Single Technology Appraisal

Amivantamab with carboplatin and pemetrexed for untreated EGFR exon 20 insertion mutation-positive advanced non-small-cell lung cancer [ID5110]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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Contents:

The following documents are made available to stakeholders:

1. **Comments on the Draft Guidance from** Johnson & Johnson Innovative Medicine
   a. DG additional analyses

2. **Consultee and commentator comments on the Draft Guidance** from:
   a. EGFR + UK

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 **External Assessment Group critique of company comments on the Draft Guidance**

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

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Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Wednesday 26 March 2025.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

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	No Disclosures
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	No Disclosures
Name of commentator person completing form:	[redacted]

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Comment number	Comments
	Thank you for the opportunity to comment on the draft guidance for amivantamab with carboplatin and pemetrexed in patients with untreated epidermal growth factor receptor (EGFR) Exon20 insertion mutation-positive advanced non-small-cell lung cancer (NSCLC). Johnson & Johnson are disappointed with the preliminary decision not to recommend amivantamab with chemotherapy within its marketing authorisation given it represents an opportunity to address the significant unmet need in this rare population, where there are currently no recommended therapies. Johnson & Johnson would like to highlight several points that are relevant to the committee's conclusions, and present additional analyses requested by the committee. The key points raised are: • A clear and statistically significant overall survival (OS) benefit is observed when amivantamab with chemotherapy is compared to chemotherapy after adjusting for treatment switching • Data from the PAPILLON trial show that the majority of efficacy benefit for chemotherapy occurs after progression, meaning that it is appropriate for the majority of efficacy benefit/QALYs to be accrued in the progressed disease state for chemotherapy and for amivantamab with chemotherapy too • This is further supported by the PAPILLON trial demonstrating a clear post-progression benefit for amivantamab with chemotherapy • A long-term benefit associated with amivantamab with chemotherapy is also expected based on clinical opinion and this is supported by the long-term benefits demonstrated by amivantamab in other indications • The OS extrapolation curves selected in the company base-case are aligned with the consensus achieved at the advisory board, have a robust visual and statistical fit to the observed data, and are aligned with the observed hazard function • The distributions selected for the OS of amivantamab with chemotherapy and chemotherapy in the company base-case are similar to one another and using the same parametric models for both treatments leads to a reduction in the incremental cost-effectiveness ratio (ICER) versus the company's base case • With the additional analysis, there is sufficient evidence to conclude that it is not appropriate to model a waning effect for amivantamab • In most scenarios, utilising different methodologies to estimate the long-term benefit of amivantamab with chemotherapy versus chemotherapy leads to a reduction in the ICER versus the company's base case • EQ-5D data from the PAPILLON trial is the most robust source of evidence to derive utilities for the population in this decision problem, and using utilities from other appraisals in EGFR Exon20 insertion mutation-positive NSCLC has a minor impact on the ICER • Given the unmet need, the robustness of the data from the PAPILLON trial, and the additional analyses provided to address the uncertainties cited in the draft

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	guidance, the acceptable ICER should be positioned at the upper end of the range that NICE considers to be a cost-effective use of NHS resources. In summary, nearly all of the additional scenarios presented demonstrate the robustness of the company's base case. Furthermore, in almost all the additional clinically plausible scenarios requested, the ICER is lower than the figure put forward by the company as the base-case. The new company base-case incorporates the committee's preferred assumptions with regards to the comparator, adverse event (AE) costs, and dosing. In the updated base-case, the deterministic ICER of amivantamab with chemotherapy versus chemotherapy is £36,255 per quality adjusted life year (QALY) with the current Patient Access Scheme (PAS).
1	**Section 3.3 (Treatment options and comparators)**: The committee concluded that the only relevant comparator for this appraisal was carboplatin with pemetrexed (from here, chemotherapy). **Johnson & Johnson have provided an updated model to show the cost-effectiveness results versus chemotherapy.** Johnson & Johnson acknowledge the discussion during the committee meeting where the Cancer Drugs Fund lead confirmed that use of immunotherapies for EGFR mutation-positive advanced NSCLC is not allowed given recent updates to the NHS commissioning criteria (BluTeq). Therefore, Johnson & Johnon have updated the company base-case to compare amivantamab with chemotherapy to chemotherapy. In the updated model, the base-case ICER of amivantamab with chemotherapy versus chemotherapy is £36,255 per QALY. Johnson & Johnson would like to reiterate that clinical expert opinion and real-world evidence (RWE) have highlighted that carboplatin with pemetrexed is not the only treatment being used to treat patients with untreated EGFR Exon20 insertion mutation-positive advanced NSCLC in the UK.[1-4] The current approach of only comparing amivantamab with chemotherapy to chemotherapy excludes approximately 30% of treatment options being used on the NHS. This narrow decision-making prioritises the least expensive treatment, resulting in a conservative estimate of cost-effectiveness. Clinical expert opinion has, on multiple occasions, explicitly cited that pembrolizumab with chemotherapy is used to treat this population. This includes opinion from the evidence assessment group's (EAG's) clinical expert and from both clinical expert nominees in this appraisal. • At a company advisory board in May 2024 which comprised six clinical experts, it was agreed that the standard of care was chemotherapy (carboplatin with pemetrexed) with or without immunotherapy (pembrolizumab), with the split between these being 70% and 30%, respectively.[1] • At a company advisory board held in August 2024 which comprised two clinical experts, one of whom attended the May 2024 advisory board, it was highlighted that the predominant treatments being prescribed in this population are chemotherapy (carboplatin with pemetrexed) and IO combination therapies (pembrolizumab with chemotherapy).[2]

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	• As per the stakeholder comments to this submission which are presented within the committee papers, both clinical experts (one of whom attended the company May 2024 advisory board) answered 'Yes' to question 23 "Does the blended comparator (70% chemo to 30% pembro) reflect what might occur in clinical practice?"[5] • As per the EAG report, the EAG's clinical expert indicated that clinical practice comprises carboplatin with pemetrexed (60%), carboplatin or cisplatin (10%) and pembrolizumab with carboplatin and pemetrexed (30%). This is similar to the company estimate of 70% chemotherapy (carboplatin and pemetrexed) and 30% pembrolizumab plus chemotherapy, which is noted within the draft guidance.
2	**Section 3.4 (PAPILLON trial)**: The committee concluded that amivantamab–chemotherapy improved PFS compared with chemotherapy alone and that the relative effectiveness on OS was uncertain. **There is sufficient evidence to conclude that amivantamab with chemotherapy improves OS versus chemotherapy given a statistically significant OS benefit has been demonstrated versus chemotherapy after adjusting for treatment switching.** Although a statistically significant OS benefit over chemotherapy was not reached in the intention to treat analysis, this was demonstrated after the chemotherapy data had been adjusted to account for treatment switching via inverse probability of censoring weighting (IPCW). There is, therefore, sufficient evidence to conclude that amivantamab with chemotherapy improved OS compared with chemotherapy.[6] Johnson & Johnson acknowledge that, at the October 2023 data-cut off (DCO), with a median follow-up of 20.9 months across both treatment arms, median OS was not reached for amivantamab with chemotherapy whereas it was reached for chemotherapy (28.6 months).[7] This is considered positive given it means that patients receiving amivantamab with chemotherapy remain alive for longer than patients receiving chemotherapy alone. At the October 2023 DCO, 73.9% of patients in the amivantamab with chemotherapy arm remained alive compared with 66.5% in the chemotherapy alone arm.[7] The failure to achieve median overall survival should not be interpreted as a sign of uncertainty; instead, it should be regarded as a significant indicator that the intervention exerts a notably positive effect on survival outcomes. Although the median OS was not reached, there was a strong trend towards improved survival over chemotherapy at the October 2023 DCO, where the median follow-up across both treatment arms was 20.9 months. At this point, amivantamab with chemotherapy demonstrated a 24% reduction in the risk of death compared with chemotherapy (hazard ratio [HR]: 0.76 [95% CI: 0.50-1.14]; p=0.1825).[7] This benefit was despite the OS in the chemotherapy arm being over-estimated due to a significant proportion ([redacted]%) of patients receiving amivantamab monotherapy after blinded independent central review (BICR)-confirmed disease progression. Receiving amivantamab monotherapy after progression led to an overestimation of chemotherapy OS given amivantamab monotherapy is an efficacious treatment that is not available through routine clinical practice in the UK. Therefore, the OS HR achieved in the intention to treat population (0.76 [95% CI, 0.50 to 1.14, *p*=0.1825]), which is cited in the draft guidance, does not accurately describe the OS benefit that amivantamab with chemotherapy achieves over chemotherapy in a UK population.

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	Johnson & Johnson followed the guidance in technical support document (TSD) 24 to adjust the OS data in the chemotherapy arm to account for the observed treatment switching. Following treatment switching adjustment via IPCW, amivantamab with chemotherapy demonstrated a statistically significant and clinically meaningful improvement in OS, with a 48% reduction in the risk of death compared with chemotherapy (HR: [redacted], CI: [redacted], p=[redacted]). The separation of OS Kaplan-Meier (KM) curves between amivantamab with chemotherapy and IPCW-adjusted chemotherapy data is clearly shown below: [redacted]
3	**Section 3.7 (plausibility of extrapolated benefits)**: Modelling in which the majority of QALY gains accrue in the progressed-disease health state was associated with uncertainty. **Data from the PAPILLON trial show that the majority of efficacy benefit for chemotherapy occurs after progression. It is therefore appropriate for the majority of efficacy benefit/QALYs to be accrued in the progressed disease state for amivantamab with chemotherapy.** In this section, Johnson & Johnson aims to address a common misconception regarding progression-free survival (PFS) and OS. Through the analysis provided below, we seek to clarify that a clear benefit is observed after disease progression. To begin, it is essential to examine the trial data related to chemotherapy. <u>Chemotherapy:</u> The median OS for patients receiving chemotherapy was [redacted] months after adjustment for treatment switching, which was [redacted] times greater than the median PFS of 6.7 months. This shows a clear post-progression benefit has been observed for chemotherapy in the PAPILLON trial.

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	Amivantamab with chemotherapy: Amivantamab with chemotherapy achieved a median PFS of 11.37 months, while the median OS had not been reached after a median follow-up of 20.9 months. At this point there were 40 death events, representing 26.1% of patients in the amivantamab with chemotherapy arm.[7] Consequently, the median OS benefit of amivantamab in combination with chemotherapy is expected to extend well beyond the median PFS of 11.37 months. It is reasonable to anticipate that the median OS will be at least [redacted] times greater than the median PFS given amivantamab in combination with chemotherapy uses the same chemotherapy regimen as the control group (carboplatin with pemetrexed). Additionally, although the median PFS was reached, the median progression-free survival after first subsequent therapy (PFS2) was not reached, which shows a clear delay to second progression well-beyond the first progression. This is also shown through the event-free rates where, even after 24-months, 57% of patients receiving amivantamab with chemotherapy had still not experienced a PFS2 event. These data clearly show a delay to second progression beyond the first progression, and a prolonged survival well beyond PFS. Importantly, amivantamab with chemotherapy demonstrated a 51% reduction in the risk of PFS2 compared to chemotherapy at the May 2023 DCO (HR: 0.49 [95% CI: 0.32-0.76; nominal p=0.0010]). This supports the notion that the relative benefit of OS vs PFS is expected to be greater for amivantamab with chemotherapy than what has been observed for chemotherapy (i.e., more than [redacted] times larger).
4	**Section 3.8 (OS extrapolations)**: The company fitted a Weibull distribution to the OS data for amivantamab–chemotherapy to extrapolate it to the 40-year time horizon of the model. The company felt that this was the most appropriate curve because it fit with the clinical expert opinion from its advisory board (27.5% survival at 5 years) and provided a good visual fit. **Validation of the Weibull (and Gamma) curve as the most appropriate extrapolation of OS data for amivantamab with chemotherapy was obtained through a 3-step SHELF methodology process. The Weibull curve was selected by the company as the more conservative of the validated extrapolations and because of robust visual and statistical fit and alignment with the observed hazard function. It is inaccurate to state that the "27.5% survival at 5 years" obtained at step 1 in the 3-step process was the basis for curve selection.** Johnson & Johnson would like to re-iterate that, during the advisory board, the focus was validating appropriate extrapolation curves rather than fixating on the proportions alive at specific timepoints. Johnson & Johnson followed a three-step process to validating extrapolation curves, which reflected the methodology set out by the Sheffield elicitation framework (SHELF). Obtaining responses from individual advisors through a pre-meeting survey was step 1. Steps 2 and 3 comprised advisors discussing the pre-meeting survey results and then arriving at a discussion-based group consensus as to the most appropriate extrapolation curve. "27.5% survival after 5-years" reflects the average of the individual responses obtained via the pre-meeting survey (step 1). During the advisory board, after discussing the pre-meeting survey responses, advisors arrived at a consensus that the Weibull and Gamma curves provided the most appropriate long-term estimates for the OS of amivantamab with chemotherapy.[2] This consensus was reached across four advisors, comprising two health economic experts and two clinical experts with experience of using

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	amivantamab through trial or private use. Although both the Weibull and Gamma curves were deemed plausible by advisor experts, the more conservative Weibull curve was chosen in the company base-case. This predicts a survival rate of 32.1% at 5 years (the Gamma curve predicts 35.0% alive at 5-years). Johnson & Johnson would also like to highlight that the Weibull curve has a good visual and statistical (3rd-best) fit to the observed KM data and the risk of death overtime predicted by the Weibull curve is also aligned to the hazard function over time associated with the observed KM data, based on an analysis of the smoothed hazard plots. As such, statements in the draft guidance that the Weibull curve was selected based on clinical expert opinion of 27.5% survival at 5 years are factually inaccurate. Referencing data from the pre-meeting survey rather than the consensus reached at the advisory board was previously highlighted by Johnson & Johnson as a factual inaccuracy during the factual inaccuracy check carried out on the EAG report earlier this year. Johnson & Johnson firmly stress that the emphasis should be on the consensus rather than solely on the pre-meeting survey numbers, which represent only the first step of a three-step process in the SHELF methodology.
5	**Section 3.8 (OS extrapolations):** The EAG felt that long-term estimates of OS with amivantamab–chemotherapy were very uncertain. It used the Weibull distribution in its base case but used a scenario with the Gompertz distribution to explore more pessimistic survival in keeping with its expert's estimates. **There is sufficient evidence to conclude that the Gompertz curve for the OS of amivantamab with chemotherapy is implausible.** Clinical and HTA expert opinion: At the company advisory board held in August 2024, advisor experts explicitly noted that the Gompertz and generalised gamma extrapolations for the OS of amivantamab with chemotherapy were overly pessimistic.[2] The company's methodology of utilising the SHELF protocol to elicit survival estimates and validate extrapolation curves across a group of advisor experts is in-line with what is recommended within NICE TSD 26.[8] This methodology, considering a consensus across multiple advisors, is more robust than using insight from a single clinician expert. Additionally, at a company advisory board held in May 2024, the six clinical experts agreed that they would expect to see a tail to the survival of amivantamab with chemotherapy, where a proportion of patients remain alive beyond 10 years, which does not happen with the Gompertz curve which predicts 0% alive beyond 6.5 years.[1] Assessment of hazard functions: The Gompertz curve for the OS of amivantamab with chemotherapy predicts a rapidly increasing hazard which is not consistent with the evolution of the per-cycle OS hazards for amivantamab with chemotherapy observed in the PAPILLON trial. Given the different trajectories of the associated hazard functions, selecting the Gompertz curve for amivantamab with chemotherapy OS (rapidly increasing hazard function) alongside the Gamma curve for chemotherapy OS (monotonically increasing hazard) means that the OS hazards cross. Therefore, this scenario predicts that patients receiving amivantamab with chemotherapy are more likely to die compared with patients receiving chemotherapy after a certain point. This is implausible given the survival benefit that

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	amivantamab with chemotherapy has demonstrated over chemotherapy, as shown through the separation of OS curves, in the PAPILLON trial. Visual fit to KM data: The Gompertz curve presents a poor visual fit to the observed data, sitting well below the KM curve.
6	**Section 3.8 (OS extrapolations)**: For chemotherapy, the company fitted a gamma distribution to the OS data for chemotherapy. This was based on the clinical expert opinion from its advisory board (10% survival at 5 years) and fit to the observed data. **Validation of the Gamma curve as the most appropriate curve to extrapolate OS data for chemotherapy was obtained through a 3-step SHELF methodology process. It is inaccurate to state that the "10% survival at 5 years" obtained at step 1 in the 3-step process was the basis for curve selection.** Johnson & Johnson strongly recommend referencing the curve validated at the advisory board rather than citing a single result for the survival at one timepoint from the pre-meeting survey when referencing expert opinion from the company advisory board.
7	**Section 3.8 (OS extrapolations):** The EAG had concerns that the company's choice of curve underestimated the OS for chemotherapy based on the company's advisory board and the EAG's own clinical expert input (5% at 5 years). **The Gamma curve selected in the company base-case for chemotherapy OS provides the best match to the curve that was validated at the advisory board, as per the group consensus reached. Further, the Gamma curve has good visual and statistical fit to the PAPILLON data and closely matches the observed hazard. As such, there is sufficient evidence to conclude that the Gamma curve is the most appropriate for extrapolating OS for chemotherapy.** At the company advisory board held in August 2024, clinical and health economic experts arrived at a consensus that the Weibull curve was the most clinically plausible OS extrapolation for chemotherapy, after the data had been adjusted for treatment switching via the two-stage estimation approach (which was one of the plausible company base-cases at the time of the advisory board).[2] The Weibull extrapolation of two-stage-adjusted chemotherapy OS data predicted survival rates of 22%, 2%, and 0% at 3-, 5-, and 10-years respectively. These were most closely aligned to the survival estimates predicted by the gamma extrapolation of IPCW-adjusted chemotherapy OS data (19%, 3%, and 0%, respectively). This supported the selection of the gamma curve for the OS of chemotherapy in the company base-case. As well as being the best match to the consensus from the advisory board, the Gamma curve for chemotherapy OS predicts a risk of death over time that very closely matches the observed data in the PAPILLON trial (based on the smoothed hazard plot of the KM data). It also has a very good visual plus statistical (2nd best) fit to the observed data. These are salient pieces of evidence that have been presented throughout the submission and support a conclusion that the extrapolation curve chosen in the company's base case accurately represents OS for chemotherapy.
8	**Section 3.8 (OS extrapolations):** The EAG preferred to use a log-logistic curve to extrapolate OS for chemotherapy alone.

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	There is sufficient evidence to conclude that the log-logistic curve for the OS of chemotherapy is implausible. Clinical and HTA expert opinion: At the company advisory board held in August 2024, advisor experts explicitly noted that the log-logistic curve for chemotherapy OS was unrealistic given patients receiving chemotherapy have a particularly poor survival.[2] The company's methodology of utilising the SHELF protocol to elicit survival estimates and validate extrapolation curves across a group of advisor experts is in-line with what is recommended within NICE TSD 26.[8] Assessment of hazard functions: The log-logistic curve for chemotherapy OS predicts an increasing hazard at first, which decreases after around 20 months. This is not consistent with the evolution of the per-cycle hazards for chemotherapy OS observed in the PAPILLON trial. Given the different trajectories of the associated hazard functions, selecting the log-logistic curve for chemotherapy OS (increasing and then decreasing after 20 months) alongside the Weibull curve for amivantamab with chemotherapy OS (monotonically increasing hazard) means that the OS hazards cross. Therefore, this scenario predicts that patients receiving chemotherapy are less likely to die compared to patients receiving amivantamab with chemotherapy after a certain point. This is implausible given the survival benefit that amivantamab with chemotherapy has demonstrated over chemotherapy, as shown through the clear and early separation of OS curves in the PAPILLON trial.
9	**Section 3.9 (uncertainties in extrapolating OS beyond the trial)**: The committee recalled that the Decision Support Unit's Technical Support Document 14 states that fitting different models allows for very differently shaped distributions, and strong evidence is required to justify this approach. **Johnson & Johnson acknowledge that TSD 14 recommends fitting the same parametric models to all treatments and would like to highlight that, although different, the OS extrapolations selected in the company base-case are similar.** In the company base-case, the OS curves for amivantamab with chemotherapy (using the Weibull distribution) and chemotherapy (using the Gamma distribution) exhibit similar shapes. This similarity arises from the fact that the underlying hazard functions for both distributions increase monotonically. This means that, in the company base-case, the risk of death over time evolves in a very similar way for both amivantamab with chemotherapy and chemotherapy. This mitigates the risk that "very differently shaped distributions" have been chosen in the company base-case. Conversely, the EAG base-case (ACP = Weibull, CP = log-logistic) and scenarios proposed by the EAG (ACP = Gompertz, CP = log-logistic) provide very differently shaped distributions as the underlying hazard functions over time are very different. These predict hazard functions over time that are clinically implausible and not aligned with the OS benefit that amivantamab with chemotherapy has demonstrated over chemotherapy in the PAPILLON trial. In response to the committee's request, Johnson & Johnson have provided an updated model which explores scenarios where the same parametric models are fitted to all outcomes for both amivantamab with chemotherapy and chemotherapy. The different parametric curves selected reflect the company and EAG base-cases. All these scenarios

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	resulted in a decrease to the ICER versus chemotherapy compared with the company base-case: • Company base-case: ICER = £36,255[a,b] • All endpoints for ACP & CP = Weibull: ICER = £34,263 • All endpoints for ACP & CP = Gamma: ICER = £33,737 • All endpoints for ACP & CP = Log-logistic: ICER = £31,335 a. Company base-case: ACP OS = Weibull, CP OS = Gamma, ACP TTDD = Weibull (both Ami and CP components), CP TTDD = Gamma, ACP PFS = Gamma, CP PFS = Gamma. b. The results presented are at the proposed PAS price of amivantamab The same trend (i.e., a decrease to the ICER versus chemotherapy compared with the company base-case) is observed when the same parametric models were applied to the OS of both treatments, rather than to all outcomes. • Company base-case: ICER = £36,255 • ACP & CP OS = Weibull: ICER = £34,186 • ACP & CP OS = Gamma: ICER = £32,436 • ACP & CP OS = Log-logistic: ICER = £24,192 This analysis shows that using the same parametric models for each treatment yields a lower ICER compared with the company's base-case. Therefore, the company's base-case can be considered realistic or in-fact conservative given that using the same parametric models for both treatments results in lower ICER.
10	**Section 3.9 (uncertainties in extrapolating OS beyond the trial)**: The committee also felt that the extrapolations of OS suggested that the benefit of amivantamab–chemotherapy over chemotherapy extends into the long term, even when the majority of people had stopped treatment. This implies a post-progression benefit, which is uncertain **Data from the PAPILLON trial demonstrate a clear post-progression benefit, mitigating the uncertainty associated with modelling this. Additionally, a long-term benefit for amivantamab has been observed in the CHRYSALIS and MARIPOSA trials, and clinical experts have stated they would expect this for amivantamab with chemotherapy.** PAPILLON data show a clear post-progression benefit associated with amivantamab with chemotherapy In the PAPILLON trial, amivantamab with chemotherapy achieved a median PFS of 11.37 months and the median OS had not been reached after a median follow-up across both treatment arms of 20.9 months (26.1% death events at this point).[7] Additionally, the median PFS2 had not been reached either and although the median PFS was 11.37 months, the PFS2 event-free rate at 24-months was 57%. These data show that the OS benefit for amivantamab with chemotherapy extends well beyond the PFS benefit, and there is a clear post-progression benefit.

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	A long-term benefit of amivantamab has been demonstrated in other indications The long-term survival benefit of amivantamab has been demonstrated across other licensed indications. In the CHRYSALIS trial, a Phase 1b registrational trial in patients with EGFR Exon20 insertion mutation-positive advanced NSCLC who had received prior chemotherapy, after a median follow-up of 19.2 months, the median OS of patients receiving amivantamab monotherapy was 23 months (95% CI, 18.5–29.5).[9] It is reasonable to expect that the OS benefit of amivantamab with chemotherapy in an untreated population (i.e., first-line setting) will exceed the OS benefit observed in the CHRYSALIS trial, which represented a heavily pre-treated population of patients who had already progressed on chemotherapy (i.e., second-line setting). Strong survival results have also been reported by the MARIPOSA trial, a Phase 3 registrational trial assessing amivantamab in combination with lazertinib in patients with untreated advanced NSCLC with common EGFR mutations (exon19 deletions or exon21 L858R substitutions). In the final analysis, after a median study follow-up of 37.8 months, the median OS was not reached for amivantamab-lazertinib, and there were [redacted] deaths in the amivantamab-lazertinib arm, showing that the majority of patients remained alive at this point (HR: 0.75; 95% CI: 0.61, 0.92; p=0.0048). A plateau to the survival of amivantamab with lazertinib was also observed at this timepoint. Importantly, the OS benefit observed for amivantamab with lazertinib in the MARIPOSA trial (median not reached after 37.8 months) extends well beyond the PFS benefit achieved (median PFS = 23.7 months, 95% CI: 19.1, 27.7, p<0.001). Although the populations and interventions differ, these long-term data present compelling evidence that amivantamab significantly extends OS, particularly in comparison to PFS. Based on expert opinion, amivantamab with chemotherapy is expected to achieve a long-term benefit At a company advisory board held in May 2024, clinical experts highlighted they would expect a tail to the survival curve of amivantamab with chemotherapy given the mechanism of action which incorporates an immune-modulating effect as well as targeting both EGFR and MET which are pathways involved in resistance mechanisms and cancer progression.[1]
11	**Section 3.10 (treatment-effect waning)**: The committee concluded that treatment-effect waning could not be ruled out and should be explored through selecting appropriate OS curves or explicit modelling of treatment-effect waning. **There is sufficient evidence to conclude that it is not appropriate to model a waning effect for amivantamab, including survival data from the PAPILLON trial.** Johnson & Johnson consider it inappropriate to explicitly model a treatment waning effect for amivantamab given the short time on treatment, the fact that any waning is implicitly captured in the selected OS extrapolations, and the fact that the committee explicitly concluded it is appropriate to exclude treatment-effect waning from the modelling of amivantamab monotherapy in NICE technology appraisal (TA) 850. Survival data from the PAPILLON trial does not indicate treatment-effect waning Additionally, survival data for amivantamab with chemotherapy indicates a sustained benefit with no evidence of treatment effect waning. Due to the separation of OS curves, the OS HR between amivantamab with chemotherapy and chemotherapy alone falls

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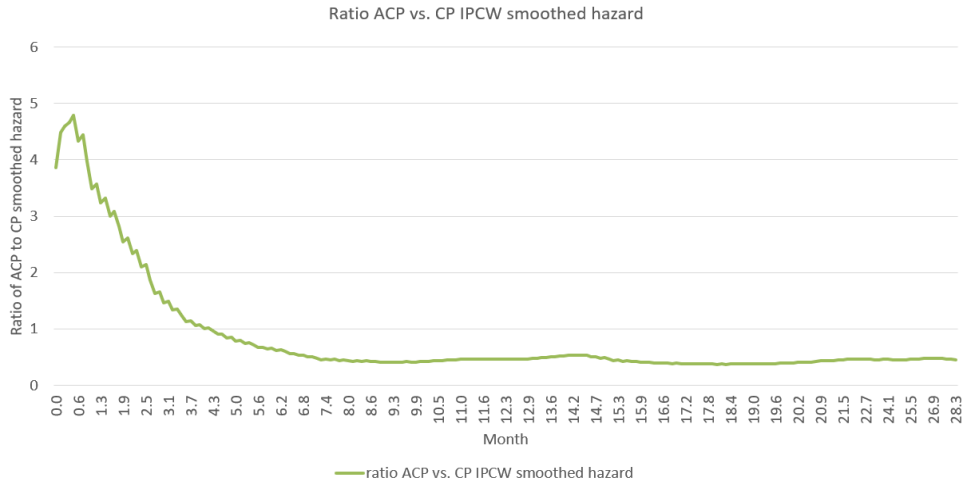
below 1 after only 4.2 months (indicating a reduced risk of death for amivantamab with chemotherapy) and remains below 1 for the remainder of the observed period. Crucially, the OS HR does not change in any significant way, remaining constant for the remainder of the observed period, demonstrating no waning or diminishing effect relative to chemotherapy.

This is illustrated in the graph below showing the smoothed hazard ratio over time for amivantamab with chemotherapy and chemotherapy OS data:



The sustained benefit associated with amivantamab can be attributed to its mechanisms of action. Amivantamab exerts anti-tumour activity via three mechanisms comprising EGFR/mesenchymal-epithelial transition (MET) receptor degradation, inhibition of ligand binding, and immune cell-directing activity. These distinct mechanisms work in parallel to achieve prolonged inhibition of tumour growth and a sustained efficacy benefit.

Implied hazard ratios

To further explore whether a diminishing effect relative to chemotherapy is present, Johnson & Johnson have provided analyses on the implied hazard ratios over time that are predicted in the company and EAG base-cases, and in scenarios where the same parametric models are selected for amivantamab with chemotherapy and chemotherapy.

In the company base-case (ACP OS = Weibull, CP OS = Gamma), the implied hazard ratio very gradually increases after around five years, showing a reduction in the efficacy benefit of amivantamab combined with chemotherapy compared to chemotherapy alone beyond this point. This observation supports the notion that any treatment effect waning over time is reflected in the OS curves themselves.

In the EAG base-case (ACP OS = Weibull, CP OS = log-logistic), the implied hazard ratio increases after around 2 years and exceeds 1 after around 7.5 years. This is because the log-logistic extrapolation for chemotherapy predicts a decreasing hazard function after around 2 years which crosses below the hazard function for the Weibull extrapolation of amivantamab with chemotherapy at around 7.5 years. This scenario therefore predicts that patients receiving chemotherapy are less likely to experience a death event after 2 years compared to patients receiving amivantamab with chemotherapy and after around 7.5 years chemotherapy is outperforming amivantamab and chemotherapy. This prediction is not consistent with the OS benefit that amivantamab with chemotherapy has

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	demonstrated over chemotherapy in the PAPILLON trial, as shown through the early and clear separation of survival curves. Selecting the Gamma and Weibull curves for the OS of both treatments predicts a decreasing implied hazard overtime. Neither scenario shows a diminishing efficacy benefit of amivantamab with chemotherapy relative to chemotherapy. Selecting the log-logistic curve for the OS of both treatment arms predicts an increasing implied hazard after around two years, showing a diminishing efficacy benefit of amivantamab with chemotherapy relative to chemotherapy. <u>Additional analyses to estimate the long-term survival of amivantamab with chemotherapy</u> Modelling the hazards of both treatments as being equal is not supported by any data and is unrealistic, given the demonstrated benefit of amivantamab with chemotherapy over chemotherapy alone in the PAPILLON trial. However, Johnson & Johnson have explored different methods of estimating the long-term survival of amivantamab with chemotherapy. The first estimation method involves fixing the modelled implied hazard ratio of amivantamab with chemotherapy OS vs chemotherapy OS from the last observation (2.8 years in the amivantamab with chemotherapy arm) onwards and applying this to the OS of chemotherapy. This models a situation where the OS benefit of amivantamab with chemotherapy relative to chemotherapy does not change after the last observation (i.e., constant implied hazard ratio). The ICERs versus chemotherapy for the company base-case and from this estimation method are provided below: • Company base-case: £36,255 Applying fixed implied hazard ratio to CP OS: • ACP = Weibull / CP = Gamma: £36,999 • ACP and CP OS = Weibull: £42,115 • ACP and CP OS = Gamma: £34,780 • ACP and CP OS = Log-logistic: £21,496 • ACP = Weibull / CP OS = Log-logistic: £25,182 The second estimation method involves applying the per-cycle hazard ratio between the OS and PFS of chemotherapy to the PFS of amivantamab with chemotherapy. This models a situation where the relative difference between PFS and OS for amivantamab with chemotherapy is equal to the relative difference observed for chemotherapy. The ICERs versus chemotherapy for the company base-case and from this estimation method are provided below: • Company base-case: £36,255 Scenarios when applying per-cycle HR of CP OS vs PFS to ACP PFS:

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	• ACP = Weibull / CP = Gamma: £32,756 • ACP and CP OS = Weibull: £35,663 • ACP and CP OS = Gamma: £32,756 • ACP and CP OS = Log-logistic: £34,909 • ACP = Weibull / CP OS = Log-logistic: £34,909 Implementing these methodologies leads to a reduction in the ICER versus chemotherapy compared with the company's base case in all but two of the extrapolation scenarios. This further supports the credibility of the company's selected base case. The only scenario that results in a notably higher ICER is when the fixed OS HR for the Weibull / Weibull scenario is applied to chemotherapy OS. The Weibull curve for chemotherapy OS predicts the lowest survival out of all the scenarios and is not aligned to the company's or EAG's base-cases. Therefore, it should not be considered clinically realistic or useful for decision-making. Notably, when using the EAG's base-case (ACP = Weibull / CP = log-logistic), both estimation methodologies result in significantly lower ICERs which suggests that the log-logistic curve overestimates the OS of chemotherapy.
12	**Section 3.13 (utility values)**: The EAG noted that there was missing data from both health states, with a substantial amount missing from the progressed-disease health state. The EAG was concerned that if the data was not missing at random then the utility values might not be accurate. **There is sufficient data to conclude that missingness was indeed at random, reducing the risk that the utility values derived from the trial data are not accurate.** Johnson & Jonson acknowledge there is no empirical evidence to show that health related quality of life (HRQL) data were missing at random. However, both arms had similar degrees of missingness and there was no discernible pattern to the degree of missingness over cycles 0 to 27. Additionally, individual patient profiles over that time period did not indicate a systematic pattern in missingness, and missingness was not associated with any prognostic baseline characteristic. The plot below shows that missingness is not increasing overtime, and equally spread between treatment arms:

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	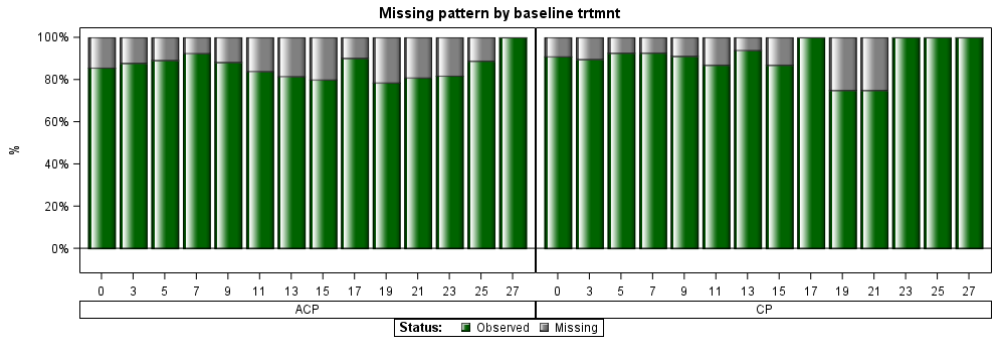 Additional information to show that individual patient profiles over time do not indicate a systematic pattern in missingness (e.g., missingness is not higher in the visits preceding progression) is available in the document containing the additional analyses. This evidence suggests that the missing data within the PAPILLON trial occurred at random. This finding alleviates the concerns raised by the EAG regarding the accuracy of the utility values derived from the PAPILLON trial, indicating that these utility values from the trial can be regarded as reliable and accurate.
13	**Section 3.13 (utility values)**: The committee noted that the utility values in this appraisal were higher in both health states than in several other appraisals in NSCLC. **EQ-5D data from the PAPILLON trial is the most robust source of evidence to derive utilities for the population in this decision problem.** As the PAPILLON trial was conducted in the specific patient population under consideration in this decision problem, it is the most robust and appropriate source of data for deriving utility values. It is inappropriate to consider utility values from other appraisals in NSCLC given that these are: not specific to patients with EGFR Exon 20 insertion mutations, are associated with different interventions and treatment history, and they may reflect significantly varied yet important differences in patient characteristics. Utilities accepted in the appraisal of amivantamab monotherapy after prior chemotherapy (TA850) may, to a limited extent, be relevant. The utility value for the progressed-disease state which is derived from PAPILLON trial data ([redacted]) is similar to the utility value for the progression-free state that was used in the appraisal of amivantamab after prior chemotherapy (0.713), which the committee accepted.[10] It is important to note that the population in TA850 was more heavily pre-treated than the progressed patients from the PAPILLON trial, where the median number of previous treatments in the CHRYSALIS trial was two. Had the population been less pre-treated, the utility values would likely have been even closer to, or even exceeded, the progressed utility value observed in the PAPILLON trial. The progressed disease state in the PAPILLON trial closely resembles the progression-free population in the CHRYSALIS trial, as both represent patients with EGFR Exon 20 insertion mutation-positive advanced NSCLC who have progressed on at least one line of therapy. However, it is crucial to emphasise that the CHRYSALIS trial included a higher proportion of pre-treated patients which could explain the slightly lower utility value. Using 0.713 as the progressed disease utility has a small impact on the ICER:

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	• Company base-case: £36,255 • Using 0.713 as PD utility: £37,234
14	**Section 3.14 (adverse event costs): unit costs for AEs** **Johnson & Johnson have updated the model to incorporate the committee's preferred assumption regarding AE costs (i.e., only including unit costs for the severest AEs).** The new company base-case versus chemotherapy is £36,255 at the proposed PAS price of amivantamab. This is similar to the ICER presented in the company base-case at the first committee meeting, which was £35,820.
15	**Section 3.15 (dosing in the model):** The committee concluded that it would prefer to model doses of amivantamab in the cycles in which they were due **Johnson & Johnson have updated the model to incorporate the committee's preferred assumption with regards to dosing frequency (i.e., treatment costs incurred in the cycles in which administrations were due, following dosing frequency in the PAPILLON trial).** The new company base-case versus chemotherapy is £36,255 at the proposed PAS price of amivantamab. This is similar to the ICER presented in the company base-case at the first committee meeting, which was £35,820.
16	**Section 3.16 (vial sharing)**: The company did not think that its model allowed vial sharing. The committee considered the expert testimony that vial sharing would not be possible in clinical practice and concluded that vial sharing should not be permitted in the model. **Vial sharing is not allowed in the model. This is explicit within the calculation for the number of vials per administration, shown below.** The fractional value for the average number of vials per administration for amivantamab across the cohort arises because individual patients can receive a reduced number of **full vials**, as per Table 3 in the summary of product characteristics (SmPC).[7] Calculation: The average number of units (vials) per administration is calculated by multiplying the number of expected vials per administration by the average proportion of dose given. The average proportion of dose given is calculated by dividing the total dose given in the trial by the total expected dose. The total dose given is lower than the total expected dose (due to dose reductions), and the difference equates to a number of full vials (i.e., a multiple of 350mg). This shows that patients only received dose reductions in terms of full vials of amivantamab and no vial sharing was permitted.

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An example calculation for a hypothetical cohort of 10 patients < 80kg at baseline for the first cycle is given below, to show that dose reductions are only given in terms of full vials:

- Expected dose for 1 patient < 80kg in cycle 1 = 1400mg = 4 full vials
- Total expected number of vials for the cohort of 10 patients = 4 * 10 = 40 vials (assuming all patients received 100% of the expected dose)
- However, in this scenario, two patients are assumed to have received a reduced dose of 1150mg (**3 full vials**) given this is permitted within the SmPC of amivantamab.[7] This means that two patients in this cohort received 3 vials rather than 4.
- Therefore, the total number of vials actually given across the cohort = 40 – 2 = 38 full vials
- The average number of vials given per treatment across the cohort = 38 / 40 = 95%
- 95% is an average across all patients. However, as shown through the calculation above, individual patients only receive full vials of amivantamab (i.e., no vial sharing). The average proportion arises as individuals can receive a reduced number of **full vials** (e.g., 3 vials not 4).

The actual calculation used in the model for patients with weight < 80 kg at baseline is given below:

Amivantamab:

- Total dose given (PAPILLON) = [redacted] mg ([redacted] **full vials of amivantamab**)
- Total dose expected (PAPILLON) = [redacted] mg **([redacted] full vials of amivantamab)**
- Difference = 257,600 mg ([redacted] **full vials of amivantamab**)
- Average proportion of dose given (cohort) = [redacted] mg / [redacted] mg = [redacted]%. This means that, on average, patients will receive 93.7% of the dose compared to the expected dose over their treatment.
- Average units per administration (cohort) = 1400 mg / 350 mg (expected number of vials per administration) * [redacted]% = [redacted]. This represents an average across all patients where, in some cases, patients will receive 3 vials, and in some cases, patients will receive 4 vials.

The calculation in the model gives a fractional value for the number of units of amivantamab per administration ([redacted] for patients <80kg at baseline) given it is done at a cohort level. It should be stressed that, at an individual level, no vial sharing is allowed in the model.

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	Carboplatin and pemetrexed: The calculation for the units per administration for carboplatin and pemetrexed is done using the same methodology as described above. However, dose reductions in terms of full vials are not recommended in the SmPCs of carboplatin and pemetrexed. Therefore, if a patient receives a reduced dose of these treatments, they would still incur the full number of expected vials. As such, it is necessary to round the number of vials per administration up after applying the relative dose intensity (RDI) in order to reflect the expected number of vials.
17	**Section 3.17 (dose skipping)**: The committee concluded that it would like the company to report dose-skipping estimates from the first and subsequent cycles of the PAPILLON trial and for the modelling to reflect any differences in these values. It would also like to see a scenario that explores modelling no dose skipping across all treatments in both arms and one where dose skipping was modelled to be equal across all treatments and arms. **Johnson & Johnson have provided an updated model which includes the requested scenarios for dose skipping. These scenarios resulted in a minor decrease to the ICER versus chemotherapy compared with the base-case.** When dose skipping is modelled to reflect the per-cycle proportions observed in the PAPILLON trial, the ICER versus chemotherapy slightly decreases given a higher proportion of patients skipped doses of amivantamab in subsequent cycles compared with the first cycle, which reduces the cost of amivantamab. Johnson & Johnson have kept the base-case to model dose skipping based on the average proportion of missed doses across all treatment cycles given this models a lower proportion of doses skipped, which is in-line with the committee's preference. The dose skipping proportion is calculated by dividing the number of doses that were missed in the PAPILLON trial by the number of doses that were expected to be given. Dosing scenarios: • Company base-case: ICER = £36,255[a] • Dose skipping by cycle: ICER = £36,012[b] • Equal dose skipping across ACP and CP: ICER = £36,122[c] a. ICER results at the proposed PAS price of amivantamab b. This scenario incorporates different dose-skipping estimates for the first and subsequent cycles c. The dose skipping rate for patients receiving CP is equated to the rate observed for patients receiving ACP (across the treatments) who had a weight of <80kg at baseline ([redacted]%). This scenario is not anticipated to reflect clinical practice given different dose skipping rates between amivantamab and chemotherapy is expected Johnson & Johnson consider the scenario that includes no dose skipping is not appropriate given this does not reflect the data observed in the PAPILLON trial and is not expected in clinical practice based on expert opinion. At the May 2024 company advisory board, clinical experts explicitly concluded that dose skipping is expected to be seen in practice and should be accounted for in the cost calculation in the model.[1] The clinical experts also agreed that it is appropriate to use trial data on skipped doses within the model.

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18.	**Section 3.20 (acceptable ICER)**: The committee was unable to identify a threshold because this would need to account for both the resolvable uncertainties in the analyses requested and the currently unresolvable uncertainties. **Given the unmet need, the robustness of the data from the PAPILLON trial, and the additional analyses provided to address the uncertainties cited in the draft guidance, the acceptable ICER should be positioned at the upper end of the range that NICE considers to be a cost-effective use of NHS resources.** Patients with advanced NSCLC and EGFR Exon20 insertion mutations have a very high unmet need owing to the lack of efficacious, targeted therapies which are available in other advanced NSCLC indications. Resulting in particularly poor outcomes for these patients, with UK RWE showing that patients with untreated, EGFR Exon20 insertion mutation-positive advanced NSCLC have a median OS of just 19.1 months.[3] This unmet need has been cited by both clinical experts and patient groups within the committee papers and was also vocalised at the committee meeting by the clinical expert and the patients. The PAPILLON trial provides robust evidence to demonstrate that amivantamab with chemotherapy addresses this urgent unmet need. The robustness of the PAPILLON trial is shown through the fact that data from the chemotherapy arm, after adjusting for treatment switching, (mOS = [redacted] months) are very closely aligned to real-world data for chemotherapy from the NECTAR study, after adjusting (via average treatment effect in the treated [ATT] weighting) to match the PAPILLON trial, (mOS = 23.7 months); the NECTAR study was associated with a much longer follow-up (50.5 months).[3] The close alignment between the PAPILLON trial data and real-world data reduces the degree of uncertainty associated with the PAPILLON trial. The degree of uncertainty has also been reduced by the additional analyses and scenarios that Johnson & Johnson have provided following the requests outlined in the draft guidance. These have included running scenarios for dose skipping (using per-cycle proportions and equating dose skipping rates across treatments), exploring different utilities from TA850 to model the PD utility, using the same parametric curves for all outcomes for both treatments and for the OS of both treatments, and exploring the implied hazard ratios associated with each extrapolation scenario. Additionally, Johnson & Johnson have provided analyses exploring different ways of estimating the long-term benefit of amivantamab with chemotherapy (fixing the OS HR from the end of the observation period onwards and equating the relative difference between PFS and OS to the difference observed for chemotherapy) and have provided information on the smoothed OS HR of amivantamab with chemotherapy over time to show whether a waning effect is observed in the PAPILLON trial. In nearly all scenarios explored and the additional analyses suggested by the committee, no clinically realistic or methodologically sound scenarios emerged that presented a significantly higher ICER than the company's base-case. This reinforces the credibility and robustness of the company's base-case, effectively addressing concerns regarding uncertainty. Johnson & Johnson strongly advocate for NICE to consider a willingness to pay threshold towards the upper end of the willingness to pay range. This is supported considering the critical unmet need, the severity of the disease (with a 1.2x severity modifier being accepted), the efficacy benefit demonstrated, and the robustness of the data (shown through scenarios and the base case), together with the small patient population (with [redacted] patients eligible for treatment in England and Wales in 2024, based on NICE's

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	budget impact assessment) and consequently low risk associated with funding amivantamab with chemotherapy.

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- Do not paste other tables into this table – type directly into the table.
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- Do not include medical information about yourself or another person from which you or the person could be identified.
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- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

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References

1. Johnson & Johnson Data on File. Advisory Board Report for Amivantamab PAPILLON HTA Submissions. 2nd May 2024.
2. Johnson & Johnson Data on File. Advisory Board Report for Amivantamab PAPILLON HTA Submissions. 1st August 2024.
3. Johnson & Johnson Data on File. The NECTAR Study. Technical Report. 2024.
4. Johnson & Johnson Data on File. RWE NCRAS Data Aggregated Report. 2024.
5. NICE. Amivantamab with carboplatin and pemetrexed for untreated EGFR exon20 insertion mutation-positive advanced non-small-cell lung cancer [ID5110] Committee papers: https://www.nice.org.uk/guidance/gid-ta11023/documents/committee-papers [Last accessed 14 April 2025].
6. Johnson & Johnson Data on File. Statistical Analyses to Adjust Overall Survival for Treatment Switching in PAPILLON Trial. Technical Report focused on Oct23 OS data cut. 06August2024.
7. Medicines & Healthcare Products Regulatory Agency. Summary of Product Characteristics. RYBREVANT 50 mg/mL concentrate for solution for infusion. Available from: https://www.medicines.org.uk/emc/product/13084/smpc. [Last accessed 14 April 2025].
8. NICE technical support document (TSD) 26: Expert elicitation for long-term survival outcomes. https://www.sheffield.ac.uk/media/94031/download?attachment [Last Accessed 18 April 2025].
9. Lopez PG, Girard N, Cho BC, et al. 30 Long-term efficacy, safety, and predictors of response to amivantamab among patients with post-platinum EGFR Ex20ins-mutated advanced NSCLC. Journal of Thoracic Oncology 2023;18:S36-S37.
10. National Institute of Health and Care Excellence (NICE). Amivantamab for treating EGFR Exon 20 insertion mutation-positive advanced non-small-cell lung cancer after platinum-based chemotherapy. TA850. Available at: https://www.nice.org.uk/guidance/ta850 [Last accessed 17 April 2025]

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Single Technology Appraisal

Amivantamab with carboplatin and pemetrexed for untreated EGFR Exon20 insertion mutation-positive advanced non-small-cell lung cancer [ID5110]

Company Additional Analyses

[April 2025]

File name	Version	Contains confidential information	Date
ID5110_Amivantamab_Additional_Analyses_Redacted.docx	V1	Yes	April 2025

Introduction

This document provides additional analyses requested by NICE in the draft guidance of amivantamab with carboplatin and pemetrexed for untreated epidermal growth factor receptor (EGFR) Exon20 insertion mutation-positive advanced non-small-cell lung cancer (NSCLC).

Section A: Summary of the updated base case

In response to the draft guidance, Johnson & Johnson have revised the cost-effectiveness model and provided an updated base-case. The updated base-case includes the committee's preferred assumptions with regards to comparator (chemotherapy), time to treatment discontinuation (TTDD) extrapolations (Weibull for amivantamab and chemotherapy components), vial sharing (no vial sharing is allowed in the model), adverse event (AE) costs (using codes only for the most severe non-elective short-stay AEs), and dosing (treatment costs accrued in the cycles in which administrations were due). A x1.2 severity modifier has been maintained, and the results incorporate the current amivantamab patient access scheme (PAS).

Deterministic and probabilistic results of the updated base-case are presented in **Table 1** and **Table 2**, respectively.

Table 1: Deterministic base-case results for amivantamab-chemotherapy versus chemotherapy at amivantamab PAS price, based on the updated model incorporating the committee's preferred assumptions

	Total[a]			Incremental[a]			ICER[a] (£/QALY)
	Costs (£)	QALYs	LYs	Costs	QALYs	LYs	
Amivantamab with chemotherapy	[redacted]	[redacted]	3.76	[redacted]	[redacted]	-	36,255
Chemotherapy	[redacted]	[redacted]	1.96	[redacted]	[redacted]	1.80	

a. Results are presented with the 1.2x QALY weighting (severity modifier) applied

Table 2: Probabilistic base-case results for amivantamab-chemotherapy versus chemotherapy at amivantamab PAS price, based on the updated model incorporating the committee's preferred assumptions

	Total[a]			Incremental[a]			ICER[a] (£/QALY)
	Costs (£)	QALYs	LYs	Costs	QALYs	LYs	
Amivantamab with chemotherapy	[redacted]	[redacted]	3.80	[redacted]	[redacted]	-	36,094
Chemotherapy	[redacted]	[redacted]	1.97	[redacted]	[redacted]		

a. Results are presented with the 1.2x QALY weighting (severity modifier) applied

Section B: Summary of additional scenarios and analyses

Johnson & Johnson have provided additional scenarios and analyses that were requested in the draft guidance document to address uncertainties raised by the committee.

The additional scenarios and analyses pertain to the choice of parametric model (using the same models for all treatments), showing data on the implied hazard ratios over time associated with the chosen extrapolation curves, exploring different methods of estimating the long-term benefit of amivantamab with chemotherapy, and presenting scenarios using different assumptions related to dose skipping (per-cycle and equated across treatment arms) and utilities (using utilities from other appraisals to model the progressed-disease utility).

All clinically plausible additional scenarios demonstrate the robustness of the company's base case and provide lower incremental cost-effective ratios (ICERs) to the company base-case.

Using the same parametric model for all treatments

In the draft guidance (section 3.11 and section 3.19), the committee requested exploring the impact of fitting the same parametric models to the overall survival (OS) of both treatment arms.

Johnson & Johnson have provided these analyses in **Table 3** and **Table 4**. The different parametric curves selected reflect the company and EAG base-cases. In all scenarios, using the same parametric model for both treatments resulted in a decrease to the ICER versus chemotherapy compared with the company base-case.

Table 3: Deterministic results for scenarios exploring the impact of selecting the same parametric model for all outcomes for both treatment arms

Scenario		WITH PAS		
		Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Base case		[redacted]	[redacted]	**36,255**
1.	All endpoints ACP & CP: Weibull	[redacted]	[redacted]	34,263
2.	All endpoints ACP & CP: Gamma	[redacted]	[redacted]	33,737
3.	All endpoints ACP & CP: Log-logistic	[redacted]	[redacted]	31,335

Table 4: Deterministic results for scenarios exploring the impact of selecting the same parametric model for the OS of both treatment arms

Scenario		WITH PAS		
		Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Base case		[redacted]	[redacted]	**36,255**
1.	ACP & CP OS: Weibull	[redacted]	[redacted]	34,186
2.	ACP & CP OS: Gamma	[redacted]	[redacted]	32,436
3.	ACP & CP OS: Log-logistic	[redacted]	[redacted]	24,192

This analysis shows that using the same parametric models for each treatment yields a lower ICER compared with the company's base-case. This applies to when the same parametric model is applied to all outcomes and to OS only.

Evolution of hazard functions over time

In the company base-case, the OS curves for amivantamab with chemotherapy (using the Weibull distribution) and chemotherapy (using the Gamma distribution) exhibit similar shapes. This similarity arises from the fact that the underlying hazard functions for both distributions increase monotonically. This is illustrated in **Figure 1** and **Figure 2**. This means that, in the company base-case, the risk of death over time evolves in a very similar way for both amivantamab with chemotherapy and chemotherapy. This mitigates the risk that “very differently shaped distributions” have been chosen in the company base-case.

Figure 1: OS extrapolations for the Weibull and Gamma curves for amivantamab with chemotherapy and chemotherapy

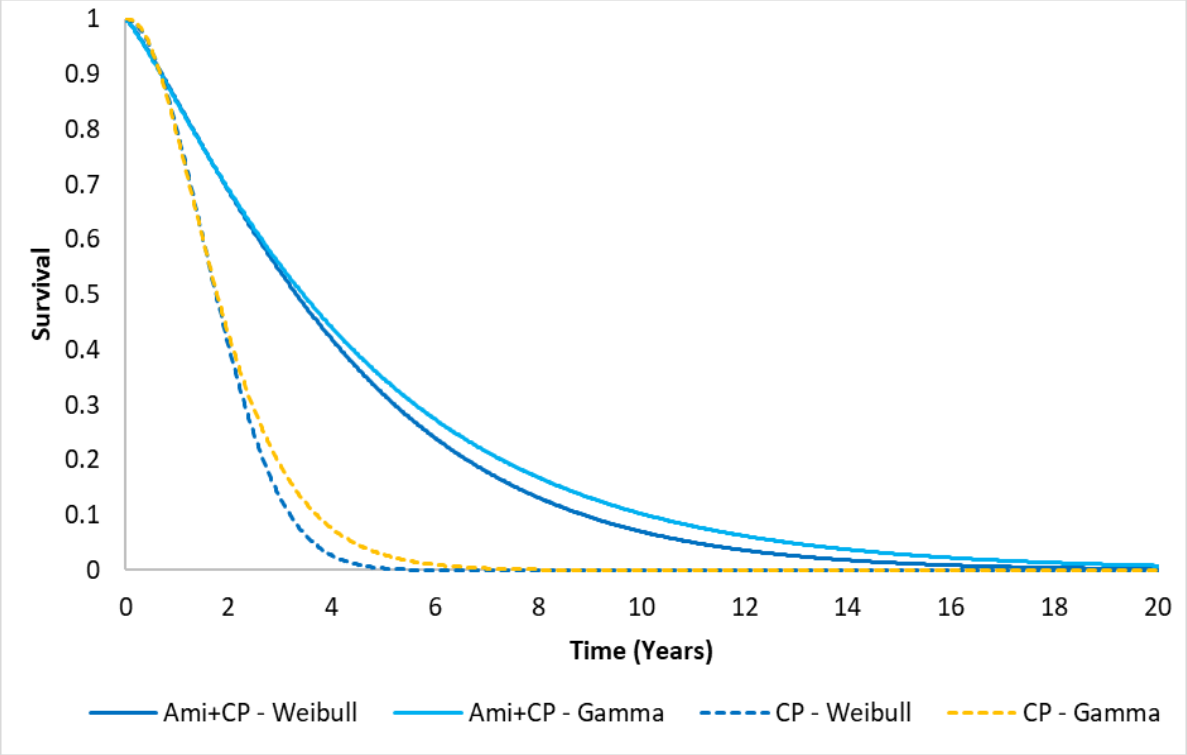
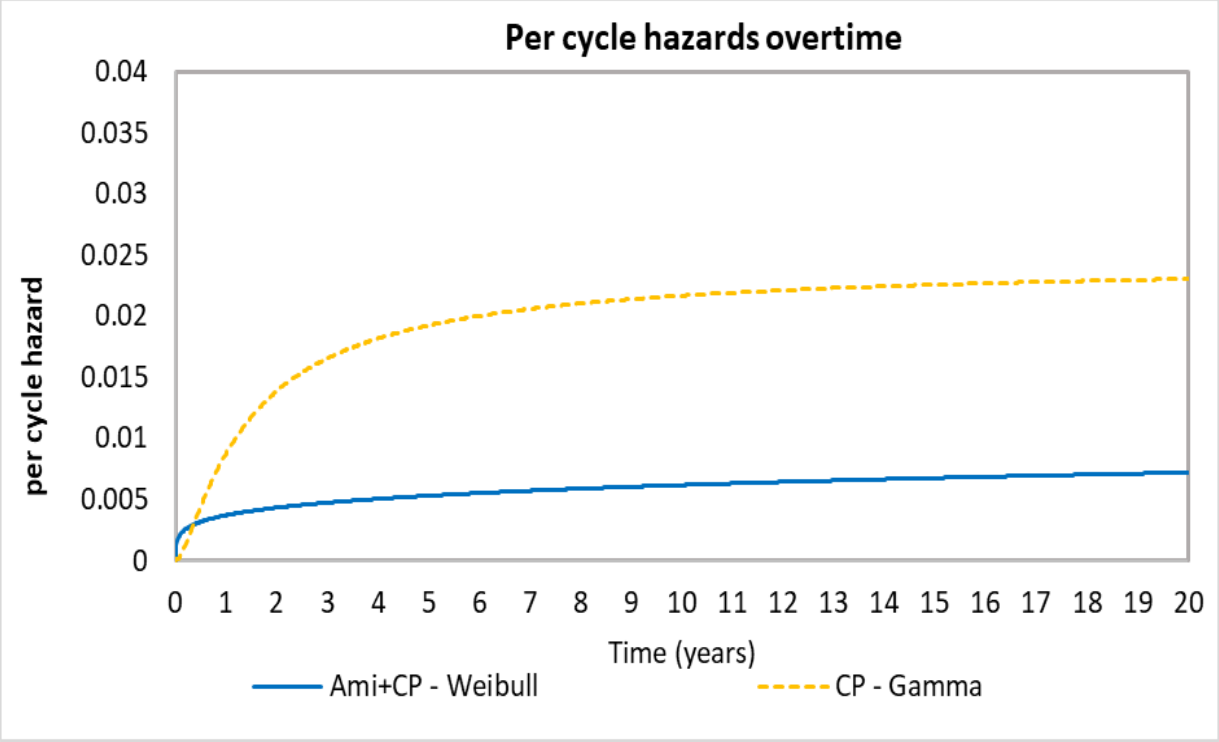
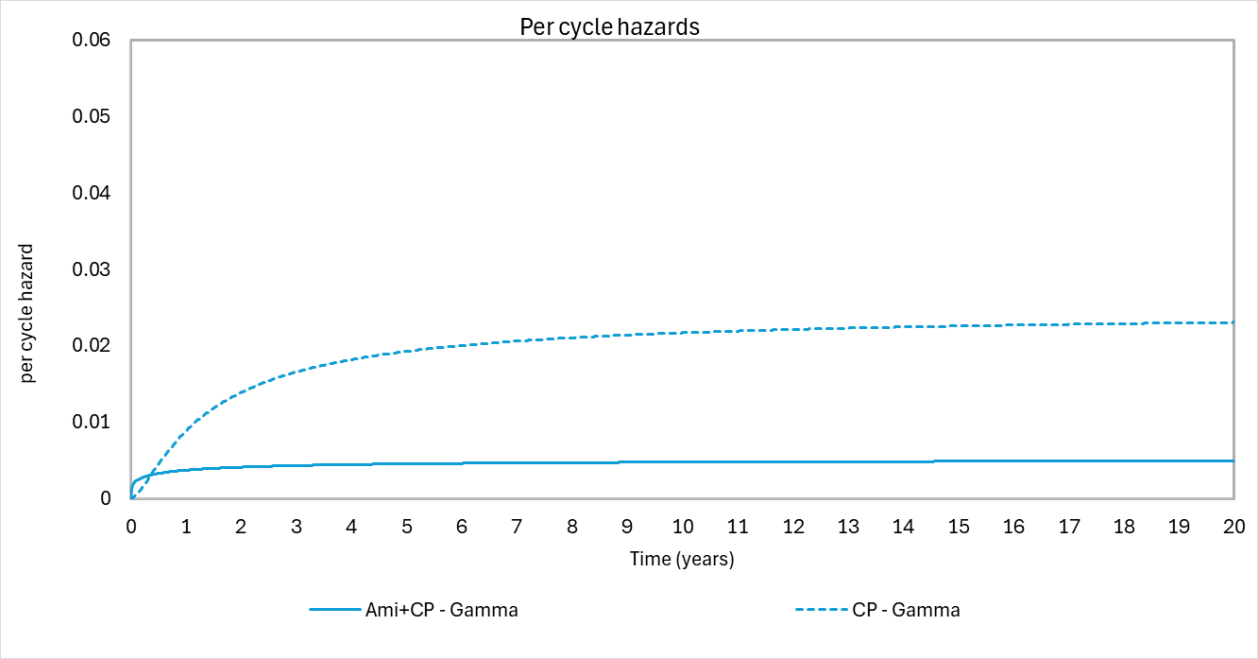


Figure 2: Plot of the per-cycle hazards over time predicted by the OS extrapolations of ACP (Weibull) and CP (Gamma) selected in the company base-case



A similar evolution of the per-cycle hazards over time is also observed for the scenario where the Gamma distribution is selected for the OS of both amivantamab with chemotherapy and for chemotherapy, as illustrated in **Figure 3**.

Figure 3: Plot of the per-cycle hazards over time predicted when the Gamma distribution is selected for the OS extrapolations of both amivantamab with chemotherapy and chemotherapy



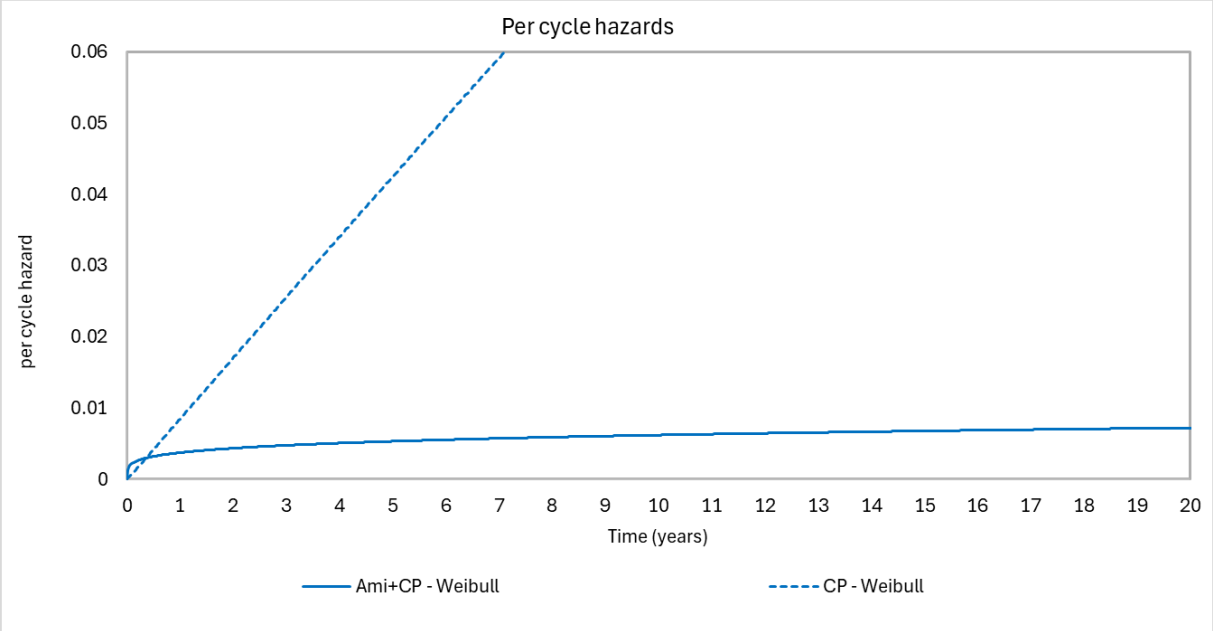
However, the per-cycle hazards over time evolve differently in the scenarios where the Weibull or log-logistic distributions are selected for the OS of both amivantamab with chemotherapy and chemotherapy, and in the EAG base-case (ACP = Weibull, CP = log-logistic), as illustrated in **Figure 4**, **Figure 5**, and **Figure 6**. These scenarios predict hazard functions over time that are clinically implausible and not aligned with the OS benefit that amivantamab with chemotherapy has demonstrated over chemotherapy in the PAPILLON trial.

In the EAG base-case, patients treated with amivantamab with chemotherapy are predicted to have an increasing hazard function whereas patients receiving chemotherapy have an increasing hazard at first, which then decreases after around 20 months. This is not consistent with the per-cycle hazards over time for chemotherapy OS that is observed in the PAPILLON trial. Additionally, this scenario predicts that the hazards cross each other at around 7.5 years, meaning patients

receiving amivantamab with chemotherapy are more likely to die compared with patients receiving chemotherapy after this timepoint. This is inconsistent with the separation of OS curves observed in the PAPILLON trial.

In the scenario when the Weibull distribution is selected for the OS of both treatments, the per-cycle hazard for chemotherapy increases at a constant rate until around 10 years. This also does not reflect the per-cycle hazards observed for IPCW-adjusted chemotherapy data or the evolution of the per-cycle hazards for amivantamab with chemotherapy.

Figure 4: Plots (with different y-axis scales) of the per-cycle hazards over time predicted when the Weibull distribution is selected for the OS extrapolations of both amivantamab with chemotherapy and chemotherapy



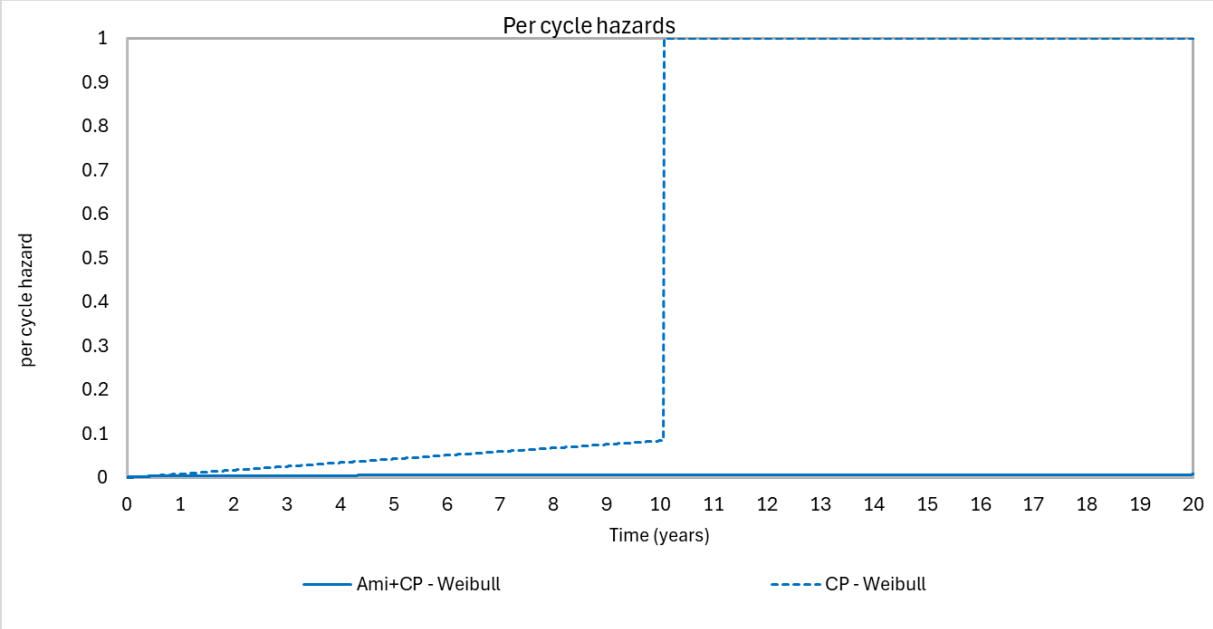


Figure 5: Plot of the per-cycle hazards over time predicted when the log-logistic distribution is selected for the OS extrapolations of both amivantamab with chemotherapy and chemotherapy

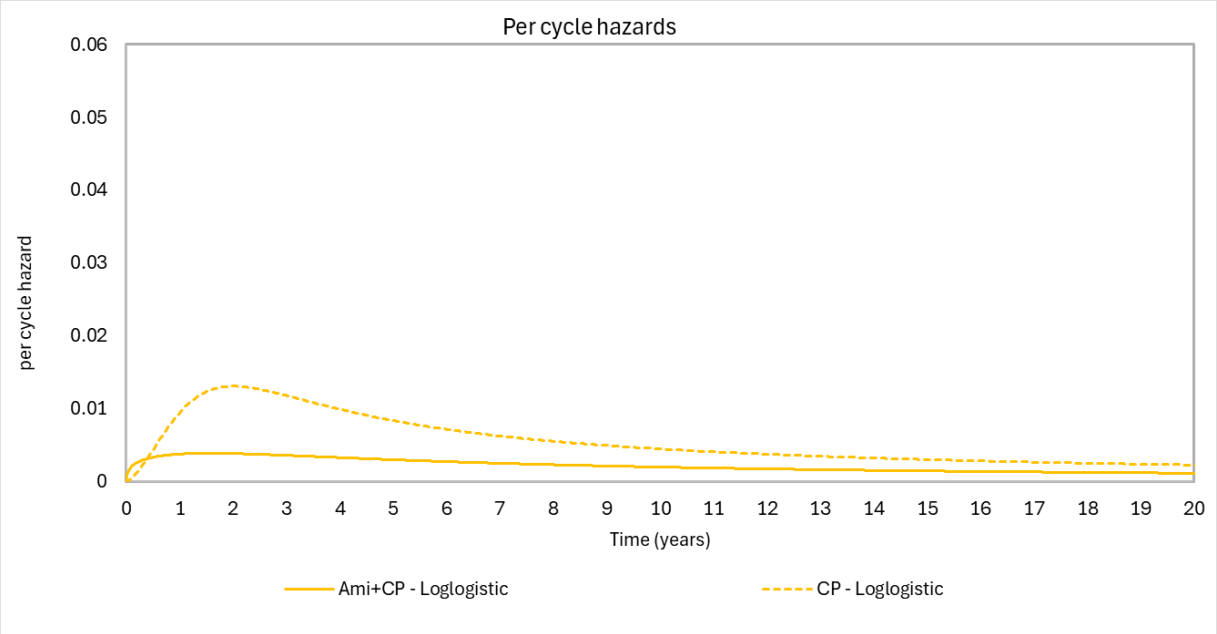
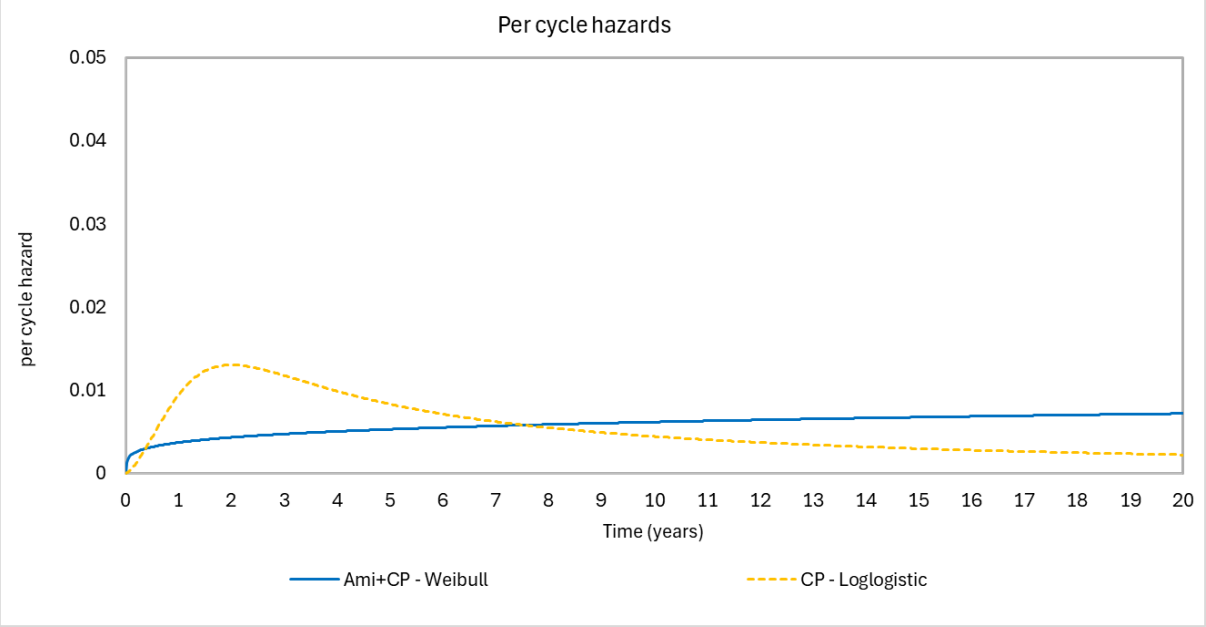


Figure 6: Plot of the per-cycle hazards over time predicted by the OS extrapolations of ACP (Weibull) and CP (log-logistic) selected in the EAG base-case



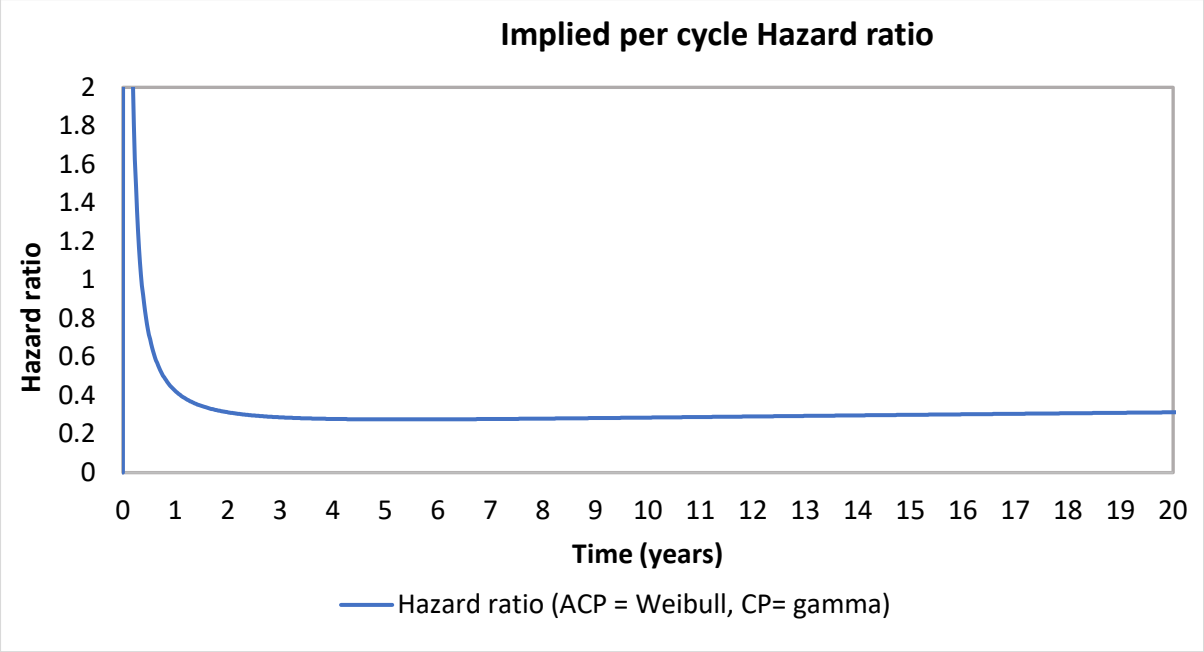
Implied hazard ratios

In the draft guidance (section 3.11 and section 3.19), the committee requested an analysis of the implied OS hazard ratio over time, to provide more information on the post-progression benefit and treatment-effect waning. This is presented below.

In the company base-case (ACP OS = Weibull, CP OS = Gamma), the implied hazard ratio very gradually increases after around five years, showing a reduction in the efficacy benefit of amivantamab combined with chemotherapy compared to chemotherapy alone beyond this point, as illustrated in **Figure 7**. This observation supports the notion that any treatment effect waning over time is reflected in the OS curves themselves.

The relatively constant implied hazard ratio in this scenario is explained through **Figure 2**, which shows that the risks of death per-cycle predicted for both amivantamab with chemotherapy and chemotherapy evolve in a similar way. Although both treatments are modelled to have an increasing probability of death over time, amivantamab with chemotherapy shows a slightly decreasing benefit relative to chemotherapy given the risk of death per cycle rises over time at a slightly increased rate compared with chemotherapy. A further description of this is provided within the company response to the NICE draft guidance.

Figure 7: Plot of the implied per cycle hazard ratio over time predicted by the OS extrapolations of ACP (Weibull) and CP (Gamma) selected in the company base-case



The implied hazard ratios predicted by the OS extrapolations selected in the EAG base-case (ACP = Weibull, CP = log-logistic) and in the requested scenarios (same distributions applied to both treatment arms) are shown in **Figure 8**.

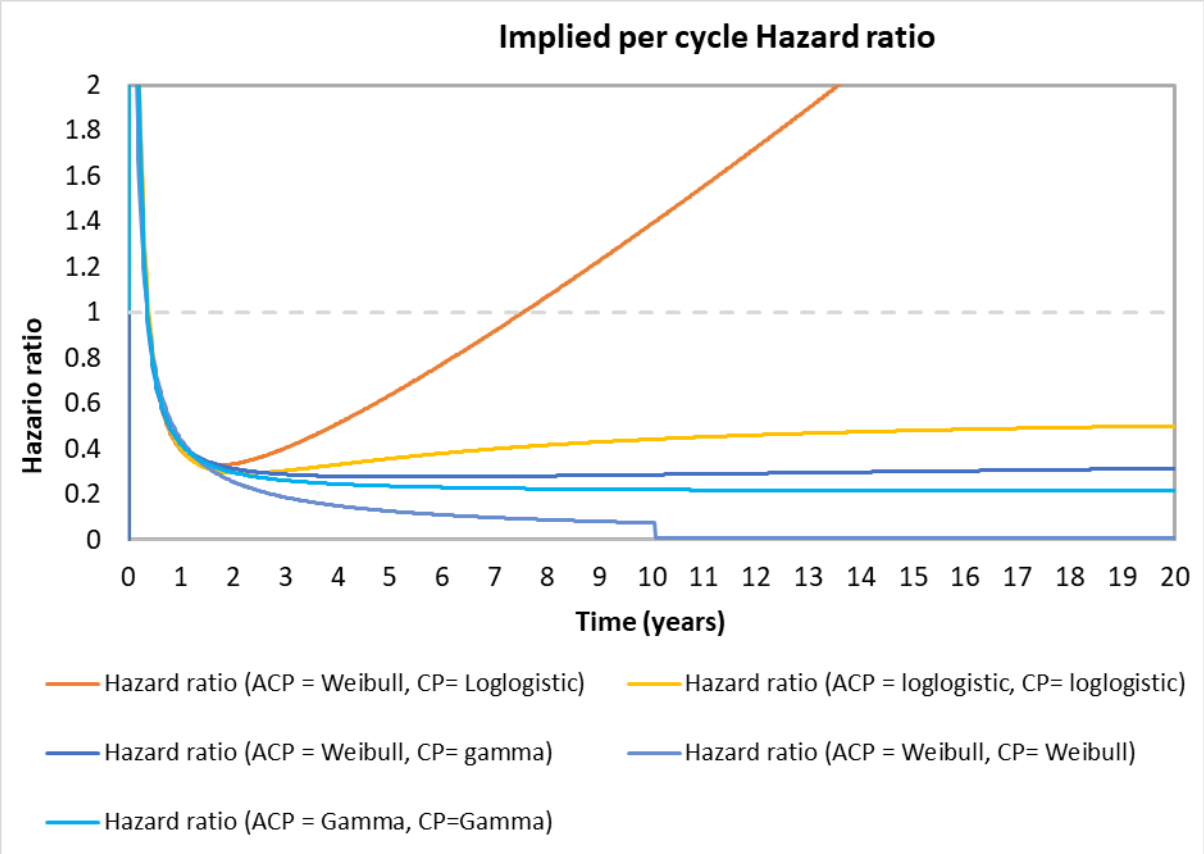
In the EAG base-case (ACP OS = Weibull, CP OS = log-logistic), the implied hazard ratio increases after around 2 years and exceeds 1 after around 8 years. This scenario therefore predicts that patients receiving chemotherapy are less likely to experience a death event after 2 years compared to patients receiving amivantamab with chemotherapy and after around 7.5 years chemotherapy is outperforming amivantamab and chemotherapy. This prediction is not consistent with the OS benefit that amivantamab with chemotherapy has demonstrated over chemotherapy in the PAPILLON trial, as shown through the early and clear separation of survival curves.

Selecting the Gamma and Weibull curves for the OS of both treatments predicts a decreasing implied hazard over time. Neither scenario shows a diminishing efficacy benefit of amivantamab with chemotherapy relative to chemotherapy.

Selecting the log-logistic curve for the OS of both treatment arms predicts an increasing implied hazard after around two years, showing a diminishing efficacy benefit of amivantamab with chemotherapy relative to chemotherapy.

Notably, all scenarios other than the EAG base-case predict a relatively similar pattern whereby the implied hazard ratio decreases until around two years, after which point the implied hazard ratio remains relatively constant or gradually increases but still staying well below 1 for the full time horizon.

Figure 8: Plot of the implied per cycle hazard ratios over time predicted by the OS extrapolations of ACP and CP selected in the EAG base-case (ACP = Weibull, Gamma = log-logistic) and requested scenarios (using the same OS distribution for both treatments)

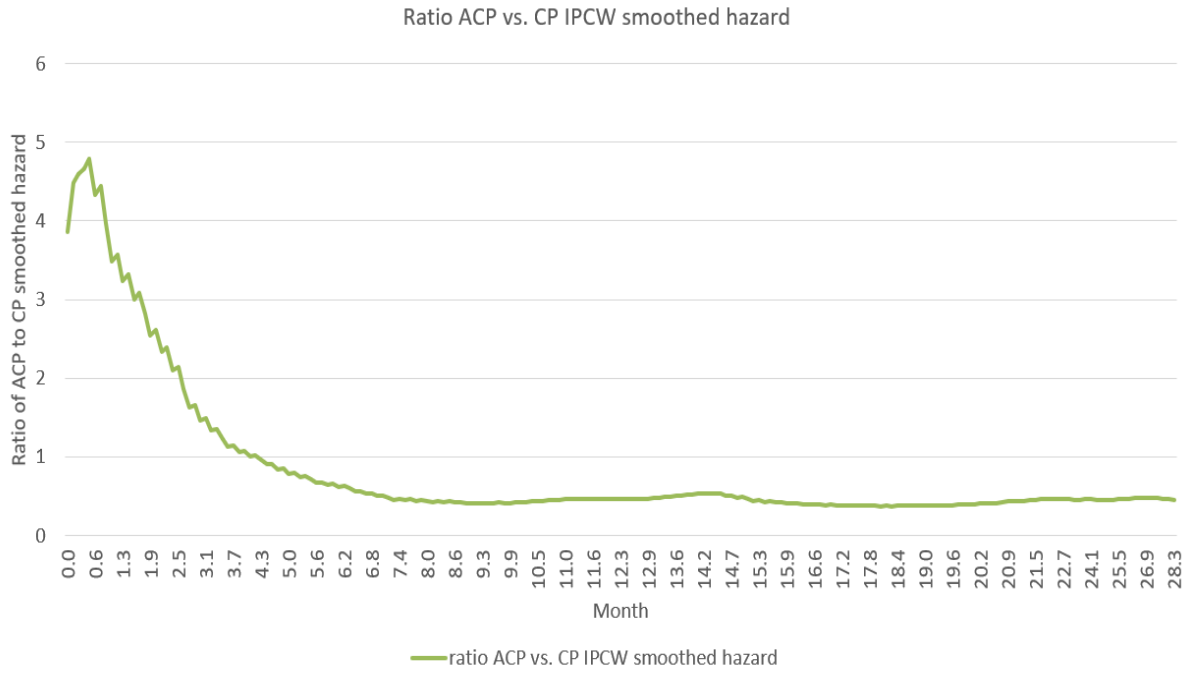


Exploration of the OS HR over time between amivantamab with chemotherapy and chemotherapy

To assess whether the observed OS data indicate treatment effect waning, Johnson & Johnson have explored the smoothed OS HR over time between amivantamab with chemotherapy and chemotherapy, as shown in **Figure 9**.

Survival data for amivantamab with chemotherapy indicates a sustained benefit with no evidence of treatment effect waning. Due to the separation of OS curves, the OS HR between amivantamab with chemotherapy and chemotherapy alone falls below 1 after only 4.2 months (indicating a reduced risk of death for amivantamab with chemotherapy) and remains below 1 for the remainder of the observed period. Crucially, the OS HR does not change in any significant way, remaining constant for the remainder of the observed period, demonstrating no waning or diminishing effect relative to chemotherapy.

Figure 9: Smoothed hazard ratio for amivantamab with chemotherapy and chemotherapy OS data



Estimating the long-term survival of amivantamab with chemotherapy

Modelling the hazards of both treatments as being equal is not supported by any data and is unrealistic, given the demonstrated benefit of amivantamab with chemotherapy over chemotherapy alone in the PAPILLON trial.

However, in response to the draft guidance, Johnson & Johnson have explored different methods for estimating the long-term survival benefit of amivantamab with chemotherapy.

Johnson & Johnson employed two methodologies for calculating this

- The first estimation method involves fixing the modelled implied hazard ratio of amivantamab with chemotherapy OS vs chemotherapy OS from the last observation (2.8 years in the amivantamab with chemotherapy arm) onwards and applying this to the OS of chemotherapy. This models a situation where the OS benefit of amivantamab with chemotherapy relative to chemotherapy after the last observation does not change over time (i.e., constant implied hazard ratio).

- The second estimation method involves applying the per-cycle hazard ratio between the OS and PFS of chemotherapy to the PFS of amivantamab with chemotherapy. This models a situation where the relative difference between PFS and OS for amivantamab with chemotherapy is equal to the relative difference observed for chemotherapy.

The ICERs versus chemotherapy when using these two methodologies for each extrapolation scenario are presented in **Table 5** and **Table 6**. Implementing these methodologies across the extrapolation scenarios results in a decrease to the ICER versus chemotherapy compared with the company base-case in all but two scenarios.

The only scenario that results in a notably higher ICER is when the fixed OS HR for the Weibull / Weibull scenario is applied to chemotherapy OS. The Weibull curve for

chemotherapy OS predicts the lowest survival out of all the scenarios and is not aligned to the company's or EAG's base-cases.

Notably, when using the EAG's base-case (ACP = Weibull / CP = log-logistic), both estimation methodologies result in significantly lower ICERs which suggests that the log-logistic curve overestimates the OS of chemotherapy.

Table 5: Deterministic results for each OS extrapolation scenario when the long-term survival of ACP is estimated by fixing the modelled implied hazard ratio from the last observation onwards and applying this to CP OS

Scenario		WITH PAS		
		Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Base case		[redacted]	[redacted]	**36,255**
1.	ACP = Weibull / CP = Gamma[a]	[redacted]	[redacted]	36,999
2.	ACP and CP OS = Weibull	[redacted]	[redacted]	42,115
3.	ACP and CP OS = Gamma	[redacted]	[redacted]	34,780
4.	ACP and CP OS = Log-logistic	[redacted]	[redacted]	21,496
5.	ACP = Weibull / CP OS = Log-logistic[b]	[redacted]	[redacted]	25,182

a. OS extrapolations selected in the company base-case
b. OS extrapolations selected in the EAG base-case

Table 6: Deterministic results for each OS extrapolation scenario when the long-term survival of ACP is estimated by applying the per-cycle hazard ratio of OS vs PFS for CP to the PFS of ACP

Scenario		WITH PAS		
		Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Base case		[redacted]	[redacted]	**36,255**
1.	ACP = Weibull / CP = Gamma[a]	[redacted]	[redacted]	32,756
2.	ACP and CP OS = Weibull	[redacted]	[redacted]	35,663
3.	ACP and CP OS = Gamma	[redacted]	[redacted]	32,756
4.	ACP and CP OS = Log-logistic	[redacted]	[redacted]	34,909
5.	ACP = Weibull / CP OS = Log-logistic[b]	[redacted]	[redacted]	34,909

a. OS extrapolations selected in the company base-case
b. OS extrapolations selected in the EAG base-case

Dose skipping

In the draft guidance (section 3.17 and section 3.19), the committee requested data on dose-skipping for the first and subsequent cycles of the PAPILLON trial, and for the modelling to reflect any differences in these values. The committee also

requested that different scenarios for dose skipping were explored (i.e., equal dose skipping across treatment arms).

Johnson & Johnson have provided these data and the associated analyses. Dose-skipping data for the first and subsequent 3-week cycles within the PAPILLON trial are presented in **Table 7** and **Table 8**.

Table 7: Dose skipping data for the first and subsequent cycles of patients receiving amivantamab with chemotherapy in the PAPILLON trial

Amivantamab with chemotherapy								
	Patients < 80kg at baseline				**Patients ≥ 80kg at baseline**			
Number of patients	**132**				**21**			
Amivantamab								
	Doses given	Doses expected	Doses missed	% missed	Doses given	Doses expected	Doses missed	% missed
Cycle 1	[redacted]	524	[redacted]	[redacted]	[redacted]	84	[redacted]	[redacted]
Cycle 1 day 1	[redacted]	132	[redacted]	[redacted]	[redacted]	21	[redacted]	[redacted]
Cycle 1 day 2	[redacted]	132	[redacted]	[redacted]	[redacted]	21	[redacted]	[redacted]
Cycle 1 days 8 and 15	[redacted]	260	[redacted]	[redacted]	[redacted]	42	[redacted]	[redacted]
Cycles 2+	[redacted]	2012	[redacted]	[redacted]	[redacted]	312	[redacted]	[redacted]
Cycle 2 day 1	[redacted]	129	[redacted]	[redacted]	[redacted]	21	[redacted]	[redacted]
Cycle 3 day 1 onwards	[redacted]	1883	[redacted]	[redacted]	[redacted]	291	[redacted]	[redacted]
	All amivantamab-chemotherapy patients							
Number of patients	**153**							
Pemetrexed								
Cycle 1	[redacted]	153	[redacted]	[redacted]				
Cycles 2+	[redacted]	2186	[redacted]	[redacted]				
Carboplatin								
Cycle 1	[redacted]	153	[redacted]	[redacted]				
Cycles 2+	[redacted]	439	[redacted]	[redacted]				

Table 8: Dose skipping data for the first and subsequent cycles of patients receiving chemotherapy in the PAPILLON trial

Chemotherapy				
	All patients			
Number of patients	155			
	Doses given	Doses expected	Doses missed	% missed
Pemetrexed				
Cycle 1	[redacted]	155	[redacted]	[redacted]
Cycles 2+	[redacted]	1706	[redacted]	[redacted]
Carboplatin				
Cycle 1	[redacted]	155	[redacted]	[redacted]
Cycles 2+	[redacted]	456	[redacted]	[redacted]

The results from the requested scenarios exploring dose skipping are presented in **Table 9**. These scenarios resulted in a minor decrease to the ICER versus chemotherapy compared with the base-case.

When dose skipping is modelled to reflect the per-cycle proportions observed in the PAPILLON trial, the ICER versus chemotherapy slightly decreases given a higher proportion of patients skipped doses of amivantamab in subsequent cycles compared with the first cycle, which reduces the cost of amivantamab.

Johnson & Johnson have kept the base-case to model dose skipping based on the average proportion of missed doses across all treatment cycles given this models a lower proportion of doses skipped, which is in-line with the committee's preference.

Table 9: Deterministic results for the scenarios where dose skipping is modelled by cycle and equated across treatments

Scenario	WITH PAS		
	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Base case	[redacted]	[redacted]	**36,255**
1. Dose skipping by cycle	[redacted]	[redacted]	36,012
2. Equal dose skipping across ACP and CP[a]	[redacted]	[redacted]	36,122

a. The dose skipping rate across the treatments of patients receiving amivantamab with chemotherapy who were <80kg at baseline was applied to patients receiving chemotherapy

The scenario that includes no dose skipping is not appropriate given this does not reflect the data observed in the PAPILLON trial and is not expected in clinical practice based on expert opinion.

Exploring different utilities

In the draft guidance (section 3.11 and 3.19), the committee requested using utility values from previous appraisals in NSCLC.

It is inappropriate to consider utility values from other appraisals in NSCLC given that these are: not specific to patients with EGFR Exon 20 insertion mutations, are associated with different interventions and treatment history, and they may reflect significantly varied yet important differences in patient characteristics. Utilities accepted in the appraisal of amivantamab monotherapy after prior chemotherapy (TA850) may, to a limited extent, be relevant.

Johnson & Johnson have provided a scenario for when the utility value for the progressed disease state is based on the utility value for the progression-free state that was accepted in the appraisal of amivantamab after prior chemotherapy, TA850 (0.713). The results are shown in **Table 10**. Basing the progressed disease utility on TA850 led to a small increase in the ICER versus chemotherapy compared with the base-case.

Table 10: Deterministic results for the scenario where the progressed utility value is based on the progression-free utility used in the CHRYSALIS appraisal (TA850)

Scenario	WITH PAS		
	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Base case	[redacted]	[redacted]	**36,255**
PD utility = PF utility from TA850 (0.713)	[redacted]	[redacted]	37,234

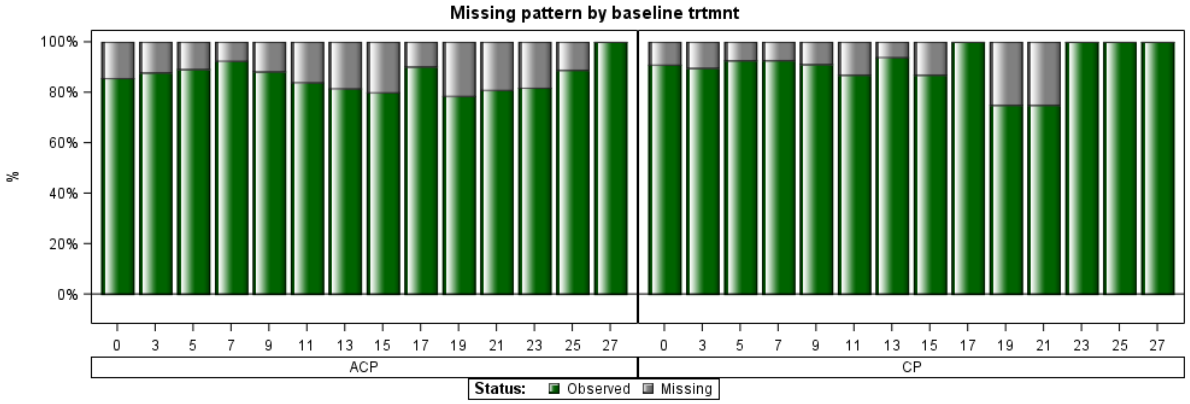
The utility value for the progressed-disease state which is derived from PAPILLON trial data (0.74) is similar to the utility value for the progression-free state that was used in the appraisal of amivantamab after prior chemotherapy (0.713), which the committee accepted. This is because the both represent patients with EGFR Exon 20 insertion mutation-positive advanced NSCLC who have progressed on at least one line of therapy. However, it is crucial to emphasise that the CHRYSALIS trial

included a higher proportion of pre-treated patients which could explain the slightly lower utility value. The population in TA850 was more heavily pre-treated than the progressed patients from the PAPILLON trial as the median number of previous treatments in the CHRYSALIS trial was two.

Missingness within the PAPILLON trial

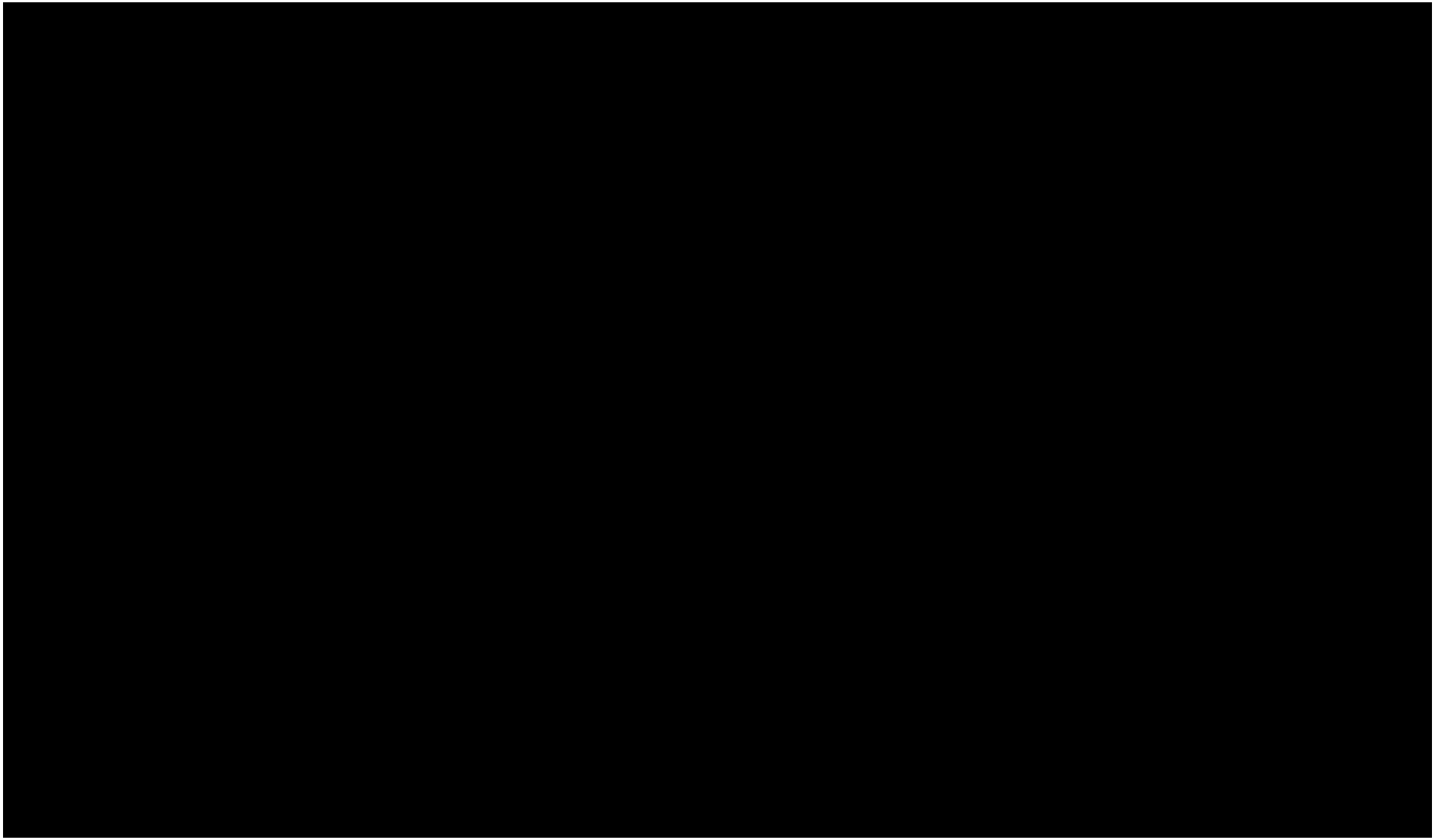
The plot below, in **Figure 10** shows that missingness is not increasing over time, and equally spread between treatment arms:

Figure 10: Plot showing the degree of missingness across cycles 0-27 for amivantamab-chemotherapy and chemotherapy within the PAPILLON trial



Additionally, individual patient profiles over time do not indicate a systematic pattern in missingness. For example, the degree of missingness is not higher in the visits immediately preceding a progression event. This is illustrated below in **Figure 11**.

Figure 11: Plot showing patient-level data for the degree of missingness in relation to key events



NICE National Institute for Health and Care Excellence

Amivantamab with carboplatin and pemetrexed for untreated EGFR exon 20 insertion mutation-positive advanced non-small-cell lung cancer [ID5110]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Wednesday 26 March 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

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	In the last 12 months we have received £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.	N/A
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..

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1	While we accept that there is considerable uncertainty in a number of aspects of the modelling, we are concerned that not enough weight has been placed on factors we are certain about.
2	First – we are certain that there is currently no standard pathway for these patients, and there is a dearth of treatment options available for Exon 20 mutations. And we are certain that this has a significant impact on patient quality of life, which can be seen in terms of the high levels of anxiety and depression seen in Exon 20 patients compared to EGFR patients with common mutations (Harrison, 2024). However, we feel these more qualitative impacts have not been fully considered or costed into the current guidance.
3	Second, we are certain that EGFR Exon 20 only occurs in a small number of patients. For example, in the UK, EGFR mutations will occur in about 12% of lung cancer patients (Melosky et al, 2002). Exon 20 accounts for about 5% of them. Based on the 2018 data, there are approx. 48,000 people diagnosed with lung cancer in the UK every year. That's 5,760 with EGFR lung cancer, and 288 with Exon 20. As this is such as small number of patients who are currently catastrophically underserved (and therefore overall costs for this particular patient group are likely to be low in the grand scheme of things), should they not be considered as a rare disease – which could afford them more flexibility in terms of costs? If Amivantamab was not being considered as a potential medicine in other contexts, this medicine would likely be eligible for consideration under the HST pathway; so it seems grossly unfair not to consider Exon 20 patients in the rare context they find themselves in.
4	Finally, while there are costs associated with this type of IV treatment, it also seems very likely that these costs are only going to be needed for a relatively short window of time. For example, there are new drug lines and modalities in the pipeline (for example, Amivantamab is being trialled in a sub-cutaneous context, and fourth generation TKIs are being developed that also seem to have activity with Exon 20 patients). So not only are total costs likely to be relatively low due to small patient numbers, they are also not likely to be long term costs overall.
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.
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information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.

- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

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

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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	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

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	No Disclosures
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	No Disclosures

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Name of commentator person completing form:	xxxxxxxxxxxxxxxxxxxx

#	Comments	EAG
	Thank you for the opportunity to comment on the draft guidance for amivantamab with carboplatin and pemetrexed in patients with untreated epidermal growth factor receptor (EGFR) Exon20 insertion mutation-positive advanced non-small-cell lung cancer (NSCLC). Johnson & Johnson are disappointed with the preliminary decision not to recommend amivantamab with chemotherapy within its marketing authorisation given it represents an opportunity to address the significant unmet need in this rare population, where there are currently no recommended therapies. Johnson & Johnson would like to highlight several points that are relevant to the committee's conclusions, and present additional analyses requested by the committee. The key points raised are: • A clear and statistically significant overall survival (OS) benefit is observed when amivantamab with chemotherapy is compared to chemotherapy after adjusting for treatment switching • Data from the PAPILLON trial show that the majority of efficacy benefit for chemotherapy occurs after progression, meaning that it is appropriate for the majority of efficacy benefit/QALYs to be accrued in the progressed disease state for chemotherapy and for amivantamab with chemotherapy too • This is further supported by the PAPILLON trial demonstrating a clear post-progression benefit for amivantamab with chemotherapy	Please see the EAG's comments on these points in the following sections.

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	• A long-term benefit associated with amivantamab with chemotherapy is also expected based on clinical opinion and this is supported by the long-term benefits demonstrated by amivantamab in other indications • The OS extrapolation curves selected in the company base-case are aligned with the consensus achieved at the advisory board, have a robust visual and statistical fit to the observed data, and are aligned with the observed hazard function • The distributions selected for the OS of amivantamab with chemotherapy and chemotherapy in the company base-case are similar to one another and using the same parametric models for both treatments leads to a reduction in the incremental cost-effectiveness ratio (ICER) versus the company's base case • With the additional analysis, there is sufficient evidence to conclude that it is not appropriate to model a waning effect for amivantamab • In most scenarios, utilising different methodologies to estimate the long-term benefit of amivantamab with chemotherapy versus chemotherapy leads to a reduction in the ICER versus the company's base case • EQ-5D data from the PAPILLON trial is the most robust source of evidence to derive utilities for the population in this decision problem, and using utilities from other appraisals in EGFR Exon20 insertion mutation-positive NSCLC has a minor impact on the ICER • Given the unmet need, the robustness of the data from the PAPILLON trial, and the additional analyses provided to address the uncertainties cited in the draft guidance, the acceptable ICER should be positioned at the upper end of the range that NICE considers to be a cost-effective use of NHS resources. In summary, nearly all of the additional scenarios presented demonstrate the robustness of the company's base case. Furthermore, in almost all the additional clinically plausible scenarios requested, the ICER is lower than the figure put forward by the company as the base-case. The	

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	new company base-case incorporates the committee's preferred assumptions with regards to the comparator, adverse event (AE) costs, and dosing. In the updated base-case, the deterministic ICER of amivantamab with chemotherapy versus chemotherapy is £36,255 per quality adjusted life year (QALY) with the current Patient Access Scheme (PAS).	
1	**Section 3.3 (Treatment options and comparators)**: The committee concluded that the only relevant comparator for this appraisal was carboplatin with pemetrexed (from here, chemotherapy). **Johnson & Johnson have provided an updated model to show the cost-effectiveness results versus chemotherapy.** Johnson & Johnson acknowledge the discussion during the committee meeting where the Cancer Drugs Fund lead confirmed that use of immunotherapies for EGFR mutation-positive advanced NSCLC is not allowed given recent updates to the NHS commissioning criteria (BluTeq). Therefore, Johnson & Johnson have updated the company base-case to compare amivantamab with chemotherapy to chemotherapy. In the updated model, the base-case ICER of amivantamab with chemotherapy versus chemotherapy is £36,255 per QALY. Johnson & Johnson would like to reiterate that clinical expert opinion and real-world evidence (RWE) have highlighted that carboplatin with pemetrexed is not the only treatment being used to treat patients with untreated EGFR Exon20 insertion mutation-positive advanced s in the UK.[1-4] The current approach of only comparing amivantamab with chemotherapy to chemotherapy excludes approximately 30% of treatment options being used on the NHS. This narrow decision-making prioritises the least expensive treatment, resulting in a conservative estimate of cost-effectiveness. Clinical expert opinion has, on multiple occasions, explicitly cited that pembrolizumab with chemotherapy is used to treat this population. This includes opinion from the evidence assessment group's (EAG's) clinical expert and from both clinical expert nominees in this appraisal.	Please see EAG's comments in relevant sections relating to cost-effectiveness.

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	• At a company advisory board in May 2024 which comprised six clinical experts, it was agreed that the standard of care was chemotherapy (carboplatin with pemetrexed) with or without immunotherapy (pembrolizumab), with the split between these being 70% and 30%, respectively.[1] • At a company advisory board held in August 2024 which comprised two clinical experts, one of whom attended the May 2024 advisory board, it was highlighted that the predominant treatments being prescribed in this population are chemotherapy (carboplatin with pemetrexed) and IO combination therapies (pembrolizumab with chemotherapy).[2] • As per the stakeholder comments to this submission which are presented within the committee papers, both clinical experts (one of whom attended the company May 2024 advisory board) answered 'Yes' to question 23 "Does the blended comparator (70% chemo to 30% pembro) reflect what might occur in clinical practice?"[5] • As per the EAG report, the EAG's clinical expert indicated that clinical practice comprises carboplatin with pemetrexed (60%), carboplatin or cisplatin (10%) and pembrolizumab with carboplatin and pemetrexed (30%). This is similar to the company estimate of 70% chemotherapy (carboplatin and pemetrexed) and 30% pembrolizumab plus chemotherapy, which is noted within the draft guidance.	
2	**Section 3.4 (PAPILLON trial)**: The committee concluded that amivantamab–chemotherapy improved PFS compared with chemotherapy alone and that the relative effectiveness on OS was uncertain. **There is sufficient evidence to conclude that amivantamab with chemotherapy improves OS versus chemotherapy given a statistically significant OS benefit has been demonstrated versus chemotherapy after adjusting for treatment switching.**	The EAG's perspective remains unchanged. The company provided updated results in OS at longer follow-up by adjusting for treatment switching adjustment via IPCW in the company's response to DG comments. Based on the updated results with longer follow-up by adjusting for treatment switching via IPCW, amivantamab with chemotherapy demonstrated a statistically significant improvement in OS compared with chemotherapy. The EAG considers that treatment-switching adjustment methods used

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	Although a statistically significant OS benefit over chemotherapy was not reached in the intention to treat analysis, this was demonstrated after the chemotherapy data had been adjusted to account for treatment switching via inverse probability of censoring weighting (IPCW). There is, therefore, sufficient evidence to conclude that amivantamab with chemotherapy improved OS compared with chemotherapy.[6] Johnson & Johnson acknowledge that, at the October 2023 data-cut off (DCO), with a median follow-up of 20.9 months across both treatment arms, median OS was not reached for amivantamab with chemotherapy whereas it was reached for chemotherapy (28.6 months).[7] This is considered positive given it means that patients receiving amivantamab with chemotherapy remain alive for longer than patients receiving chemotherapy alone. At the October 2023 DCO, 73.9% of patients in the amivantamab with chemotherapy arm remained alive compared with 66.5% in the chemotherapy alone arm.[7] The failure to achieve median overall survival should not be interpreted as a sign of uncertainty; instead, it should be regarded as a significant indicator that the intervention exerts a notably positive effect on survival outcomes. Although the median OS was not reached, there was a strong trend towards improved survival over chemotherapy at the October 2023 DCO, where the median follow-up across both treatment arms was 20.9 months. At this point, amivantamab with chemotherapy demonstrated a 24% reduction in the risk of death compared with chemotherapy (hazard ratio [HR]: 0.76 [95% CI: 0.50-1.14]; p=0.1825).[7] This benefit was despite the OS in the chemotherapy arm being over-estimated due to a significant proportion ([redacted]%) of patients receiving amivantamab monotherapy after blinded independent central review (BICR)-confirmed disease progression. Receiving amivantamab monotherapy after progression led to an overestimation of chemotherapy OS given amivantamab monotherapy is an efficacious treatment that is not available through routine clinical practice in the UK. Therefore, the OS HR achieved in the intention to treat population (0.76 [95% CI, 0.50 to 1.14, *p*=0.1825]), which is cited in the draft guidance, does not accurately describe the OS benefit that amivantamab with chemotherapy achieves over chemotherapy in a UK population.	by the company appear to be appropriate. These updated results of OS were consistent with those results of OS being presented in the EAG report.

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	Johnson & Johnson followed the guidance in technical support document (TSD) 24 to adjust the OS data in the chemotherapy arm to account for the observed treatment switching. Following treatment switching adjustment via IPCW, amivantamab with chemotherapy demonstrated a statistically significant and clinically meaningful improvement in OS, with a 48% reduction in the risk of death compared with chemotherapy (HR: [redacted], CI: [redacted], p=[redacted]). The separation of OS Kaplan-Meier (KM) curves between amivantamab with chemotherapy and IPCW-adjusted chemotherapy data is clearly shown below: [redacted]	

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3	**Section 3.7 (plausibility of extrapolated benefits)**: Modelling in which the majority of QALY gains accrue in the progressed-disease health state was associated with uncertainty. **Data from the PAPILLON trial show that the majority of efficacy benefit for chemotherapy occurs after progression. It is therefore appropriate for the majority of efficacy benefit/QALYs to be accrued in the progressed disease state for amivantamab with chemotherapy.** In this section, Johnson & Johnson aims to address a common misconception regarding progression-free survival (PFS) and OS. Through the analysis provided below, we seek to clarify that a clear benefit is observed after disease progression. To begin, it is essential to examine the trial data related to chemotherapy. <u>Chemotherapy:</u> The median OS for patients receiving chemotherapy was [redacted] months after adjustment for treatment switching, which was [redacted] times greater than the median PFS of 6.7 months. This shows a clear post-progression benefit has been observed for chemotherapy in the PAPILLON trial. <u>Amivantamab with chemotherapy:</u> Amivantamab with chemotherapy achieved a median PFS of 11.37 months, while the median OS had not been reached after a median follow-up of 20.9 months. At this point there were 40 death events, representing 26.1% of patients in the amivantamab with chemotherapy arm.[7] Consequently, the median OS benefit of amivantamab in combination with chemotherapy is expected to extend well beyond the median PFS of 11.37 months. It is reasonable to anticipate that the median OS will be at least [redacted] times greater than the median PFS given amivantamab in combination with chemotherapy uses the same chemotherapy regimen as the control group (carboplatin with pemetrexed). Additionally, although the median PFS was reached, the median progression-free survival after first subsequent therapy (PFS2) was not reached, which shows a clear delay to second progression well-beyond the first progression. This is also shown through the event-free rates	The EAG's perspective is unchanged. See EAG report key issue 12: "*The majority of LY gains and QALY gains for the intervention and comparators were modelled to occur in the progressed disease health state. The EAG is unsure whether this is plausible, as patients were treated until disease progression (or unacceptable toxicity). Moreover, considering the increments versus amivantamab with chemotherapy, approximately* [redacted] *(or more) of the LYs are gained beyond the observed data period when compared with chemotherapy only and pembrolizumab chemotherapy respectively.*" Related to this, even if there would be a residual treatment effect after amivantamab discontinuation, the magnitude and duration is largely uncertain. Hence, the EAG considers the assumption of no explicit waning of the relative treatment effect to be uncertain and thus believes that it would have been informative for the company to explore the potential impact of treatment waning (EAG report Key issue 8). Specifically, to provide scenario analyses while assuming treatment waning (at different time points), as requested in clarification question B11 (rather than the analyses provided in item 11).

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	where, even after 24-months, 57% of patients receiving amivantamab with chemotherapy had still not experienced a PFS2 event. These data clearly show a delay to second progression beyond the first progression, and a prolonged survival well beyond PFS. Importantly, amivantamab with chemotherapy demonstrated a 51% reduction in the risk of PFS2 compared to chemotherapy at the May 2023 DCO (HR: 0.49 [95% CI: 0.32-0.76; nominal p=0.0010]). This supports the notion that the relative benefit of OS vs PFS is expected to be greater for amivantamab with chemotherapy than what has been observed for chemotherapy (i.e., more than [redacted] times larger).	
4	**Section 3.8 (OS extrapolations)**: The company fitted a Weibull distribution to the OS data for amivantamab–chemotherapy to extrapolate it to the 40-year time horizon of the model. The company felt that this was the most appropriate curve because it fit with the clinical expert opinion from its advisory board (27.5% survival at 5 years) and provided a good visual fit. **Validation of the Weibull (and Gamma) curve as the most appropriate extrapolation of OS data for amivantamab with chemotherapy was obtained through a 3-step SHELF methodology process. The Weibull curve was selected by the company as the more conservative of the validated extrapolations and because of robust visual and statistical fit and alignment with the observed hazard function. It is inaccurate to state that the "27.5% survival at 5 years" obtained at step 1 in the 3-step process was the basis for curve selection.** Johnson & Johnson would like to re-iterate that, during the advisory board, the focus was validating appropriate extrapolation curves rather than fixating on the proportions alive at specific timepoints. Johnson & Johnson followed a three-step process to validating extrapolation curves, which reflected the methodology set out by the Sheffield elicitation framework (SHELF). Obtaining responses from individual advisors through a pre-meeting survey was step 1. Steps 2 and 3 comprised advisors discussing the pre-meeting survey results and then arriving at a discussion-based group consensus as to the most appropriate extrapolation curve. "27.5% survival after 5-	The EAG's perspective is unchanged. See EAG report Section 4.2.6 and EAG report Key issue 7. Moreover, (further) details on the methods and results of the SHELF process as applied by the company might be informative.

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	years" reflects the average of the individual responses obtained via the pre-meeting survey (step 1). During the advisory board, after discussing the pre-meeting survey responses, advisors arrived at a consensus that the Weibull and Gamma curves provided the most appropriate long-term estimates for the OS of amivantamab with chemotherapy.[2] This consensus was reached across four advisors, comprising two health economic experts and two clinical experts with b experience of using amivantamab through trial or private use. Although both the Weibull and Gamma curves were deemed plausible by advisor experts, the more conservative Weibull curve was chosen in the company base-case. This predicts a survival rate of 32.1% at 5 years (the Gamma curve predicts 35.0% alive at 5-years). Johnson & Johnson would also like to highlight that the Weibull curve has a good visual and statistical (3rd-best) fit to the observed KM data and the risk of death overtime predicted by the Weibull curve is also aligned to the hazard function over time associated with the observed KM data, based on an analysis of the smoothed hazard plots. As such, statements in the draft guidance that the Weibull curve was selected based on clinical expert opinion of 27.5% survival at 5 years are factually inaccurate. Referencing data from the pre-meeting survey rather than the consensus reached at the advisory board was previously highlighted by Johnson & Johnson as a factual inaccuracy during the factual inaccuracy check carried out on the EAG report earlier this year. Johnson & Johnson firmly stress that the emphasis should be on the consensus rather than solely on the pre-meeting survey numbers, which represent only the first step of a three-step process in the SHELF methodology.	
5	**Section 3.8 (OS extrapolations):** The EAG felt that long-term estimates of OS with amivantamab–chemotherapy were very uncertain. It used the Weibull distribution in its base case but used a scenario with the Gompertz distribution to explore more pessimistic survival in keeping with its expert's estimates. **There is sufficient evidence to conclude that the Gompertz curve for the OS of amivantamab with chemotherapy is implausible.**	See previous comment (item 4). As mentioned in the EAG report: "*a) The OS estimated using the Weibull distribution for amivantamab with chemotherapy was overestimated based on the company's advisory board report as well as clinical opinion obtained by the EAG. As none of the distributions (CS Table 52) did align very well with the long-term expert estimates obtained, the EAG adopted a more conservative*

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	Clinical and HTA expert opinion: At the company advisory board held in August 2024, advisor experts explicitly noted that the Gompertz and generalised gamma extrapolations for the OS of amivantamab with chemotherapy were overly pessimistic.[2] The company's methodology of utilising the SHELF protocol to elicit survival estimates and validate extrapolation curves across a group of advisor experts is in-line with what is recommended within NICE TSD 26.[8] This methodology, considering a consensus across multiple advisors, is more robust than using insight from a single clinician expert. Additionally, at a company advisory board held in May 2024, the six clinical experts agreed that they would expect to see a tail to the survival of amivantamab with chemotherapy, where a proportion of patients remain alive beyond 10 years, which does not happen with the Gompertz curve which predicts 0% alive beyond 6.5 years.[1] Assessment of hazard functions: The Gompertz curve for the OS of amivantamab with chemotherapy predicts a rapidly increasing hazard which is not consistent with the evolution of the per-cycle OS hazards for amivantamab with chemotherapy observed in the PAPILLON trial. Given the different trajectories of the associated hazard functions, selecting the Gompertz curve for amivantamab with chemotherapy OS (rapidly increasing hazard function) alongside the Gamma curve for chemotherapy OS (monotonically increasing hazard) means that the OS hazards cross. Therefore, this scenario predicts that patients receiving amivantamab with chemotherapy are more likely to die compared with patients receiving chemotherapy after a certain point. This is implausible given the survival benefit that amivantamab with chemotherapy has demonstrated over chemotherapy, as shown through the separation of OS curves, in the PAPILLON trial. Visual fit to KM data: The Gompertz curve presents a poor visual fit to the observed data, sitting well below the KM curve.	*distribution (i.e., the Gompertz distribution) in a scenario analysis. Moreover, it is recommended that the company explores alternative parametric models to estimate OS for amivantamab with chemotherapy."* Consistent with this quote from the EAG report, the ACD stated (3.9): "*The committee was aware that the Weibull and Gompertz distributions gave substantially different predictions, and considered that there may be merit in exploring curves in between the 2 distributions.*"

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6	**Section 3.8 (OS extrapolations)**: For chemotherapy, the company fitted a gamma distribution to the OS data for chemotherapy. This was based on the clinical expert opinion from its advisory board (10% survival at 5 years) and fit to the observed data. **Validation of the Gamma curve as the most appropriate curve to extrapolate OS data for chemotherapy was obtained through a 3-step SHELF methodology process. It is inaccurate to state that the "10% survival at 5 years" obtained at step 1 in the 3-step process was the basis for curve selection.** Johnson & Johnson strongly recommend referencing the curve validated at the advisory board rather than citing a single result for the survival at one timepoint from the pre-meeting survey when referencing expert opinion from the company advisory board.	See previous comment (item 4).
7	**Section 3.8 (OS extrapolations):** The EAG had concerns that the company's choice of curve underestimated the OS for chemotherapy based on the company's advisory board and the EAG's own clinical expert input (5% at 5 years). **The Gamma curve selected in the company base-case for chemotherapy OS provides the best match to the curve that was validated at the advisory board, as per the group consensus reached. Further, the Gamma curve has good visual and statistical fit to the PAPILLON data and closely matches the observed hazard. As such, there is sufficient evidence to conclude that the Gamma curve is the most appropriate for extrapolating OS for chemotherapy. All the world's a stage, And all the men and women merely players; They have their exits and their entrances; And one man in his time plays many parts** At the company advisory board held in August 2024, clinical and health economic experts arrived at a consensus that the Weibull curve was the most clinically plausible OS extrapolation for chemotherapy, after the data had been adjusted for treatment switching via the two-stage estimation approach (which was one of the plausible company base-cases at the time of the advisory board).[2] The Weibull extrapolation of two-stage-adjusted chemotherapy OS data predicted survival rates of 22%, 2%, and 0% at 3-, 5-, and 10-years respectively. These were most closely aligned to the survival estimates predicted by the Gamma extrapolation of IPCW-	See previous comment (item 4). Specifically: "*The OS estimated for chemotherapy only using the gamma distribution underestimated OS. Therefore, the EAG adopted the log-logistic for estimating OS for chemotherapy only in its base-case as this aligned more with the company's advisory board report as well as clinical expert estimates obtained by the EAG.*"

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	adjusted chemotherapy OS data (19%, 3%, and 0%, respectively). This supported the selection of the Gamma curve for the OS of chemotherapy in the company base-case. As well as being the best match to the consensus from the advisory board, the Gamma curve for chemotherapy OS predicts a risk of death over time that very closely matches the observed data in the PAPILLON trial (based on the smoothed hazard plot of the KM data). It also has a very good visual plus statistical (2nd best) fit to the observed data. These are salient pieces of evidence that have been presented throughout the submission and support a conclusion that the extrapolation curve chosen in the company's base case accurately represents OS for chemotherapy.	
8	**Section 3.8 (OS extrapolations):** The EAG preferred to use a log-logistic curve to extrapolate OS for chemotherapy alone. **There is sufficient evidence to conclude that the log-logistic curve for the OS of chemotherapy is implausible.** Clinical and HTA expert opinion: At the company advisory board held in August 2024, advisor experts explicitly noted that the log-logistic curve for chemotherapy OS was unrealistic given patients receiving chemotherapy have a particularly poor survival.[2] The company's methodology of utilising the SHELF protocol to elicit survival estimates and validate extrapolation curves across a group of advisor experts is in-line with what is recommended within NICE TSD 26.[8] Assessment of hazard functions: The log-logistic curve for chemotherapy OS predicts an increasing hazard at first, which decreases after around 20 months. This is not consistent with the evolution of the per-cycle hazards for chemotherapy OS observed in the PAPILLON trial.	See previous comment (items 4 and 8).

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	Given the different trajectories of the associated hazard functions, selecting the log- logistic curve for chemotherapy OS (increasing and then decreasing after 20 months) alongside the Weibull curve for amivantamab with chemotherapy OS (monotonically increasing hazard) means that the OS hazards cross. Therefore, this scenario predicts that patients receiving chemotherapy are less likely to die compared to patients receiving amivantamab with chemotherapy after a certain point. This is implausible given the survival benefit that amivantamab with chemotherapy has demonstrated over chemotherapy, as shown through the clear and early separation of OS curves in the PAPILLON trial.	
9	**Section 3.9 (uncertainties in extrapolating OS beyond the trial)**: The committee recalled that the Decision Support Unit's Technical Support Document 14 states that fitting different models allows for very differently shaped distributions, and strong evidence is required to justify this approach. **Johnson & Johnson acknowledge that TSD 14 recommends fitting the same parametric models to all treatments and would like to highlight that, although different, the OS extrapolations selected in the company base-case are similar.** In the company base-case, the OS curves for amivantamab with chemotherapy (using the Weibull distribution) and chemotherapy (using the Gamma distribution) exhibit similar shapes. This similarity arises from the fact that the underlying hazard functions for both distributions increase monotonically. This means that, in the company base-case, the risk of death over time evolves in a very similar way for both amivantamab with chemotherapy and chemotherapy. This mitigates the risk that "very differently shaped distributions" have been chosen in the company base-case. Conversely, the EAG base-case (ACP = Weibull, CP = log-logistic) and scenarios proposed by the EAG (ACP = Gompertz, CP = log-logistic) provide very differently shaped distributions as the underlying hazard functions over time are very different. These predict hazard functions over time that are clinically implausible and not aligned with the OS benefit that amivantamab with chemotherapy has demonstrated over chemotherapy in the PAPILLON trial.	Indeed, consistent with the CS base-case the EAG did not select the same distributions for estimation OS for both treatment strategies. The EAG did not adjust the CS base-case for the aspect given the different mechanism of action for both treatments. Moreover, the EAG did not consider the OS extrapolations when selecting the same distributions for both strategies to be consistent with the expert opinion obtained. Therefore, as mentioned in responses 5 and 8 it might be informative for the company to explore alternative approaches to estimates OS.

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	In response to the committee's request, Johnson & Johnson have provided an updated model which explores scenarios where the same parametric models are fitted to all outcomes for both amivantamab with chemotherapy and chemotherapy. The different parametric curves selected reflect the company and EAG base-cases. All these scenarios resulted in a decrease to the ICER versus chemotherapy compared with the company base-case: • Company base-case: ICER = £36,255[a,b] • All endpoints for ACP & CP = Weibull: ICER = £34,263 • All endpoints for ACP & CP = Gamma: ICER = £33,737 • All endpoints for ACP & CP = Log-logistic: ICER = £31,335 a. Company base-case: ACP OS = Weibull, CP OS = Gamma, ACP TTDD = Weibull (both Ami and CP components), CP TTDD = Gamma, ACP PFS = Gamma, CP PFS = Gamma. b. The results presented are at the proposed PAS price of amivantamab The same trend (i.e., a decrease to the ICER versus chemotherapy compared with the company base-case) is observed when the same parametric models were applied to the OS of both treatments, rather than to all outcomes. • Company base-case: ICER = £36,255 • ACP & CP OS = Weibull: ICER = £34,186 • ACP & CP OS = Gamma: ICER = £32,436 • ACP & CP OS = Log-logistic: ICER = £24,192	

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	This analysis shows that using the same parametric models for each treatment yields a lower ICER compared with the company's base-case. Therefore, the company's base-case can be considered realistic or in-fact conservative given that using the same parametric models for both treatments results in lower ICER.	
10	**Section 3.9 (uncertainties in extrapolating OS beyond the trial)**: The committee also felt that the extrapolations of OS suggested that the benefit of amivantamab–chemotherapy over chemotherapy extends into the long term, even when the majority of people had stopped treatment. This implies a post-progression benefit, which is uncertain **Data from the PAPILLON trial demonstrate a clear post-progression benefit, mitigating the uncertainty associated with modelling this. Additionally, a long-term benefit for amivantamab has been observed in the CHRYSALIS and MARIPOSA trials, and clinical experts have stated they would expect this for amivantamab with chemotherapy.** PAPILLON data show a clear post-progression benefit associated with amivantamab with chemotherapy In the PAPILLON trial, amivantamab with chemotherapy achieved a median PFS of 11.37 months and the median OS had not been reached after a median follow-up across both treatment arms of 20.9 months (26.1% death events at this point).[7] Additionally, the median PFS2 had not been reached either and although the median PFS was 11.37 months, the PFS2 event-free rate at 24-months was 57%. These data show that the OS benefit for amivantamab with chemotherapy extends well beyond the PFS benefit, and there is a clear post-progression benefit. A long-term benefit of amivantamab has been demonstrated in other indications The long-term survival benefit of amivantamab has been demonstrated across other licensed indications. In the CHRYSALIS trial, a Phase 1b registrational trial in patients with EGFR Exon20 insertion mutation-positive advanced NSCLC who had received prior chemotherapy, after a median follow-up of 19.2 months, the median OS of patients receiving amivantamab monotherapy was	See previous comment (item 3).

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	23 months (95% CI, 18.5–29.5).[9] It is reasonable to expect that the OS benefit of amivantamab with chemotherapy in an untreated population (i.e., first-line setting) will exceed the OS benefit observed in the CHRYSALIS trial, which represented a heavily pre-treated population of patients who had already progressed on chemotherapy (i.e., second-line setting). Strong survival results have also been reported by the MARIPOSA trial, a Phase 3 registrational trial assessing amivantamab in combination with lazertinib in patients with untreated advanced NSCLC with common EGFR mutations (exon19 deletions or exon21 L858R substitutions). In the final analysis, after a median study follow-up of 37.8 months, the median OS was not reached for amivantamab-lazertinib, and there were [redacted] deaths in the amivantamab-lazertinib arm, showing that the majority of patients remained alive at this point (HR: 0.75; 95% CI: 0.61, 0.92; p=0.0048). A plateau to the survival of amivantamab with lazertinib was also observed at this timepoint. Importantly, the OS benefit observed for amivantamab with lazertinib in the MARIPOSA trial (median not reached after 37.8 months) extends well beyond the PFS benefit achieved (median PFS = 23.7 months, 95% CI: 19.1, 27.7, p<0.001). Although the populations and interventions differ, these long-term data present compelling evidence that amivantamab significantly extends OS, particularly in comparison to PFS. <u>Based on expert opinion, amivantamab with chemotherapy is expected to achieve a long-term benefit</u> At a company advisory board held in May 2024, clinical experts highlighted they would expect a tail to the survival curve of amivantamab with chemotherapy given the mechanism of action which incorporates an immune-modulating effect as well as targeting both EGFR and MET which are pathways involved in resistance mechanisms and cancer progression.[1]	
11	**Section 3.10 (treatment-effect waning)**: The committee concluded that treatment-effect waning could not be ruled out and should be explored through selecting appropriate OS curves or explicit modelling of treatment-effect waning. **There is sufficient evidence to conclude that it is not appropriate to model a waning effect for amivantamab, including survival data from the PAPILLON trial.**	See previous comment (item 3).

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	Johnson & Johnson consider it inappropriate to explicitly model a treatment waning effect for amivantamab given the short time on treatment, the fact that any waning is implicitly captured in the selected OS extrapolations, and the fact that the committee explicitly concluded it is appropriate to exclude treatment-effect waning from the modelling of amivantamab monotherapy in NICE technology appraisal (TA) 850. <u>Survival data from the PAPILLON trial does not indicate treatment-effect waning</u> Additionally, survival data for amivantamab with chemotherapy indicates a sustained benefit with no evidence of treatment effect waning. Due to the separation of OS curves, the OS HR between amivantamab with chemotherapy and chemotherapy alone falls below 1 after only 4.2 months (indicating a reduced risk of death for amivantamab with chemotherapy) and remains below 1 for the remainder of the observed period. Crucially, the OS HR does not change in any significant way, remaining constant for the remainder of the observed period, demonstrating no waning or diminishing effect relative to chemotherapy. This is illustrated in the graph below showing the smoothed hazard ratio over time for amivantamab with chemotherapy and chemotherapy OS data:	

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	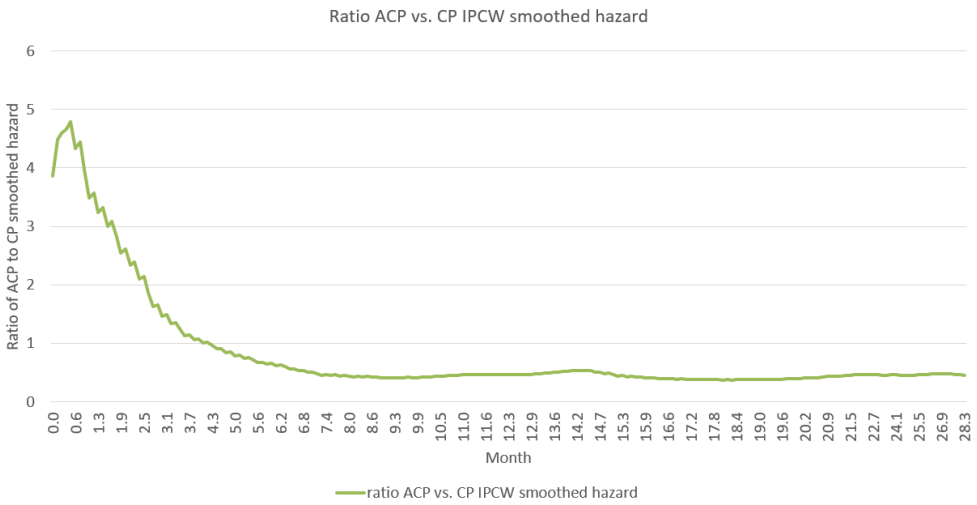 The sustained benefit associated with amivantamab can be attributed to its mechanisms of action. Amivantamab exerts anti-tumour activity via three mechanisms comprising EGFR/mesenchymal-epithelial transition (MET) receptor degradation, inhibition of ligand binding, and immune cell-directing activity. These distinct mechanisms work in parallel to achieve prolonged inhibition of tumour growth and a sustained efficacy benefit. <u>Implied hazard ratios</u> To further explore whether a diminishing effect relative to chemotherapy is present, Johnson & Johnson have provided analyses on the implied hazard ratios over time that are predicted in the company and EAG base-cases, and in scenarios where the same parametric models are selected for amivantamab with chemotherapy and chemotherapy.	

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	In the company base-case (ACP OS = Weibull, CP OS = Gamma), the implied hazard ratio very gradually increases after around five years, showing a reduction in the efficacy benefit of amivantamab combined with chemotherapy compared to chemotherapy alone beyond this point. This observation supports the notion that any treatment effect waning over time is reflected in the OS curves themselves. In the EAG base-case (ACP OS = Weibull, CP OS = log-logistic), the implied hazard ratio increases after around 2 years and exceeds 1 after around 7.5 years. This is because the log-logistic extrapolation for chemotherapy predicts a decreasing hazard function after around 2 years which crosses below the hazard function for the Weibull extrapolation of amivantamab with chemotherapy at around 7.5 years. This scenario therefore predicts that patients receiving chemotherapy are less likely to experience a death event after 2 years compared to patients receiving amivantamab with chemotherapy and after around 7.5 years chemotherapy is outperforming amivantamab and chemotherapy. This prediction is not consistent with the OS benefit that amivantamab with chemotherapy has demonstrated over chemotherapy in the PAPILLON trial, as shown through the early and clear separation of survival curves. Selecting the Gamma and Weibull curves for the OS of both treatments predicts a decreasing implied hazard overtime. Neither scenario shows a diminishing efficacy benefit of amivantamab with chemotherapy relative to chemotherapy. Selecting the log-logistic curve for the OS of both treatment arms predicts an increasing implied hazard after around two years, showing a diminishing efficacy benefit of amivantamab with chemotherapy relative to chemotherapy. <u>Additional analyses to estimate the long-term survival of amivantamab with chemotherapy</u> Modelling the hazards of both treatments as being equal is not supported by any data and is unrealistic, given the demonstrated benefit of amivantamab with chemotherapy over chemotherapy alone in the PAPILLON trial.	

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	However, Johnson & Johnson have explored different methods of estimating the long-term survival of amivantamab with chemotherapy. The first estimation method involves fixing the modelled implied hazard ratio of amivantamab with chemotherapy OS vs chemotherapy OS from the last observation (2.8 years in the amivantamab with chemotherapy arm) onwards and applying this to the OS of chemotherapy. This models a situation where the OS benefit of amivantamab with chemotherapy relative to chemotherapy does not change after the last observation (i.e., constant implied hazard ratio). The ICERs versus chemotherapy for the company base-case and from this estimation method are provided below: • Company base-case: £36,255 Applying fixed implied hazard ratio to CP OS: • ACP = Weibull / CP = Gamma: £36,999 • ACP and CP OS = Weibull: £42,115 • ACP and CP OS = Gamma: £34,780 • ACP and CP OS = Log-logistic: £21,496 • ACP = Weibull / CP OS = Log-logistic: £25,182 The second estimation method involves applying the per-cycle hazard ratio between the OS and PFS of chemotherapy to the PFS of amivantamab with chemotherapy. This models a situation where the relative difference between PFS and OS for amivantamab with chemotherapy is equal to the relative difference observed for chemotherapy.	

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	The ICERs versus chemotherapy for the company base-case and from this estimation method are provided below: • Company base-case: £36,255 Scenarios when applying per-cycle HR of CP OS vs PFS to ACP PFS: • ACP = Weibull / CP = Gamma: £32,756 • ACP and CP OS = Weibull: £35,663 • ACP and CP OS = Gamma: £32,756 • ACP and CP OS = Log-logistic: £34,909 • ACP = Weibull / CP OS = Log-logistic: £34,909 Implementing these methodologies leads to a reduction in the ICER versus chemotherapy compared with the company's base case in all but two of the extrapolation scenarios. This further supports the credibility of the company's selected base case. The only scenario that results in a notably higher ICER is when the fixed OS HR for the Weibull / Weibull scenario is applied to chemotherapy OS. The Weibull curve for chemotherapy OS predicts the lowest survival out of all the scenarios and is not aligned to the company's or EAG's base-cases. Therefore, it should not be considered clinically realistic or useful for decision-making. Notably, when using the EAG's base-case (ACP = Weibull / CP = log-logistic), both estimation methodologies result in significantly lower ICERs which suggests that the log-logistic curve overestimates the OS of chemotherapy.	
12	**Section 3.13 (utility values)**: The EAG noted that there was missing data from both health states, with a substantial amount missing from the progressed-disease health state. The EAG was concerned that if the data was not missing at random then the utility values might not be accurate.	The additional information provided by the company it is helpful. However, the EAG did not find supporting evidence for the statement "*missingness was not associated with any prognostic baseline characteristic*" (also not provided in the

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	There is sufficient data to conclude that missingness was indeed at random, reducing the risk that the utility values derived from the trial data are not accurate. Johnson & Jonson acknowledge there is no empirical evidence to show that health related quality of life (HRQL) data were missing at random. However, both arms had similar degrees of missingness and there was no discernible pattern to the degree of missingness over cycles 0 to 27. Additionally, individual patient profiles over that time period did not indicate a systematic pattern in missingness, and missingness was not associated with any prognostic baseline characteristic.	document containing the additional analyses). It would be informative to explore whether missingness is more prominent in subgroups based on patient characteristics. It therefore remains unclear to the EAG whether and to what extent the missing data impacted the estimated PF and PD health state utility values. Further evidence to support the company's assumption that data was missing (completely) at random would be helpful to address this issue.

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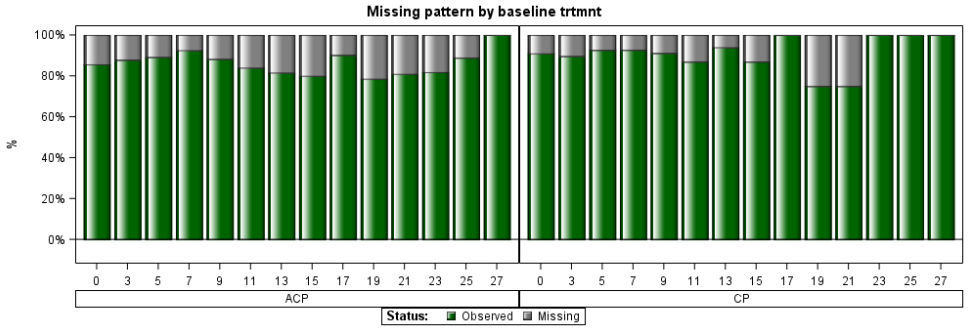
	The plot below shows that missingness is not increasing overtime, and equally spread between treatment arms:  Additional information to show that individual patient profiles over time do not indicate a systematic pattern in missingness (e.g., missingness is not higher in the visits preceding progression) is available in the document containing the additional analyses. This evidence suggests that the missing data within the PAPILLON trial occurred at random. This finding alleviates the concerns raised by the EAG regarding the accuracy of the utility values derived from the PAPILLON trial, indicating that these utility values from the trial can be regarded as reliable and accurate.	
13	**Section 3.13 (utility values)**: The committee noted that the utility values in this appraisal were higher in both health states than in several other appraisals in NSCLC. **EQ-5D data from the PAPILLON trial is the most robust source of evidence to derive utilities for the population in this decision problem.** As the PAPILLON trial was conducted in the specific patient population under consideration in this decision problem, it is the most robust and appropriate source of data for deriving utility values.	Consistent with EAG report section 4.2.8 "*the EAG explored using the highest reported PF (0.79) and PD (0.693) utilities from TA683 in a scenario analysis. The EAG, nevertheless, agrees with the company that EQ-5D data from the PAPILLON trial is the most suitable source to inform health state utilities in the current appraisal.*"

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	It is inappropriate to consider utility values from other appraisals in NSCLC given that these are: not specific to patients with EGFR Exon 20 insertion mutations, are associated with different interventions and treatment history, and they may reflect significantly varied yet important differences in patient characteristics. Utilities accepted in the appraisal of amivantamab monotherapy after prior chemotherapy (TA850) may, to a limited extent, be relevant. The utility value for the progressed-disease state which is derived from PAPILLON trial data ([redacted]) is similar to the utility value for the progression-free state that was used in the appraisal of amivantamab after prior chemotherapy (0.713), which the committee accepted.[10] It is important to note that the population in TA850 was more heavily pre-treated than the progressed patients from the PAPILLON trial, where the median number of previous treatments in the CHRYSALIS trial was two. Had the population been less pre-treated, the utility values would likely have been even closer to, or even exceeded, the progressed utility value observed in the PAPILLON trial. The progressed disease state in the PAPILLON trial closely resembles the progression-free population in the CHRYSALIS trial, as both represent patients with EGFR Exon 20 insertion mutation-positive advanced NSCLC who have progressed on at least one line of therapy. However, it is crucial to emphasise that the CHRYSALIS trial included a higher proportion of pre-treated patients which could explain the slightly lower utility value. Using 0.713 as the progressed disease utility has a small impact on the ICER: • Company base-case: £36,255 • Using 0.713 as PD utility: £37,234	
14	**Section 3.14 (adverse event costs): unit costs for AEs** **Johnson & Johnson have updated the model to incorporate the committee's preferred assumption regarding AE costs (i.e., only including unit costs for the severest AEs).** The new company base-case versus chemotherapy is £36,255 at the proposed PAS price of amivantamab.	This EAG believes this approach is reasonable

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	This is similar to the ICER presented in the company base-case at the first committee meeting, which was £35,820.	
15	**Section 3.15 (dosing in the model):** The committee concluded that it would prefer to model doses of amivantamab in the cycles in which they were due **Johnson & Johnson have updated the model to incorporate the committee's preferred assumption with regards to dosing frequency (i.e., treatment costs incurred in the cycles in which administrations were due, following dosing frequency in the PAPILLON trial).** The new company base-case versus chemotherapy is £36,255 at the proposed PAS price of amivantamab. This is similar to the ICER presented in the company base-case at the first committee meeting, which was £35,820.	This EAG believes this approach is reasonable
16	**Section 3.16 (vial sharing)**: The company did not think that its model allowed vial sharing. The committee considered the expert testimony that vial sharing would not be possible in clinical practice and concluded that vial sharing should not be permitted in the model. **Vial sharing is not allowed in the model. This is explicit within the calculation for the number of vials per administration, shown below.** The fractional value for the average number of vials per administration for amivantamab across the cohort arises because individual patients can receive a reduced number of **full vials**, as per Table 3 in the summary of product characteristics (SmPC).[7] Calculation: The average number of units (vials) per administration is calculated by multiplying the number of expected vials per administration by the average proportion of dose given. The average proportion of dose given is calculated by dividing the total dose given in the trial by the total expected dose.	The additional clarification is informative. This EAG believes this approach is reasonable.

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	The total dose given is lower than the total expected dose (due to dose reductions), and the difference equates to a number of full vials (i.e., a multiple of 350mg). This shows that patients only received dose reductions in terms of full vials of amivantamab and no vial sharing was permitted. An example calculation for a hypothetical cohort of 10 patients < 80kg at baseline for the first cycle is given below, to show that dose reductions are only given in terms of full vials: • Expected dose for 1 patient < 80kg in cycle 1 = 1400mg = 4 full vials • Total expected number of vials for the cohort of 10 patients = 4 * 10 = 40 vials (assuming all patients received 100% of the expected dose) • However, in this scenario, two patients are assumed to have received a reduced dose of 1150mg (**3 full vials**) given this is permitted within the SmPC of amivantamab.[7] This means that two patients in this cohort received 3 vials rather than 4. • Therefore, the total number of vials actually given across the cohort = 40 – 2 = 38 full vials • The average number of vials given per treatment across the cohort = 38 / 40 = 95% • 95% is an average across all patients. However, as shown through the calculation above, individual patients only receive full vials of amivantamab (i.e., no vial sharing). The average proportion arises as individuals can receive a reduced number of **full vials** (e.g., 3 vials not 4). The actual calculation used in the model for patients with weight < 80 kg at baseline is given below:	

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	Amivantamab: • Total dose given (PAPILLON) = [redacted] mg ([redacted] **full vials of amivantamab**) • Total dose expected (PAPILLON) = [redacted] mg (**[redacted] full vials of amivantamab)** • Difference = 257,600 mg ([redacted] **full vials of amivantamab**) • Average proportion of dose given (cohort) = [redacted] mg / [redacted] mg = [redacted]%. This means that, on average, patients will receive 93.7% of the dose compared to the expected dose over their treatment. • Average units per administration (cohort) = 1400 mg / 350 mg (expected number of vials per administration) * [redacted]% = [redacted]. This represents an average across all patients where, in some cases, patients will receive 3 vials, and in some cases, patients will receive 4 vials. The calculation in the model gives a fractional value for the number of units of amivantamab per administration ([redacted] for patients <80kg at baseline) given it is done at a cohort level. It should be stressed that, at an individual level, no vial sharing is allowed in the model. Carboplatin and pemetrexed: The calculation for the units per administration for carboplatin and pemetrexed is done using the same methodology as described above. However, dose reductions in terms of full vials are not recommended in the SmPCs of carboplatin and pemetrexed. Therefore, if a patient receives a reduced dose of these treatments, they would still incur the full number of expected vials. As such, it is necessary to round the	

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	number of vials per administration up after applying the relative dose intensity (RDI) in order to reflect the expected number of vials.	
17	**Section 3.17 (dose skipping)**: The committee concluded that it would like the company to report dose-skipping estimates from the first and subsequent cycles of the PAPILLON trial and for the modelling to reflect any differences in these values. It would also like to see a scenario that explores modelling no dose skipping across all treatments in both arms and one where dose skipping was modelled to be equal across all treatments and arms. **Johnson & Johnson have provided an updated model which includes the requested scenarios for dose skipping. These scenarios resulted in a minor decrease to the ICER versus chemotherapy compared with the base-case.** When dose skipping is modelled to reflect the per-cycle proportions observed in the PAPILLON trial, the ICER versus chemotherapy slightly decreases given a higher proportion of patients skipped doses of amivantamab in subsequent cycles compared with the first cycle, which reduces the cost of amivantamab. Johnson & Johnson have kept the base-case to model dose skipping based on the average proportion of missed doses across all treatment cycles given this models a lower proportion of doses skipped, which is in-line with the committee's preference. The dose skipping proportion is calculated by dividing the number of doses that were missed in the PAPILLON trial by the number of doses that were expected to be given. Dosing scenarios: • Company base-case: ICER = £36,255[a] • Dose skipping by cycle: ICER = £36,012[b] • Equal dose skipping across ACP and CP: ICER = £36,122[c] a. ICER results at the proposed PAS price of amivantamab	The EAG believes the scenario provided by the company is informative to address ACD item 3.17.

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	b. This scenario incorporates different dose-skipping estimates for the first and subsequent cycles c. The dose skipping rate for patients receiving CP is equated to the rate observed for patients receiving ACP (across the treatments) who had a weight of <80kg at baseline ([redacted]%). This scenario is not anticipated to reflect clinical practice given different dose skipping rates between amivantamab and chemotherapy is expected Johnson & Johnson consider the scenario that includes no dose skipping is not appropriate given this does not reflect the data observed in the PAPILLON trial and is not expected in clinical practice based on expert opinion. At the May 2024 company advisory board, clinical experts explicitly concluded that dose skipping is expected to be seen in practice and should be accounted for in the cost calculation in the model.[1] The clinical experts also agreed that it is appropriate to use trial data on skipped doses within the model.	
18.	**Section 3.20 (acceptable ICER)**: The committee was unable to identify a threshold because this would need to account for both the resolvable uncertainties in the analyses requested and the currently unresolvable uncertainties. **Given the unmet need, the robustness of the data from the PAPILLON trial, and the additional analyses provided to address the uncertainties cited in the draft guidance, the acceptable ICER should be positioned at the upper end of the range that NICE considers to be a cost-effective use of NHS resources.** Patients with advanced NSCLC and EGFR Exon20 insertion mutations have a very high unmet need owing to the lack of efficacious, targeted therapies which are available in other advanced NSCLC indications. Resulting in particularly poor outcomes for these patients, with UK RWE showing that patients with untreated, EGFR Exon20 insertion mutation-positive advanced NSCLC have a median OS of just 19.1 months.[3] This unmet need has been cited by both clinical experts and patient groups within the committee papers and was also vocalised at the committee meeting by the clinical expert and the patients. The PAPILLON trial provides robust evidence to demonstrate that amivantamab with chemotherapy addresses this urgent unmet need. The robustness of the PAPILLON trial is	No comment

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	shown through the fact that data from the chemotherapy arm, after adjusting for treatment switching, (mOS = [redacted] months) are very closely aligned to real-world data for chemotherapy from the NECTAR study, after adjusting (via average treatment effect in the treated [ATT] weighting) to match the PAPILLON trial, (mOS = 23.7 months); the NECTAR study was associated with a much longer follow-up (50.5 months).[3] The close alignment between the PAPILLON trial data and real-world data reduces the degree of uncertainty associated with the PAPILLON trial. The degree of uncertainty has also been reduced by the additional analyses and scenarios that Johnson & Johnson have provided following the requests outlined in the draft guidance. These have included running scenarios for dose skipping (using per-cycle proportions and equating dose skipping rates across treatments), exploring different utilities from TA850 to model the PD utility, using the same parametric curves for all outcomes for both treatments and for the OS of both treatments, and exploring the implied hazard ratios associated with each extrapolation scenario. Additionally, Johnson & Johnson have provided analyses exploring different ways of estimating the long-term benefit of amivantamab with chemotherapy (fixing the OS HR from the end of the observation period onwards and equating the relative difference between PFS and OS to the difference observed for chemotherapy) and have provided information on the smoothed OS HR of amivantamab with chemotherapy over time to show whether a waning effect is observed in the PAPILLON trial. In nearly all scenarios explored and the additional analyses suggested by the committee, no clinically realistic or methodologically sound scenarios emerged that presented a significantly higher ICER than the company's base-case. This reinforces the credibility and robustness of the company's base-case, effectively addressing concerns regarding uncertainty. Johnson & Johnson strongly advocate for NICE to consider a willingness to pay threshold towards the upper end of the willingness to pay range. This is supported considering the critical unmet need, the severity of the disease (with a 1.2x severity modifier being accepted), the efficacy benefit demonstrated, and the robustness of the data (shown through scenarios and the base case), together with the small patient population (with [redacted] patients eligible for treatment in	

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	England and Wales in 2024, based on NICE's budget impact assessment) and consequently low risk associated with funding amivantamab with chemotherapy.	

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 [redacted]' in turquoise, and all information submitted as '[redacted]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- 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.

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Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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References

1. Johnson & Johnson Data on File. Advisory Board Report for Amivantamab PAPILLON HTA Submissions. 2nd May 2024.
2. Johnson & Johnson Data on File. Advisory Board Report for Amivantamab PAPILLON HTA Submissions. 1st August 2024.
3. Johnson & Johnson Data on File. The NECTAR Study. Technical Report. 2024.
4. Johnson & Johnson Data on File. RWE NCRAS Data Aggregated Report. 2024.
5. NICE. Amivantamab with carboplatin and pemetrexed for untreated EGFR exon20 insertion mutation-positive advanced non-small-cell lung cancer [ID5110] Committee papers: https://www.nice.org.uk/guidance/gid-ta11023/documents/committee-papers [Last accessed 14 April 2025].
6. Johnson & Johnson Data on File. Statistical Analyses to Adjust Overall Survival for Treatment Switching in PAPILLON Trial. Technical Report focused on Oct23 OS data cut. 06August2024.
7. Medicines & Healthcare Products Regulatory Agency. Summary of Product Characteristics. RYBREVANT 50 mg/mL concentrate for solution for infusion. Available from: https://www.medicines.org.uk/emc/product/13084/smpc. [Last accessed 14 April 2025].
8. NICE technical support document (TSD) 26: Expert elicitation for long-term survival outcomes. https://www.sheffield.ac.uk/media/94031/download?attachment [Last Accessed 18 April 2025].
9. Lopez PG, Girard N, Cho BC, et al. 30 Long-term efficacy, safety, and predictors of response to amivantamab among patients with post-platinum EGFR Ex20ins-mutated advanced NSCLC. Journal of Thoracic Oncology 2023;18:S36-S37.
10. National Institute of Health and Care Excellence (NICE). Amivantamab for treating EGFR Exon 20 insertion mutation-positive advanced non-small-cell lung cancer after platinum-based chemotherapy. TA850. Available at: https://www.nice.org.uk/guidance/ta850 [Last accessed 17 April 2025]

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