).

The use of an alternative OS extrapolation for osi-mono (gamma instead of Weibull) had a fairly large impact on the comparison of ami-laz vesrus osi-mono as it reduces the QALY gains from [redacted] to [redacted]* Although the choice of ITC method is not directly relevant for the comparison between ami-laz and osi-mono, both of the alternative ITC methods increase the QALY gain from [redacted] to [redacted] because they do not use the data from MARIPOSA that has been reweighted to the FLAURA2 population.

In the EAG additional scenario analysis using the alternative two-knot normal to extrapolate OS for osi-chemo (ASA1), the incremental QALYs are negative. The scenario analysis incorporating the alternative TTD for the osimertinib component of osi-chemo (ASA3) has lower cost savings due to the lower predicted costs for osi-chemo in comparison to the EAG's base case. The use of the higher PF utility for ami-laz (ASA6) resulted in an increase in the QALY gains for ami-laz versus osi-chemo from [redacted] to [redacted]. The scenario analysis using the parametric ITC (ASA5) has significantly higher cost savings for ami-laz versus osi-chemo due to the higher costs for osi-mono. However, the EAG notes that this may be because the standard parametric curve for TTD applied for osi-chemo in this scenario, in order to facilitate the parametric ITC, was not a good fit to the TTD KM data. In addition, the FP using Cox regression had a substantial impact on incremental QALYs (increasing from [redacted] to [redacted]). However, caution should be exercised when interpreting this result given that a limitation of this approach is that the modelled HR of ami-laz versus osi-chemo shows a different trend to the smoothed time-dependent HR (see Section 3.8).

The results of the probabilistic analysis for the EAG's preferred base case are consistent with the results of the deterministic analysis for the EAG base case. Furthermore, the incremental QALY gains are identical to the company's probabilistic base case as the EAG's preferred base case assumption only impact costs.

Table 17: EAG exploratory analysis results (deterministic analyses)

Option	Absolute outcomes by treatment arm			Incremental outcomes for ami-laz versus comparator			ICER (£/QALY)
	LYGs*	QALYs	Costs (£)	LYGs	QALYs	Costs (£)	
Company's updated base case							
Ami-laz	5.10	[redacted]	[redacted]				
Osi-mono	3.77	[redacted]	[redacted]	1.33	[redacted]	[redacted]	Ami-laz dominates
Osi-chemo	4.75	[redacted]	[redacted]	0.35	[redacted]	[redacted]	Ami-laz dominates
EA1: update to prices for generic drugs							
Ami-laz	5.10	[redacted]	[redacted]				
Osi-mono	3.77	[redacted]	[redacted]	1.33	[redacted]	[redacted]	Ami-laz dominates
Osi-chemo	4.75	[redacted]	[redacted]	0.35	[redacted]	[redacted]	Ami-laz dominates
EA2: EA1 + return subsequent treatments for ami-laz and osi-mono to values used at ACM2 = EAG updated basecase							
Ami-laz	5.10	[redacted]	[redacted]				
Osi-mono	3.77	[redacted]	[redacted]	1.33	[redacted]	[redacted]	Ami-laz dominates
Osi-chemo	4.75	[redacted]	[redacted]	0.35	[redacted]	[redacted]	Ami-laz dominates
ASA1: OS extrapolation for osi-mono using gamma instead of Weibull							
Ami-laz	5.10	[redacted]	[redacted]				
Osi-mono	4.08	[redacted]	[redacted]	1.03	[redacted]	[redacted]	Ami-laz dominates
Osi-chemo	4.75	[redacted]	[redacted]	0.35	[redacted]	[redacted]	Ami-laz dominates
ASA2: OS extrapolation for osi-chemo using two-knot normal instead of two-knot hazard							
Ami-laz	5.10	[redacted]	[redacted]				
Osi-mono	3.77	[redacted]	[redacted]	1.33	[redacted]	[redacted]	Ami-laz dominates
Osi-chemo	5.27	[redacted]	[redacted]	0.17	[redacted]	[redacted]	1,906,128
ASA3: TTD for osimertinib component of osi-chemo using Gompertz model with capping to stay above TTD for osi-mono							
Ami-laz	5.10	[redacted]	[redacted]				

Option	Absolute outcomes by treatment arm			Incremental outcomes for ami-laz versus comparator			ICER (£/QALY)
	LYGs*	QALYs	Costs (£)	LYGs	QALYs	Costs (£)	
Osi-mono	3.77	[redacted]	[redacted]	1.33	[redacted]	[redacted]	Ami-laz dominates
Osi-chemo	4.75	[redacted]	[redacted]	0.35	[redacted]	[redacted]	Ami-laz dominates
ASA4: Fractional polynominal ITC using Cox regression for OS and PFS with HR stabilisation at 38 months [redacted]							
Ami-laz	5.21	[redacted]	[redacted]				
Osi-mono	3.68	[redacted]	[redacted]	1.54	[redacted]	[redacted]	Ami-laz dominates
Osi-chemo	4.72	[redacted]	[redacted]	0.50	[redacted]	[redacted]	Ami-laz dominates
ASA5: Parametric ITC							
Ami-laz	5.21	[redacted]	[redacted]				
Osi-mono	3.68	[redacted]	[redacted]	1.54	[redacted]	[redacted]	Ami-laz dominates
Osi-chemo	4.90	[redacted]	[redacted]	0.32	[redacted]	[redacted]	Ami-laz dominates
ASA6: Utility values for the PF state that vary between ami-laz (0.794) and osi-chemo ([redacted])							
Ami-laz	5.10	[redacted]	[redacted]				
Osi-mono	3.77	[redacted]	[redacted]	1.33	[redacted]	[redacted]	Ami-laz dominates
Osi-chemo	4.75	[redacted]	[redacted]	0.35	[redacted]	[redacted]	Ami-laz dominates
ASA7: Varying nintedanib given alongside docetaxel down from 50% to 100%[redacted]							
Ami-laz	5.10	[redacted]	[redacted]				
Osi-mono	3.77	[redacted]	[redacted]	1.33	[redacted]	[redacted]	Ami-laz dominates
Osi-chemo	4.75	[redacted]	[redacted]	0.35	[redacted]	[redacted]	Ami-laz dominates
ASA8: Varying nintedanib given alongside docetaxel up from 50% to 100%[redacted]							
Ami-laz	5.10	[redacted]	[redacted]				
Osi-mono	3.77	[redacted]	[redacted]	1.33	[redacted]	[redacted]	Ami-laz dominates
Osi-chemo	4.75	[redacted]	[redacted]	0.35	[redacted]	[redacted]	Ami-laz dominates

Option	Absolute outcomes by treatment arm			Incremental outcomes for ami-laz versus comparator			ICER (£/QALY)
	LYGs*	QALYs	Costs (£)	LYGs	QALYs	Costs (£)	
ASA9: Set ABCP usage as third-line to 6% across all arms							
Ami-laz	5.10	[redacted]	[redacted]				
Osi-mono	3.77	[redacted]	[redacted]	1.33	[redacted]	[redacted]	Ami-laz dominates
Osi-chemo	4.75	[redacted]	[redacted]	0.35	[redacted]	[redacted]	Ami-laz dominates

*Undiscounted: **Abbreviations**: ASA, additional scenario analysis; EA - exploratory analysis; ICER - incremental cost-effectiveness ratio LYG - life year gained; TTD – time to discontinuation; QALY - quality-adjusted life year;

Table 18 EAG base case results using average outputs from the probabilistic analysis

Option	Absolute outcomes by treatment arm			Incremental			ICER (£/QALY)
	LYGs*	QALYs	Costs	LYGs	QALYs	Costs	
Pairwise comparisons versus ami-laz							
Ami-laz	5.14	[redacted]	[redacted]				
Osi-mono	3.79	[redacted]	[redacted]	1.35	[redacted]	[redacted]	Ami-laz dominates
Osi-chemo	4.86	[redacted]	[redacted]	0.28	[redacted]	[redacted]	Ami-laz dominates

6 Conclusions

Overall, the EAG did not consider that any of the alternative ITC methods explored by the company were preferable to the approach used in the company's updated base case which used an unanchored MAIC applied to data from MARIPOSA which was reweighted to adjust it to reflect the population of FLAURA2. Requiring the same parametric distributions across MARIPOSA and FLAURA2 makes the use of parametric ITC approach challenging. Fractional polynomial ITC using Cox regression provides a better estimate of the hazard ratio of ami-laz versus osi-chemo, compared to the parametric fractional polynomial ITC method and piecewise Cox regression models. However, one limitation of this approach is that the modelled HR of ami-laz versus osi-chemo shows a different trend to the smoothed time-dependent HR. In addition the Fractional polynomial ITC using Cox regression produced a HR that increased over time which the EAG did not consider to be clinically plausible. The EAG modified the fractional polynomial ITC using Cox regression approach in a scenario analysis to provide a more plausible ITC scenario (See Section 5.1.5).

The cost-effectiveness estimates generated by the EAG's preferred base case were very similar to the company's base case as the changes the EAG implemented in its base case had limited impact on costs and no impact on QALYs. However, the EAG's additional scenario analyses demonstrated that the cost-effectiveness of ami-laz versus osi-chemo is uncertain with incremental QALY gains varying from minus [redacted] (i.e. ami-laz has lower QALY gains that osi-chemo) to plus [redacted]. However, when excluding the scenario that generated negative QALYs, ami-laz dominated osi-chemo in all other scenarios. It also dominated osi-mono in all scenarios. A scenario analysis exploring an alternative OS extrapolation for osi-mono also had a significant impact on the incremental QALYs for ami-laz versus osi-mono suggesting some uncertainty in the incremental QALY gains for this comparison. The EAG refers the committee to the confidential appendix for the range of ICERs these scenario analyses generate when applying the confidential PAS discounts for comparator treatments.

This addendum to the EAG report has focused on the uncertainties identified in the company and EAG analyses presented specifically to address the committee's request for additional analyses. Other areas of uncertainty not covered by these analyses are discussed in previous addenda.

7 References

1. National Institute for Health and Care Excellence. *Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]: Additional analysis request* London, UK: National Institute for Health and Care Excellence,; 2025.
2. Johnson and Johnson Innovative Medicine. *Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]: Company response to additional analyses request*. London, UK: National Institution for Health and Care Excellence,; 2025.
3. David Planchard, Pasi A. Jänne, Kunihiko Kobayashi, James Chih-Hsin Yang, Ying Liu, Natalia Valdiviezo*, et al.* First-line Osimertinib + Chemotherapy Versus Osimertinib Monotherapy in EGFRm Advanced NSCLC: FLAURA2 Final Overall Survival. IASLC 2025 World Conference on Lung Cancer; Barcelona, Spain, abstract no. 1.
4. Valdiviezo N, Okamoto I, Hughes BGM, Ahmed S, Wu L, Hu J*, et al.* 4O First-line (1L) osimertinib (osi) ± platinum-pemetrexed in EGFR-mutated (EGFRm) advanced NSCLC: FLAURA2 post-progression outcomes. *ESMO Open* 2024;**9**. **********
5. Planchard D, Jänne PA, Cheng Y, Yang JC-H, Yanagitani N, Kim S-W*, et al.* Osimertinib with or without Chemotherapy in EGFR-Mutated Advanced NSCLC. *New England Journal of Medicine* 2023;**389**:1935-48. **********
6. Yang JC-H, Lu S, Hayashi H, Felip E, Spira AI, Girard N*, et al.* Overall Survival with Amivantamab-Lazertinib in EGFR-Mutated Advanced NSCLC. *New England Journal of Medicine* 2025;**0**. **********
7. Cho BC, Li W, Spira AI, Sauder M, Feldman J, Bozorgmehr F*, et al.* Enhanced Versus Standard Dermatologic Management With Amivantamab-Lazertinib in EGFR-Mutated Advanced NSCLC: The COCOON Global Randomized Controlled Trial. *Journal of Thoracic Oncology* 2025; 10.1016/j.jtho.2025.07.117. **********
8. Byoung Chul Cho, Weimin Li, Alexander I Spira, Maxwell Sauder, Jill Feldman, Farastuk Bozorgmehr*, et al.* Enhanced vs Standard Dermatologic Management with Amivantamab-Lazertinib in EGFRm Advanced NSCLC: the COCOON Global RCT. World Conference on Lung Cancer 2025; Barcelona, Spain, abstract no. 41.
9. Leighl NB, Akamatsu H, Lim SM, Cheng Y, Minchom AR, Marmarelis ME*, et al.* Subcutaneous Versus Intravenous Amivantamab, Both in Combination With Lazertinib, in Refractory Epidermal Growth Factor Receptor-Mutated Non-Small Cell Lung Cancer: Primary Results From the Phase III PALOMA-3 Study. *J Clin Oncol* 2024;**42**:Jco2401001. **********

10. Cope S, Chan K, Jansen JP. Multivariate network meta-analysis of survival function parameters. *Research synthesis methods* 2020;**11**:443-56.
11. Jansen JP. Network meta-analysis of survival data with fractional polynomials. *BMC medical research methodology* 2011;**11**:61.
12. Wiksten A, Hawkins N, Piepho H-P, Gsteiger S. Nonproportional hazards in network meta-analysis: efficient strategies for model building and analysis. *Value in Health* 2020;**23**:918-27.
13. Wong GY, Osborne MP, Diao Q, Yu Q. Piecewise Cox models with right-censored data. *Communications in Statistics-Simulation and Computation* 2017;**46**:7894-908.
14. Austin PC, Fang J, Lee DS. Using fractional polynomials and restricted cubic splines to model non-proportional hazards or time-varying covariate effects in the Cox regression model. *Statistics in medicine* 2022;**41**:612-24.
15. Royston P, Altman DG. Regression using fractional polynomials of continuous covariates: parsimonious parametric modelling. *Journal of the Royal Statistical Society Series C: Applied Statistics* 1994;**43**:429-53.