

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

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

Contents:

The following documents are made available to stakeholders:

Access the [final scope](#) and [final stakeholder list](#) on the NICE website.

1. **Company full submission** from Johnson & Johnson Innovative Medicine
2. **Company summary of information for patients (SIP)** from Johnson & Johnson Innovative Medicine
3. **Clarification questions and company responses**
4. **Patient group, professional group and NHS organisation submissions** from:
 - a. EGFR Positive
 - b. Roy Castle Lung Cancer Foundation
 - c. British Thoracic Oncology Group
5. **Expert personal perspectives** from:
 - a. Professor Sanjay Popat – clinical expert, nominated by Johnson & Johnson Innovative Medicine and the British Thoracic Oncology Group
 - b. Dr Spyros Gennatas – clinical expert, nominated by AstraZeneca
 - c. Gini Harrison – patient expert, nominated by EGFR Positive
 - d. Sophie McCluskey – patient expert, nominated by EGFR Positive
6. **External Assessment Report** prepared by Kleijnen Systematic Reviews
 - a. External Assessment Report
 - b. EAG addendum containing clinical expert estimates for longer-term outcomes
7. **External Assessment Report – factual accuracy check**

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

**NATIONAL INSTITUTE FOR HEALTH AND
CARE EXCELLENCE**

Single technology appraisal

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

Document B

Company evidence submission

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Company evidence submission template for amivantamab with carboplatin and pemetrexed for untreated EGFR Exon 20 insertion mutation-positive advanced non-small cell lung cancer [ID5110]

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Abbreviations

Acronym	Definition
ABCP	Atezolizumab, Bevacizumab, Carboplatin And Paclitaxel
ACP	Amivantamab In Combination With Carboplatin And Pemetrexed
AE	Adverse Event
AESI	Adverse Events Of Special Interest
AFT	Accelerated Failure Time
AIC	Akaike Information Criterion
ATO	Average Treatment Effect Among The Overlap Population
ATT	Average Effect Of The Treated
AUC	Area Under The Curve
BIC	Bayesian Information Criterion
BICR	Blinded Independent Central Review
BNF	British National Formulary
BOR	Best Overall Response
BSA	Body Surface Area
BSC	Best Supportive Care
CADTH	Canadian Agency For Drugs And Technologies In Health
CEM	Cost Effectiveness Model
CHMP	Committee For Medicinal Products For Human Use
CI	Confidence Interval
CNS	Central Nervous System
CP	Carboplatin and Pemetrexed
CR	Complete Response
CRU	Cost And Resource Use
CSR	Clinical Study Report
DCO	Data Cut-Off
DOR	Duration Of Response
DSU	Decision Support Unit
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
EMEA	Johnson & Johnson Europe
EORTC	European Organisation For Research And Treatment Of Cancer
EPAR	European Public Assessment Report
ESME	Epidemiological Strategy And Medical Economics
ESMO	European Society For Medical Oncology
FAS	Full Analysis Set
GLHs	Genomic Lab Hubs
HCHS	Hospital And Community Health Services

Company evidence submission template for amivantamab with carboplatin and pemetrexed for untreated EGFR Exon 20 insertion mutation-positive advanced non-small cell lung cancer [ID5110]

HES	Hospital Episode Statistics
HR	Hazard Ratio
HRU	Healthcare Resource Use
HTA	Health Technology Assessment
ICER	Incremental Cost Effectiveness Ratio
INV	Investigator
IO	Immuno-oncology
IPCW	Inverse Probability Of Censoring Weight
IPD	Individual Patient Data
IPTW	Inverse Probability Of Treatment Weighting
IRR	Infusion Related Reactions
ISPOR	International Society For Pharmacoeconomics And Outcomes Research
ITC	Indirect Treatment Comparison
ITT	Intention To Treat
MET	Mesenchymal-Epithelial Transition Factor
MHRA	Medicines And Healthcare Products Regulatory Agency
MMRM	Mixed-Effects Model For Repeated Measures
NCCN	National Comprehensive Cancer Network
NCRAS	National Cancer Registration And Analysis Service
NEJM	The New England Journal of Medicine
NGS	Next-Generation Sequencing
NHS	National Health Service
NICE	National Institute Of Health And Care Excellence
NLCA	National Lung Cancer Audit
NSCLC	Non-Small Cell Lung Cancer
ONS	Office For National Statistics
ORR	Objective Response Rate
OS	Overall Survival
PAS	Patient Access Scheme
PCR	Polymerase Chain Reaction
PFS	Progression-Free Survival
PR	Partial Response
PRO	Patient-Reported Outcomes
PS	Propensity Score
PSM	Partitioned Survival Model
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALE	Quality-Adjusted Life Expectancy
QALY	Quality-Adjusted Life Year
RCT	Randomised Controlled Trial
RDI	Relative Dose Intensity

Company evidence submission template for amivantamab with carboplatin and pemetrexed for untreated EGFR Exon 20 insertion mutation-positive advanced non-small cell lung cancer [ID5110]

RPSFT	Rank Preserving Structural Failure Time
RWD	Real-World Data
RWE	Real World Evidence
SACT	Systemic Anti-Cancer Therapy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCHARR	Sheffield Centre For Health And Related Research
SCLC	Small Cell Lung Cancer
SLR	Systematic Literature Review
SMD	Standard Mean Difference/ Somatic Molecular Dataset
SoC	Standard of Care
TA	Technology Appraisal
TEAE	Treatment-Emergent Adverse Events
TKI	Tyrosine Kinase Inhibitor
TSD	Technical Support Document
TSE	Two-Stage Estimation
TTD	Time To Treatment Discontinuation
TTDD	Time To Treatment Discontinuation Or Death
TTNT	Time To Next Treatment
TTSP	Time To Symptomatic Progression
TTST	Time To Subsequent Therapy
UK	United Kingdom
US	United States
VAT	Value Added Tax
VEGF	Vascular Endothelial Growth Factor
WCLC	World Conference on Lung Cancer

B.1 Decision problem, description of the technology and clinical care pathway

Submission Summary

Amivantamab with carboplatin and pemetrexed has been demonstrated to address a critical unmet need for adult patients with untreated epidermal growth factor receptor (EGFR) Exon 20 insertion-mutated advanced NSCLC

- This submission considers amivantamab in combination with carboplatin and pemetrexed for adult patients with untreated, EGFR Exon 20 insertion mutation-positive advanced non-small cell lung cancer (NSCLC).
- EGFR Exon20 insertion mutations are rare, the frequency of EGFR Exon20 insertion mutations among European patients with advanced NSCLC is reported to range from 0.3%–1.3%.^{1 2}
- Currently, there is no established standard of care (SoC) or targeted treatments available for this patient population in the United Kingdom (UK).³⁻⁵
- Non-targeted treatments that are observed to be used in the first-line setting in UK clinical practice, based on real-world evidence (RWE) and clinical opinion, are platinum-based chemotherapy and immunotherapy (IO) in combination with platinum-based chemotherapy. These treatments have limited efficacy in patients with EGFR Exon20 insertion mutations, contributing to a particularly poor prognosis for these patients.^{6, 7}
- Unlike other forms of EGFR mutations, EGFR Exon20 insertion mutations are associated with *de novo* resistance to EGFR tyrosine kinase inhibitors (TKIs), causing them to respond poorly to these treatments.⁶⁻⁹
- Amivantamab is the first targeted therapy to demonstrate efficacy in patients with untreated, EGFR Exon20 insertion mutation-positive advanced NSCLC.¹⁰ In a randomised, open-label, registrational Phase 3 trial (the PAPILLON trial), amivantamab in combination with carboplatin and pemetrexed ('amivantamab-chemotherapy') demonstrated a clinically meaningful and statistically significant increase in median progression-free survival (PFS) as assessed by blinded independent central review (BICR) versus carboplatin and pemetrexed ('chemotherapy'). The median PFS was 11.37 months (95% confidence interval [CI]: 9.79-13.70) in the amivantamab-chemotherapy arm versus 6.70 months (95% CI: 5.59-7.33) in the chemotherapy arm (hazard ratio [HR] 0.40; 95% CI: 0.30-0.53; $p < 0.0001$), meeting the primary endpoint of the PAPILLON trial (see Section B.2.6.1).¹⁰
- Following adjustment for treatment switching (via the inverse probability of censoring weighting [IPCW] approach) in the chemotherapy arm (to amivantamab monotherapy as a second line treatment), amivantamab-chemotherapy demonstrated a clinically meaningful overall survival (OS) benefit versus chemotherapy (HR: [REDACTED]). The OS benefit observed in the PAPILLON trial is reinforced by results from the indirect treatment comparison (ITC) between amivantamab-chemotherapy (from PAPILLON) versus chemotherapy (from the NECTAR real-world evidence [RWE] study) using the average treatment effect in the treated (ATT)-weighting of individual patient level data, which estimated an OS HR of [REDACTED]. Median OS ([REDACTED]) of chemotherapy in PAPILLON (following adjustment for cross-over), has high face validity as closely aligns with median OS ([REDACTED]) of chemotherapy in RWE (after ATT-weighting).

Company evidence submission template for amivantamab with carboplatin and pemetrexed for untreated EGFR Exon 20 insertion mutation-positive advanced non-small cell lung cancer [ID5110]

- Amivantamab in combination with carboplatin and pemetrexed addresses the urgent unmet need in this patient population for a targeted, efficacious and tolerable treatment.¹⁰

Patients with EGFR Exon20 insertion mutation-positive advanced NSCLC suffer a substantial disease burden, largely due to the current lack of effective treatment options for these patients

- UK RWE from a descriptive standing cohort study among patients diagnosed with advanced NSCLC between 2016–2021, collected from the National Cancer Registration and Analysis Service (NCRAS) dataset, showed that patients with untreated EGFR Exon20 insertion mutation-positive advanced NSCLC have a low median overall survival (OS) of 19.1 months (95% CI: 7.3–38.5).¹¹
- In advanced NSCLC, survival among patients with EGFR Exon20 insertion mutation-positive advanced NSCLC is poorer compared with patients with common EGFR mutated NSCLCs (Exon19 deletions or L858R substitutions in Exon21), reported as 16.2 months (95% CI: 11.04–19.38) versus 25.5 months (95% CI: 24.5–27.0) by Bazhenova et al. 2021.¹²
- Similarly, data from a non-interventional, retrospective, observational cohort study conducted by Johnson & Johnson, utilising data from [REDACTED] patients with untreated EGFR Exon20 insertion-mutated advanced NSCLC collected across four RWE datasets, including a dataset from the UK, showed that the median OS was [REDACTED] months (95% CI: [REDACTED]).³
- Available evidence indicates that patients with untreated, EGFR Exon20 insertion mutation-positive advanced NSCLC suffer a substantial burden, largely due to the lack of effective targeted treatment options for these patients, making this type of NSCLC particularly challenging to treat:
- RWE from a study in the United States (US) suggest that patients with EGFR Exon20 insertion mutation-positive advanced NSCLC have a 75% increased risk of death (HR: 1.75, [95% CI: 1.45–2.13]; p <0.0001), compared to patients with common EGFR mutations.¹²
- A patient and caregiver study conducted by Johnson & Johnson which included patients with EGFR Exon20 insertion mutation-positive advanced NSCLC indicated that there is a substantial negative impact of living with this condition on mental health/emotional wellbeing, which is greater than for patients with common EGFR mutations.^{13, 14} Symptoms such as fatigue, cough, breathlessness, nausea and/or vomiting were reported as key symptoms of lung cancer that negatively impact patients' health-related quality of life (HRQoL).¹³

Patients with untreated EGFR Exon20 insertion mutation-positive advanced NSCLC remain unable to access a targeted treatment for their disease via the National Health Service (NHS). Progress in making an effective treatment available for this patient population was hindered following the withdrawal of mobocertinib in 2024, and therefore an unmet need for an effective treatment is yet to be addressed in this population

- Amivantamab is the first targeted treatment with the potential to be made available to adult patients with untreated EGFR Exon20 insertion mutation-positive advanced NSCLC in the UK.¹⁵ This is a patient population with a high unmet need and a particularly poor prognosis due to the lack of efficacy associated with non-targeted therapies that are used in this setting in lieu of approved, efficacious targeted treatments available.
- The lack of treatment options for this patient population has been exacerbated by the outcome of the EXCLAIM-2 Phase 3 trial, investigating the safety and efficacy of mobocertinib as a first-line option in patients with EGFR Exon20 insertion mutation-positive advanced NSCLC, which did not meet its primary endpoint.¹⁶ This led to the withdrawal of the conditional marketing authorisation of mobocertinib in the second-line setting, leaving patients with EGFR Exon20

insertion mutation-positive advanced NSCLC with no targeted treatment options available on the NHS.¹⁷

- Available evidence from the PAPILLON trial and the indirect treatment comparisons (ITCs) (Section B.2.9) presented in this submission demonstrate that amivantamab in combination with carboplatin and pemetrexed addresses the significant unmet need in this patient population for an effective treatment. This treatment also features a tolerable safety profile (Section B.2.10), as evidenced by the PAPILLON trial.¹⁰
- It is expected that the reimbursement of amivantamab will therefore address the substantial difference in survival for patients with NSCLC and EGFR Exon20 insertion mutations compared to patients with NSCLC and common EGFR mutations, who currently have access to efficacious therapies and have substantially better chances of survival.⁷

B.1.1 Decision problem

The aim of this submission is to determine the clinical and cost-effectiveness of amivantamab in combination with carboplatin and pemetrexed, in line with its marketing authorisation, for the first-line treatment of adult patients with advanced NSCLC who have activating EGFR Exon 20 insertion mutations.¹⁸

Marketing authorisation for amivantamab as monotherapy for the treatment of patients with advanced NSCLC with activating EGFR Exon20 insertion mutations, after failure of platinum-based therapy was granted by the Medicines and Healthcare products Regulatory Agency (MHRA) on 15th November 2021.^{19, 20} The licence for amivantamab was subsequently expanded to the first-line setting, with approval from the MHRA granted on 15th July 2024.

This marketing authorisation for amivantamab in combination with carboplatin and pemetrexed for the first-line treatment of adult patients with advanced NSCLC with activating EGFR Exon20 insertion mutations represents the patient population considered within this submission.^{18, 21}

The decision problem addressed in this submission is largely aligned to that defined in the final scope issued by NICE. The decision problem and a comparison to the final scope issued by NICE is provided in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with untreated, locally advanced or metastatic NSCLC with an EGFR exon 20 insertion mutation.	First-line treatment of adult patients with advanced NSCLC with activating EGFR Exon 20 insertion mutations.	Aligned to the licensed indication for amivantamab, as per the marketing authorisation from the MHRA.
Intervention	Amivantamab in combination with carboplatin and pemetrexed.	As per NICE scope	Not applicable
Comparator(s)	Chemotherapy such as docetaxel, gemcitabine, paclitaxel or vinorelbine in combination with a platinum drug (carboplatin or cisplatin), with or without pemetrexed maintenance treatment Pembrolizumab (monotherapy or in combination with chemotherapy according to PD-L1 expression) Atezolizumab TKIs (gefitinib, erlotinib, afatinib, dacomitinib, osimertinib and osimertinib with chemotherapy [subject to NICE appraisal])	Carboplatin with pemetrexed Pembrolizumab with carboplatin and pemetrexed Pembrolizumab monotherapy UK RWE (collected from the NCRAS dataset) – as scenario	Advisory boards with UK oncologists (held in June 2023, May 2024, and August 2024) and UK RWE (collected from the NCRAS dataset) have highlighted that carboplatin with pemetrexed and pembrolizumab in combination with carboplatin and pemetrexed are the predominant treatment regimens used in the patient population considered in this appraisal.^{3, 5, 11, 22, 23} <u>Chemotherapy:</u> Clinical expert opinion has highlighted that carboplatin with pemetrexed is the dominant chemotherapy regimen being used, with negligible to no use of cisplatin-based chemotherapy or other chemotherapy regimens such as docetaxel, gemcitabine, paclitaxel or vinorelbine. Therefore, Johnson & Johnson does not consider other chemotherapy regimens aside from carboplatin with pemetrexed to constitute relevant comparators.^{5, 22, 23} <u>IO monotherapy</u> Atezolizumab is not NICE-recommended within the population covered by this decision problem (patients with untreated EGFR Exon20 insertion

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			mutation-positive advanced NSCLC) and clinical expert opinion plus UK RWE data have highlighted there is no use of this therapy in clinical practice. Therefore, Johnson & Johnson does not consider atezolizumab to constitute a relevant comparator. Clinical expert opinion as well as UK RWE have shown that there is limited use of pembrolizumab monotherapy in clinical practice. <u>EGFR TKIs:</u> EGFR Exon20 insertion mutations are associated with de novo resistance to EGFR TKIs.^{7, 24} Additionally, there are no EGFR TKIs that are specifically recommended within patients with EGFR Exon20 insertion mutation-positive NSCLC at any line. Although there is limited use of EGFR TKIs seen in UK RWE, clinical expert opinion has highlighted EGFR TKIs should not be used in these patients. Additionally, the response from the British Thoracic Oncology Group (BTOG) on the draft scope for this appraisal highlighted that use of standard EGFR TKIs in this population was inappropriate.²⁵ Further, in the appraisal of amivantamab for treating EGFR Exon20 insertion mutation-positive advanced NSCLC after platinum-based chemotherapy (TA 850), clinical experts explained that EGFR TKIs have limited efficacy when there are EGFR Exon20 insertion mutations and, because of this, are rarely and inappropriately used in this population.

			Therefore, Johnson & Johnson does not consider EGFR TKIs to constitute relevant comparators. ¹⁹
Outcomes	• OS • PFS • Overall response rate (ORR) • Time to subsequent treatment (TTST) • Adverse events (AEs) • HRQoL.	• PFS (primary endpoint) • ORR • Duration of response (DoR) • OS • TTST • Progression-free survival after first subsequent therapy (PFS2) • Time to symptomatic progression (TTSP) • incidence and severity of AEs and laboratory abnormalities, assessment of vital signs, and physical examination abnormalities • HRQoL Exploratory: • Time to treatment discontinuation (TTD) • EuroQol-5 Dimensions-5 Levels (EQ-5D-5L)	The outcomes listed in the NICE final scope represent those collected in the PAPILLON trial. Additional outcomes are suggested, to capture the full extent of outcomes assessed in the Phase 3 PAPILLON trial and used within the economic model to demonstrate the most important health benefits associated with amivantamab in combination with carboplatin and pemetrexed.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year (QALY). The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or	A de novo cost-utility model will be developed for the economic analysis. As per the NICE reference case: results will be expressed in terms of incremental cost per QALY. As per the NICE reference case: The time horizon in the model will be of sufficient length to capture all important differences in costs or outcomes	<u>EGFR testing costs:</u> The introduction of amivantamab with carboplatin and pemetrexed is not expected to incur additional costs to the NHS over and above the current SoC for EGFR testing requirements for all patients with NSCLC. Testing for EGFR Exon20 insertion mutations is included in the National Genomic Test Directory.²⁶ Therefore, EGFR Exon20 insertion mutations are tested routinely in clinical practice as part of a panel of genes, alongside other

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	outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services (PSS) perspective. EGFR testing costs: The final NICE scope highlights that the economic modelling should include the costs associated with diagnostic testing for EGFR Exon20 insertions in people with locally-advanced or metastatic NSCLC who would not otherwise have been tested.	between the technologies being compared. The economic model uses a 40-year time horizon. Less than 0.01% of patients are expected to survive beyond this period. EGFR testing costs: EGFR testing costs are not included within the base-case economic model.	oncogenic drivers in NSCLC, in a standardised and fully validated approach across the GLHs and different hospitals throughout the UK. Testing for EGFR Exon20 insertion mutations is included in the testing panel as part of the reflex EGFR testing pathway that is conducted at diagnosis for all patients with NSCLC. Therefore, introducing amivantamab-chemotherapy is not expected to incur additional testing costs and as such, the costs associated with diagnostic testing for EGFR in people with NSCLC are not anticipated to be included within the base case economic analysis.
Subgroups to be considered	If the evidence allows, the following subgroups will be considered: • Disease stage • Histology • Type of exon 20 alteration present and presence of co-mutations	Subgroup analyses are not considered appropriate.	Subgroups based on disease stage (squamous or non-squamous), histology, EGFR Exon20 insertion mutation type, or co-mutations are not available. Histology: The PAPILLON trial excludes squamous NSCLC and, since 99% of the trial population was of adenocarcinoma histology type, these subgroups could not be explored. Disease stage: Disease stage subgroups could not be explored as efficacy data stratified by this group are not available. Type of EGFR Exon20 alteration or presence of co-mutations:

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			Subgroups based on mutation alteration could not be explored as available sample sizes do not permit such analyses.
Special considerations including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	Amivantamab is presented within the first-line marketing authorisation for the treatment of adult patients with advanced NSCLC with activating EGFR Exon 20 insertion mutations. The impact of stigma on people living with lung cancer, including patients and caregivers, is also of relevance to this submission and is not inherently captured in the cost/QALY measure.	Lung cancer is associated with substantial stigma owing to the perception that it is 'self-inflicted' due to the public perceiving a link between lung cancer and smoking.²⁷ This stigma is compounded when considering patients with EGFR Exon20 insertion mutation-positive NSCLC given that EGFR Exon20 insertion mutations are more likely to be associated with never-smokers compared with other mutations.⁷ It should further be considered that EGFR Exon20 insertion mutations are particularly associated with women, non-smokers and people of Asian ethnicity.^{6, 7} There is evidence that symptoms of lung cancer are stigmatised in Asian communities, which could reinforce treatment delaying behaviour.²⁸ A recent study assessing differences in screening, diagnosis, and initial care between patients with newly diagnosed with lung cancer of Asian and White ethnicity reported that, compared with patients of White ethnicity, patients of Asian ethnicity were more likely to be diagnosed with later-stage lung cancer and had a longer median time to treatment initiation.²⁹ Therefore, ethnicity and stigma are considered to be relevant equality considerations for the Committee. Additionally, there are currently no targeted treatments available in the UK for patients with EGFR Exon20 insertion mutation-positive advanced NSCLC. The economic model therefore does not reflect the inequity in survival

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			outcomes faced by patients with EGFR Exon20 insertion mutation-positive NSCLC versus patients with common EGFR mutated NSCLC, who are able to access targeted treatments for their disease via the NHS.

Abbreviations: ABCP: atezolizumab, bevacizumab, carboplatin and paclitaxel; AE: adverse event; DOR: duration of response; EGFR: epidermal growth factor receptor; EORTC-QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; Exon20ins: exon 20 insertions; HRQoL: health-related quality of life; ICER: incremental cost-effectiveness ratio; IO: immuno-oncology; IV: intravenous; MHRA: Medicines and Healthcare products Regulatory Agency; N/A: not applicable; NCRAS: National Cancer Registration and Analysis Service; NHS: National Health Service; NSCLC: non-small cell lung cancer; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; PRO: patient-reported outcome; PROMIS-PF: Patient-Reported Outcomes Measurement Information System – Physical Function; PSS: Personal Social Services; QALY: quality adjusted life year; SoC: standard of care; TKI: tyrosine kinase inhibitor; TTSP: time to symptomatic progression; TTST: time to subsequent therapy.

B.1.2 Description of the technology being evaluated

A summary of the mechanism of action, marketing authorisation, costs and administration requirements for amivantamab are presented in Table 2. The summary of product characteristics (SmPC) for amivantamab is provided in Appendix C.1.

Table 2: Technology being evaluated

UK approved name and brand name	Amivantamab (Rybrevant®)
Mechanism of action	Amivantamab (JNJ-61186372) is a novel, fully human, bispecific antibody developed using Genmab's DuoBody® technology which binds to both the epidermal growth factor (EGF) and mesenchymal epithelial transition (MET) receptors.^{30, 31} Amivantamab demonstrates activity against NSCLC tumours via three mechanisms of action, thereby inhibiting tumour growth and survival regulatory pathways:³⁰ 1. EGFR/MET receptor degradation 2. Inhibition of ligand binding 3. Immune cell-directing activity
Marketing authorisation/CE mark status	Amivantamab in combination with carboplatin and pemetrexed for the first-line treatment of adult patients with advanced NSCLC with activating EGFR Exon 20 insertion mutations received full marketing authorisation from the MHRA on the 15th July 2024.³⁰ Amivantamab received marketing authorisation for this indication from the European Medicines Agency (EMA) on 27th June 2024.¹⁸ Previously, amivantamab received marketing authorisation from the MHRA in the second-line indication as monotherapy for treatment of adult patients with advanced NSCLC with activating EGFR Exon 20 insertion mutations, after failure of platinum-based therapy on 15th November 2021.³² Amivantamab received marketing authorisation from the EMA for this indication on 9th December 2021.¹⁸
Indications and any restriction(s) as described in the SmPC	Amivantamab is indicated:³⁰ In combination with carboplatin and pemetrexed for the first-line treatment of adult patients with advanced NSCLC with activating EGFR Exon20 insertion mutations (indication of interest for this evaluation) As monotherapy for treatment of adult patients with advanced NSCLC with activating EGFR Exon20 insertion mutations, after platinum-based therapy Contraindications include hypersensitivity to the active substance or to any of the excipients listed below:³⁰ • Ethylenediaminetetraacetic acid (EDTA) disodium salt dihydrate • L-Histidine • L-Histidine hydrochloride monohydrate • L-Methionine • Polysorbate 80 • Sucrose • Water for injections

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Method of administration and dosage	Amivantamab is administered in combination with carboplatin and pemetrexed, with all components administered via IV infusion at the following doses: Amivantamab <u>Less than 80 kg:</u> • 1,400 mg: weekly (total of 4 doses) from weeks 1 to 4; week 1 – split infusion on Day 1 and 2. Weeks 2 to 4 – infusion on Day 1. • 1750 mg: every 3 weeks starting at week 7 onwards. <u>Greater than or equal to 80 kg:</u> • 1750 mg: weekly (total of 4 doses) for weeks 1 to 4; week 1 – split infusion on Day 1 and 2. Weeks 2 to 4 – infusion on Day 1. • 2100 mg: every 3 weeks starting at week 7 onwards. Pemetrexed as per current NHS recommendations • 500 mg/m² (with vitamin supplementation) on Day 1 of each 21-day cycle • Given in combination with carboplatin for the first 4 cycles, and then as maintenance monotherapy until disease progression Carboplatin as per current NHS recommendations • Carboplatin area under the concentration-time curve 5 mg/mL per minute (AUC5) • Administered on Day 1 of each 21-day cycle, for up to 4 cycles A subcutaneous formulation of amivantamab is being developed with an anticipated UK launch date [REDACTED].³³
Additional tests or investigations	Before initiation of amivantamab therapy, EGFR Exon 20 insertion mutation-positive status in tumour tissue or plasma specimens must be established using a validated test method. If no mutation is detected in a plasma specimen, tumour tissue should be tested if available in sufficient amount and quality due to the potential for false negative results using a plasma-test.³⁰ EGFR Exon20 insertion mutations are included in the National Genomic Test Directory for cancer and can be routinely tested in clinical practice in the Genomic Lab Hubs (GLHs), as part of the diagnosis and treatment selection for patients with EGFR alterations.²⁶ This means that EGFR Exon20 insertion mutations can be tested routinely in clinical practice as part of a panel of genes alongside other oncogenic drivers in a standardised and fully validated approach across different centres throughout the UK. At an advisory board in August 2024, UK clinical experts confirmed that EGFR Exon20 insertion mutations are routinely tested for in clinical practice.²² Thus, the cost of mutation testing has not been factored into the economic results of this submission. The prognosis of patients with EGFR Exon20 insertion mutation-positive advanced NSCLC in the UK is poor, and there is a need to accurately identify patients with Exon20 insertion mutations to select the most appropriate treatment pathway to achieve the best possible outcomes for patients. Using the national genomic testing service as part of routine clinical practice is a key step towards achieving better outcomes for patients. EGFR Exon20 insertion mutations are included within the test directory. However, having this test on the directory will not directly

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	benefit patients unless a targeted therapy such as amivantamab is made available on the NHS.
List price and average cost of a course of treatment	The list price for amivantamab is £1,079.00 per vial. Based on the base case economic analysis, the mean time on treatment is estimated to be 16.4 months for amivantamab and 15.0 months for carboplatin and pemetrexed, resulting in an average cost of a course of treatment of £109,295 (at list price) and [REDACTED] (at PAS price).
PAS (if applicable)	A confidential simple PAS discount of [REDACTED]% has been proposed for amivantamab. Therefore, the proposed with-PAS price is £[REDACTED] per vial (excluding value added tax [VAT]).

Abbreviations: AUC5: area under the concentration-time curve 5 mg/mL per minute; CHMP: Committee for Medicinal Products for Human Use; EGFR: epidermal growth factor receptor; EMA: European Medicines Agency; Exon20ins: exon 20 insertions; MET: mesenchymal-epithelial transition factor; MHRA: Medicines and Healthcare products Regulatory Agency; NSCLC: non-small cell lung; PAS: patient access scheme.

B.1.2.1 Amivantamab

Amivantamab is a novel, fully human, bispecific antibody that simultaneously targets two proteins found on the surface of cancer cells: EGFR and MET.^{21, 34} Specifically, one portion of amivantamab's antigen-binding fragment recognises EGFR, whilst the other recognises the protooncogene MET.³⁴

The EGFR protein is a tyrosine kinase receptor that plays a key role in cell proliferation, growth, migration and survival. As such, mutations in this protein contribute to tumour growth and proliferation.³⁵ EGFR activating mutations in NSCLC cells were identified as a predictive biomarker in 2004, allowing patients with these mutations to be selected for treatment with EGFR-targeted TKIs.³⁶ However, unlike common EGFR mutations (such as Exon19 deletions or L858R substitutions on Exon21), EGFR Exon20 insertion mutations induce unique conformational changes in the EGFR protein that affect TKI binding affinity.⁷ This leads to primary resistance of tumours with EGFR Exon20 insertion mutations to most EGFR TKIs.^{7, 37, 38} By contrast, amivantamab is effective in the treatment of EGFR Exon20 insertion mutation-positive NSCLC because as it is an antibody, it binds to the extracellular domain of the EGFR protein. As a result of this, the efficacy of amivantamab is not affected by the conformational changes affecting the TKI binding pocket.³⁹

In addition to EGFR mutations, EGFR-positive tumours may also undergo activation of the MET intracellular signalling pathway through MET gene amplification and increased MET expression. This leads to further TKI resistance,³⁹ as stimulation of this pathway provides an alternative mechanism to bypass the TKI block of EGFR and facilitate the survival of cancer cells.³⁹ Therefore, by targeting both activating EGFR and MET mutations, amivantamab addresses the two major mechanisms of resistance to TKIs.³⁹

As outlined in Table 2, amivantamab exerts anti-tumour activity through three mechanisms of action which are detailed below and represented graphically in Figure 1.

1. EGFR/MET receptor degradation

Amivantamab extracellularly binds to EGFR and MET inducing a subsequent downmodulation (a reduction in production) of EGFR and MET expression on the surface of tumour cells, through

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internalisation and lysosomal degradation.^{34, 40} Trogocytosis also contributes to receptor degradation (see below).⁴⁰

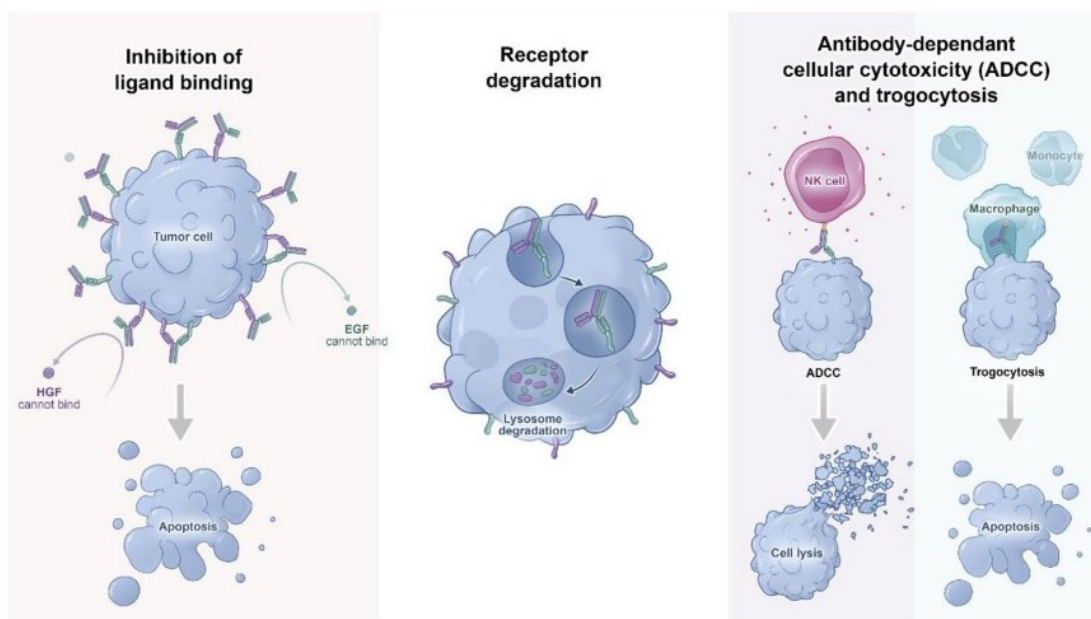
2. Inhibition of ligand binding

The binding of amivantamab to the extracellular domains of EGFR and MET further blocks ligand binding.⁴⁰ In turn, amivantamab prevents ligand-induced EGFR and MET receptor activation, which inhibits downstream pro-growth and pro-survival signalling pathways, thereby preventing tumour growth and proliferation.⁴¹

3. Immune cell-directing activity

The resulting amivantamab-EGFR-MET complex on the tumour cell surface also allows for targeting of cancer cells for destruction by immune effector cells.^{21, 40} For instance, the binding of amivantamab to EGFR and MET can induce tumour cell death through antibody-dependent cellular cytotoxicity, mediated by natural killer cells, as well as initiating trogocytosis (cell gnawing), where plasma membrane fragments are transferred from tumour cells to macrophages.⁴⁰ This immune-directing activity further increases the anti-tumour effect of amivantamab, in addition to its direct inhibitory effects on promoting tumour growth.

Figure 1: Schematic of amivantamab's three MOAs - ligand blocking, receptor degradation, and activation of immune-cell-directing activity



Abbreviations: ADCC: antibody-dependent cellular cytotoxicity; EGF: epidermal growth factor; HGF: hepatocyte growth factor; MOA: mechanism of action; NK: natural killer.

Source: Cho et al. 2022⁴²

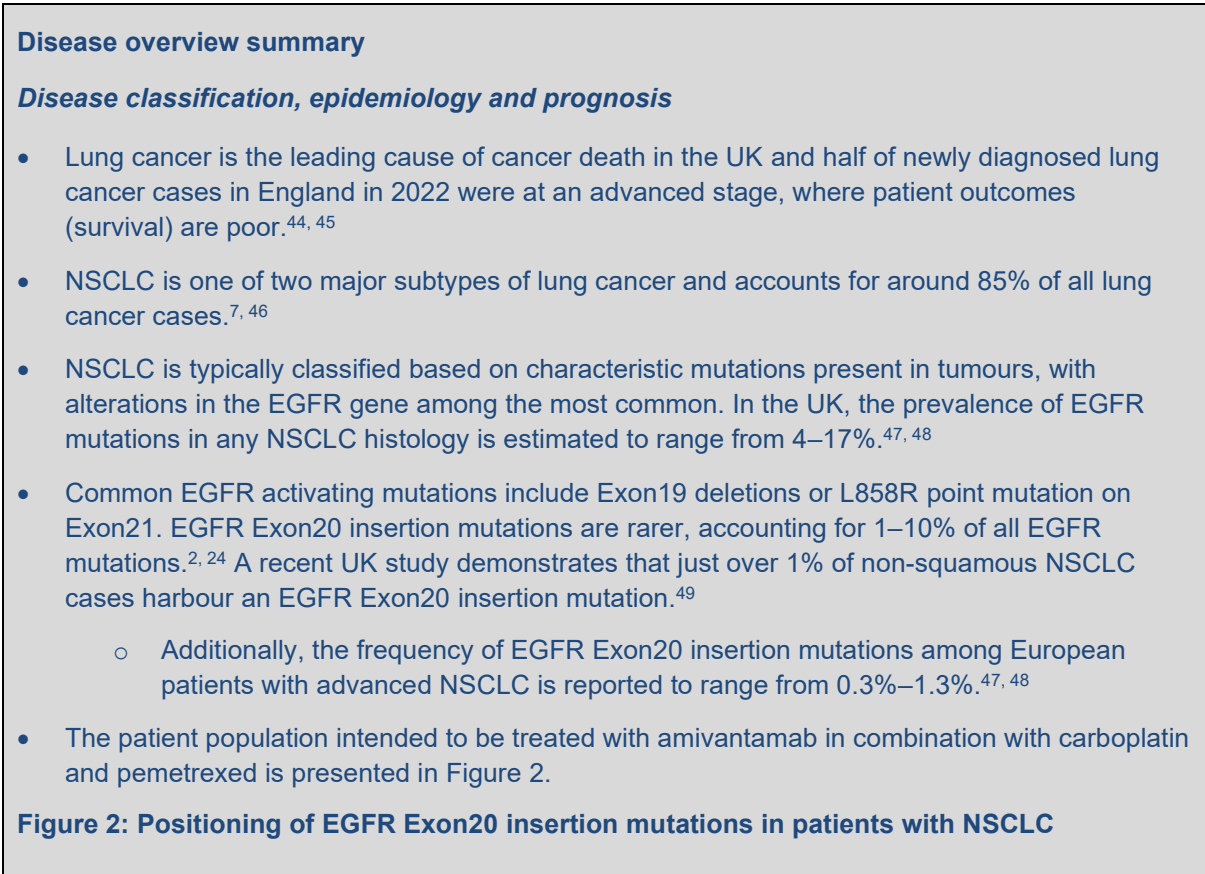
A summary of amivantamab

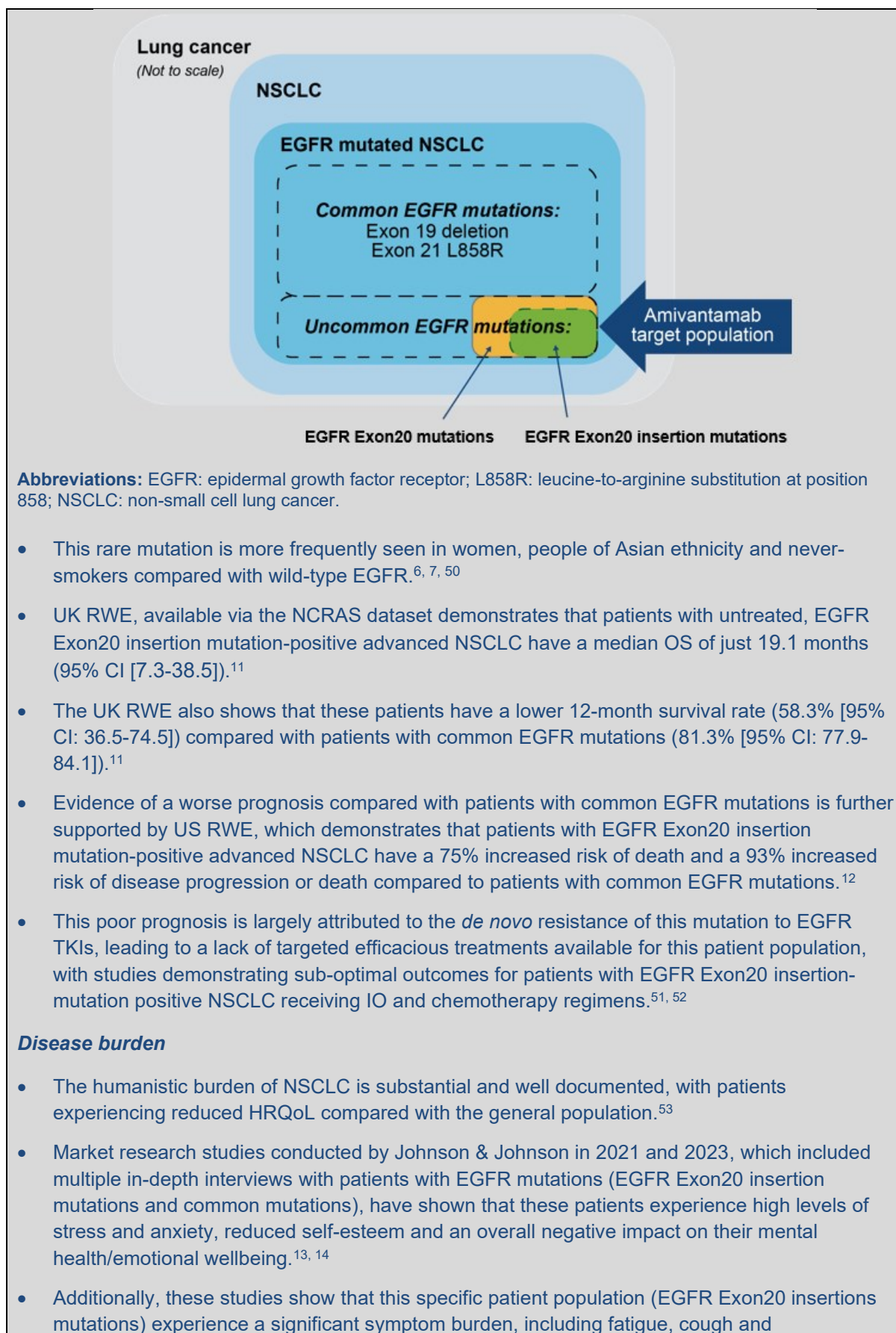
Due to its innovative mechanism of action (described above), amivantamab has the potential to be an effective treatment option against EGFR Exon20 insertion mutations, with unadjusted data from the PAPILLON trial to support this. In the PAPILLON trial, at the 3rd May 2023 DCO, amivantamab-chemotherapy achieved a 24-month event-free rate of 72% which was higher compared with the 24-month event-free rate for chemotherapy (54%; B.2.6.2.3). The observed,

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positive trend towards a survival benefit for amivantamab-chemotherapy is expected to translate into a long-term benefit for treated patients. Evidence of a long-term survival benefit associated with amivantamab has been observed in the CHRYSALIS trial, investigating amivantamab monotherapy in the second-line setting. Among 114 patients included in the long-term efficacy and safety analysis of the CHRYSALIS trial, 48 (42%) patients remained alive at a median follow-up time of 19.2 months, and median OS was 23 months (95% CI: 18.5-29.5).⁴³ This result demonstrates the long-term impact of the amivantamab mechanism of action.

B.1.3 Health condition and position of the technology in the treatment pathway





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breathlessness, leading to a negative impact on patient HRQoL and a substantial psychosocial impact.^{13, 14}

Treatment pathway

- There are currently no UK-specific treatment guidelines or NICE-recommended treatment options for EGFR Exon20 insertion mutation-positive NSCLC, at any treatment line.^{4, 37} As such, there is no established SoC for these patients in the UK.
- The lack of treatment options faced by this population has been recently exacerbated by the outcome of the EXCLAIM-2 trial, which investigated mobocertinib as a first-line option in patients with EGFR Exon20 insertion mutation-positive NSCLC, which did not meet its primary endpoint.¹⁶ This led to the withdrawal of mobocertinib from the UK in the second-line setting as well as the withdrawal of the NICE recommendation for this treatment on 8th March 2024.¹⁷ This has left patients with EGFR Exon20 insertion mutation-positive advanced NSCLC in the UK with no targeted, disease-specific therapies available on the NHS to treat their condition.
- Given the lack of targeted treatments and guidance for this population, UK clinical expert opinion obtained from multiple advisory boards and RWE studies conducted by Johnson & Johnson were used to inform the current treatment landscape:^{5, 11, 22, 23}
 - Evidence from the UK-specific NCRAS database and a non-interventional, retrospective, observational cohort study conducted by Johnson & Johnson (the NECTAR study) indicate that patients with EGFR Exon20 insertion mutation-positive NSCLC receive platinum-based chemotherapy and IO therapy in combination with platinum chemotherapy, with a small proportion of patients observed to receive EGFR TKIs and IO monotherapy.^{11, 22}
 - However, feedback from clinical experts gained through three advisory boards indicates that EGFR TKIs and IO monotherapy treatments are considered ineffective in the EGFR Exon20 insertion mutation-positive population, and that it is not considered best practice to prescribe either treatment at first-line.²²
- Feedback from advisory boards with UK clinicians therefore demonstrates that platinum-based chemotherapy (carboplatin with pemetrexed) with or without IO therapy (specifically pembrolizumab) are currently used in the first-line setting and can be considered as relevant comparators.^{5, 22, 23}

Unmet need

- Overall, an urgent unmet need exists for an efficacious, targeted treatment that can improve survival in patients with untreated, EGFR Exon20 insertion mutation-positive advanced NSCLC, with amivantamab-chemotherapy anticipated to fulfil this unmet need.
- A positive recommendation from NICE for amivantamab with carboplatin and pemetrexed as a first-line treatment in this population would make it the only treatment recommended specifically in first-line for patients with EGFR Exon20 insertion mutation-positive advanced NSCLC, able to be accessed via the NHS. This recommendation would establish a long sought SoC for these patients in UK clinical practice and transforming the lives of the individuals dealing with the substantial physical and psychosocial burden associated with this disease.

B.1.3.1 Disease overview

B.1.3.1.1 Disease classification and prognosis

Classification

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There are two major subtypes of lung cancer: small cell lung cancer (SCLC) and NSCLC. NSCLC is the most common subtype, accounting for approximately 85% of all lung cancer cases.^{7, 46} NSCLC can be further classified into three distinct histological types: squamous-cell carcinoma, adenocarcinoma and large-cell carcinoma. Adenocarcinoma is the most common, comprising 40–43% of all lung cancer cases.⁵⁴

NSCLC is generally categorised based on characteristic mutations present in tumours. Alterations in EGFR, a tyrosine kinase, are the most common targetable oncogenic driver mutation in NSCLC.²⁴ The EGFR gene is involved in cellular processes including cell survival, growth, proliferation and migration and so mutations of this gene contribute to tumour growth and spread.^{24, 55} In NSCLC, mutations in the EGFR gene typically occur in Exons 18–21.⁸ Approximately 90% of EGFR mutations comprise Exon 19 deletions and L858R substitutions in Exon 21; these are collectively referred to as the ‘common’ EGFR mutations. EGFR Exon20 insertion mutations are rarer, accounting for 1–10% of all EGFR mutations.^{2, 24} EGFR Exon20 insertion mutations are heterogeneous at the molecular level, with more than 70 types of mutations identified to date.^{7, 8, 24, 56, 57}

Prognosis

Patients with early-stage NSCLC are often either asymptomatic or present with non-specific symptoms. As such, the majority of patients are diagnosed when the disease is already advanced, with around half of patients with lung cancer in England and Wales presenting with Stage IV disease at the time of diagnosis.⁴⁵ Advanced NSCLC refers to both inoperable (unresectable), locally advanced (Stage IIIb/IIIc) and metastatic (Stage IV) disease.⁵⁸ The five-year survival rate for patients with metastatic NSCLC is poor, estimated at less than 5%.⁵⁹

Patients with EGFR Exon20 insertion mutation-positive advanced NSCLC have a poorer prognosis compared to those with common EGFR mutations, evidenced by multiple studies, which are summarised below.

RWE study conducted by Johnson & Johnson

The NECTAR study is a non-interventional, retrospective, observational cohort study conducted by Johnson & Johnson using routinely collected data from four RWE sources across multiple countries: NCRAS (England), ESME (France), ConcertAI (US), and COTA (US). This study, reporting outcomes for ■■■ patients with untreated EGFR Exon20 insertion mutation-positive NSCLC, demonstrated that the median OS for this patient population from the pooled RWE sources was under two years, at ■■■ months (95% CI: ■■■-■■■).³ Further details on the NECTAR study are provided in Section B.2.9.

Johnson & Johnson also conducted an observational, UK population-based standing cohort study specifically using data from the NCRAS database specifically (which formed part of the wider NECTAR study). From this study, patients with untreated, EGFR Exon 20 insertion mutation-positive advanced NSCLC were demonstrated to have a lower median OS (19.1 months [95% CI: 7.3-38.5]) compared with patients with common EGFR mutations (24.6 months [95% CI: 22.9-27.8]).¹¹

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Published RWE

A US cohort study conducted by Oxnard et al. (2013) recruited 1,086 patients who underwent EGFR genotyping between 2004–2012. Within the cohort, 27 (9.8%) patients harboured EGFR Exon20 insertion mutations. In this study, it was found that while EGFR Exon20 insertions feature similar clinical features to other lung cancers carrying targeted oncogenes, median survival for these patients (16.5 months) was substantially shorter than lung cancers with common EGFR mutations (33.0 months; $p=0.06$) as well as shorter than EGFR wild-type lung cancers (20.0 months; $p=0.60$).⁶

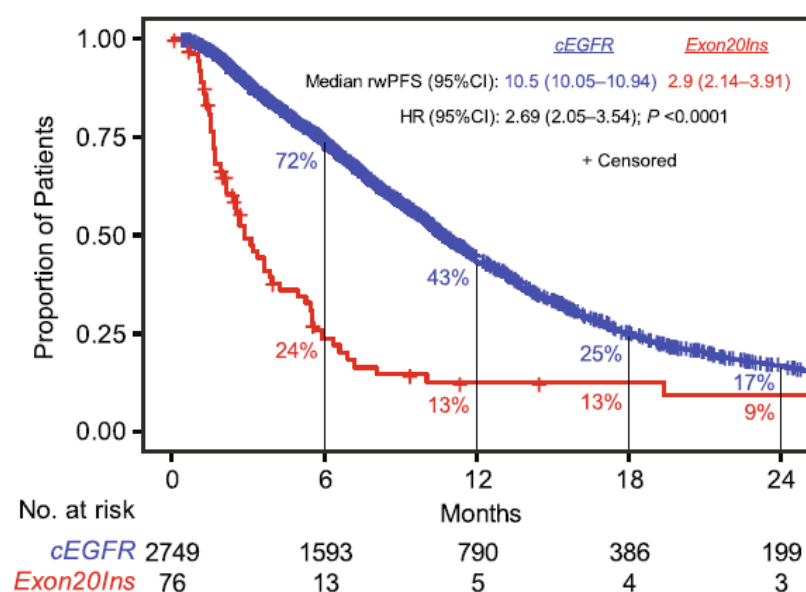
An additional US RWE study, conducted by Bazhenova et al. (2021), investigated real-world clinical outcomes for patients with EGFR Exon20 insertion mutation-positive advanced NSCLC (N=181) versus patients with common EGFR mutations (N=2,833) utilising the Flatiron registry. In this study, real-world PFS was compared for patients with EGFR Exon20 insertion mutations and common EGFR mutations, in subgroups of patients who were receiving *any* first line therapy, or specifically, EGFR TKIs in the first-line setting.¹²

For patients receiving any first-line treatment, median PFS was 5.1 months for the EGFR Exon20 insertion mutation-positive cohort versus 10.3 months for the common EGFR mutation cohort (PFS adjusted HR: 1.93 [95% CI: 1.61-2.31; $p\text{-value}<0.0001$]).

- The discrepancy observed for PFS between the two populations was exacerbated when considering the patients receiving EGFR TKIs in the first-line setting (Figure 3): median PFS was 2.9 months for the EGFR Exon20 insertion mutation-positive cohort versus 10.5 months for the common EGFR mutation cohort, resulting in an adjusted HR of 2.69 (95% CI: 2.05-3.54; $p\text{-value}<0.0001$). This HR equates to around a 170% increase in the risk of progression or death in the EGFR Exon20 insertion mutation-positive NSCLC cohort after initiating EGFR TKI treatment.

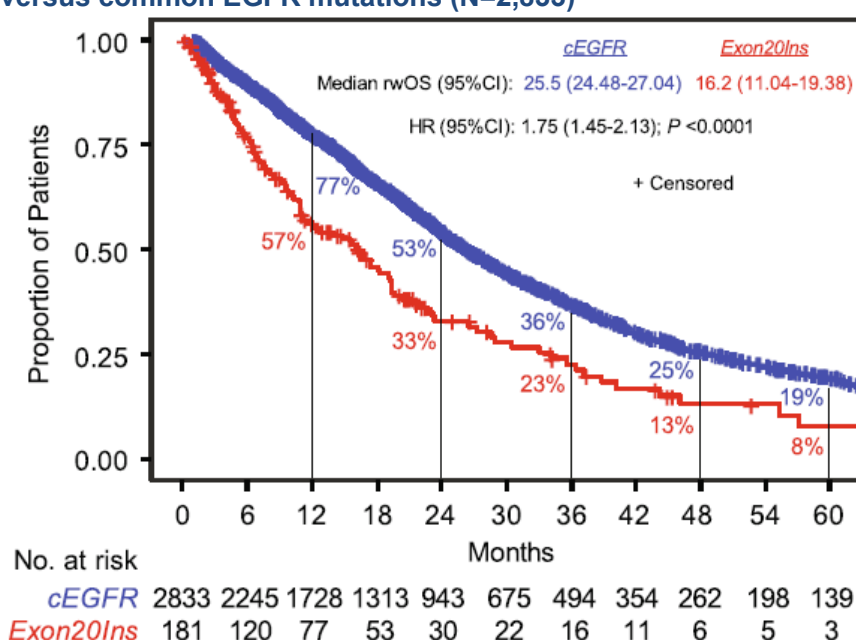
The study also investigated OS in patients receiving any first-line treatment. Median OS for the EGFR Exon20 insertion mutation-positive cohort was 16.2 months versus 25.5 months for the common EGFR mutation cohort (Figure 4), demonstrating that these patients have a 75% increased risk of death compared to patients with more common EGFR mutations (adjusted OS HR: 1.75; 95% CI: 1.45-2.13; $p\text{-value}<0.0001$) across all frontline treatments.¹²

Figure 3: Real-world PFS data for patients with EGFR Exon20 insertion mutations treated with EGFR TKIs at first-line



Abbreviations: CI: confidence interval; cEGFR: common epidermal growth factor receptor mutations; EGFR: epidermal growth factor receptor; Exon20ins: Exon 20 insertion mutations; HR: hazard ratio; PFS: progression-free survival; rwPFS: real-world progression-free survival; TKI: tyrosine kinase inhibitor.
Source: Bazhenova et al. (2021).¹²

Figure 4: Real-world OS data for patients with EGFR Exon20 insertion mutations (N=181) versus common EGFR mutations (N=2,833)



Abbreviations: CI: confidence interval; cEGFR: common epidermal growth factor receptor mutations; EGFR: epidermal growth factor receptor; Exon20ins: Exon 20 insertion mutations; HR: hazard ratio; OS = overall survival; rwOS: real-world overall survival.
Source: Bazhenova et al. (2021).¹²

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Summary

The available evidence, comprised of published literature and RWE studies conducted by Johnson & Johnson, indicate that patients with EGFR Exon20 insertion mutation-positive advanced NSCLC experience a particularly poor prognosis and have substantially poorer survival and progression free outcomes than those with common EGFR mutations.

This discrepancy in outcomes can largely be attributed to the lack of effective targeted treatments in this population compared to other types of common EGFR mutations where efficacious targeted therapies are available.⁷ Additionally, unlike common EGFR mutations, EGFR Exon20 insertion mutations have been associated with *de novo* resistance to EGFR-TKIs, as described in B.1.2.1.⁶⁻⁹ As such, these results highlight the severe unmet need for a targeted and efficacious treatment for patients with untreated EGFR Exon20 insertion mutation-positive advanced NSCLC.

B.1.3.1.2 Epidemiology

Lung cancer is the most common malignancy and the leading cause of cancer death in the UK, with approximately 39,097 patients diagnosed with lung cancer in 2022 in England and Wales.⁴⁵ Lung cancer accounts for 21% of all cancer deaths in the UK, with around 34,800 lung cancer deaths per year (2017–2019 data).⁶⁰ Lung cancer predominantly affects older individuals, with the most recent data from the National Lung Cancer Audit (NLCA) reporting an average age at the time of diagnosis of 74 years.⁴⁵

In the UK, the prevalence of EGFR mutations in any NSCLC histology is estimated to range from 4–17%.^{47, 48} In advanced NSCLC, a retrospective genomic landscape study of 2,052 patients with NSCLC in Ireland found the frequency of EGFR mutations to be 8.8% (n=181) among all patients with NSCLC.⁶¹ Additionally, a RWE study from the NLCA in collaboration with Public Health England estimated the prevalence of EGFR mutations in advanced or metastatic NSCLC be 10.1%.⁶²

The frequency of EGFR Exon20 insertion mutations among European patients with advanced NSCLC was reported to range from 0.3%–1.3%, with little variation across regions within Europe.¹ Additionally, a recent retrospective study of patients with advanced NSCLC in Ireland (n=2,052; June 2017–June 2022) reported similar results showing that EGFR Exon20 insertion mutations were present in 1.3% of advanced NSCLC tumours.⁶¹ Within the UK specifically, the Moore et al. 2021 study found that 1.23% of NSCLC cases harboured an EGFR Exon20 insertion mutation.⁴⁹

EGFR Exon20 insertion mutation-positive NSCLC is more commonly seen in women, people of Asian ethnicity and never-smokers.^{6, 7, 50} Patient demographic data from the NECTAR study and the NCRAS dataset (specific to England) demonstrate that ■■■% and 69.6% of the cohorts were female, respectively. Additionally, ■■■% of patients in the NECTAR study reported no smoking history (these data were not available in the NCRAS database); previous studies indicate that lung cancers in never smokers account for 10–25% of all lung cancers in the overall lung cancer population.^{3, 63}

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B.1.3.1.3 Burden on patients with EGFR Exon20 insertion mutation-positive NSCLC

Two market research studies have been conducted by Johnson & Johnson aiming to understand the unmet needs and societal burdens faced by patients with common EGFR and EGFR Exon20 insertion mutation-positive NSCLC, and their caregivers, in the UK. The first study, conducted in April 2021, interviewed patients with EGFR mutations to capture burden of disease more generally. Overall, 53 patients/supporters participated in an online quality of life survey, 44 in an online stigma survey and 20 in in-depth interviews. Within this patient population, four patients had EGFR Exon20 insertion mutations specifically, accompanied by four caregivers.¹³

Following this, a smaller market research study was conducted by Johnson & Johnson in 2023, specifically focussing on patients with locally advanced or metastatic EGFR Exon20 insertion mutation-positive NSCLC and their caregivers.¹⁴ This market research firstly conducted in-depth interviews with four patients with EGFR Exon20 insertion mutation-positive NSCLC and two carers. Subsequently, an online survey was conducted which involved three patients with EGFR Exon20 insertion mutation-positive NSCLC and one carer (one patient and one carer took part in both stages of the market research).

Disease burden

In-depth interviews with patients with EGFR Exon20 insertion mutation-positive advanced NSCLC in the 2021 market research study found that fatigue, cough, breathlessness, nausea and/or vomiting were the main symptoms of lung cancer and its treatment that impacted upon quality of life.¹³ These results are supported by evidence from another qualitative study, where five oncologists and ten patients with EGFR Exon20 insertion mutation-positive advanced NSCLC were interviewed. Patients reported experiencing considerable symptom burden, including shortness of breath, chest pain and bone/other pain.⁶⁴

The 2021 market research study also revealed the burden imparted to patients with EGFR Exon20 insertion mutation-positive advanced NSCLC by treatments for their disease, with these individuals reporting sickness, diarrhoea and unrelenting fatigue, in addition to mouth ulcers, rash and loss of taste. Such evidence indicates the burden of EGFR Exon20 insertion mutation-positive advanced NSCLC symptoms and the treatments used for this disease, highlighting the unmet need in this patient population for an efficacious and tolerable treatment.¹³

Impact on patients

The humanistic burden of NSCLC is substantial and well-documented, with patients experiencing reduced HRQoL compared with the general population.⁶⁵ As can be expected, greater impairments in HRQoL are observed in patients with late-stage or progressive disease.⁵³

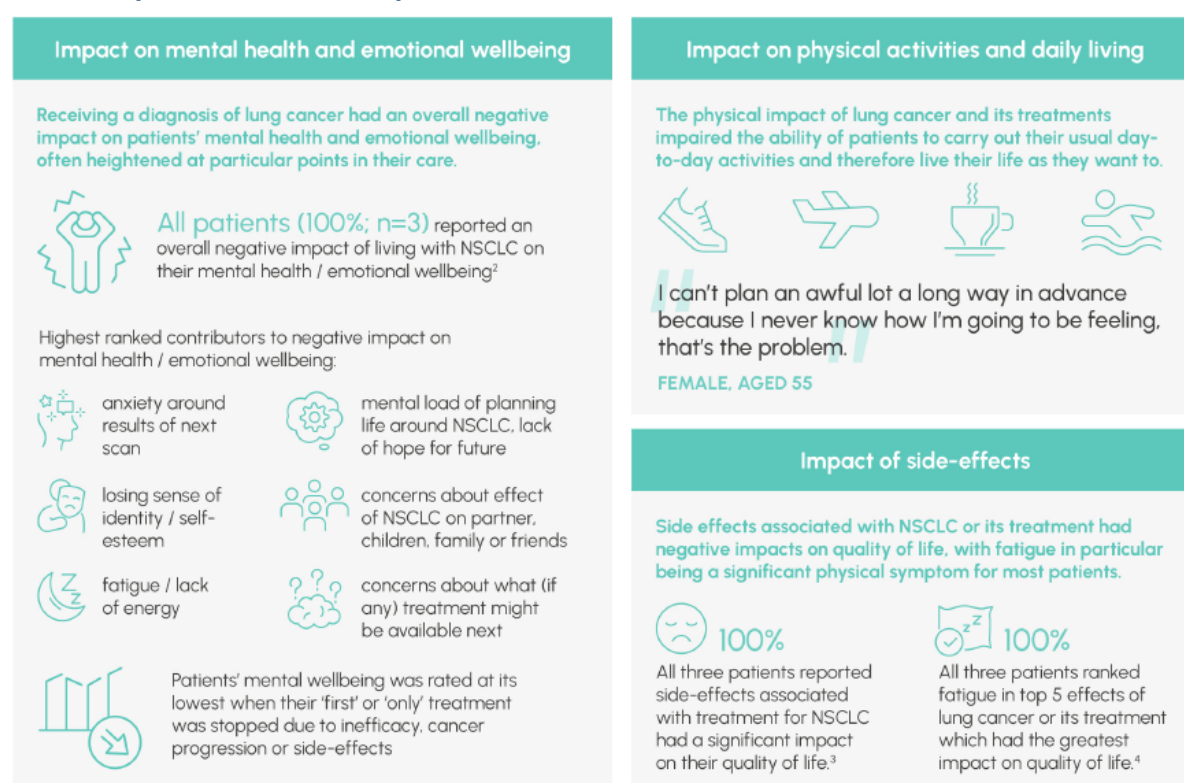
The 2021 market research study conducted by Johnson & Johnson demonstrated that EGFR-mutated NSCLC impacted the activities of 87% patients, including the ability to partake in hobbies (58%), ability to exercise (45%), ability to carry out work or study (43%) and ability to take part in social activities or gatherings (43%).¹³ This was additionally supported by the 2023 EGFR Exon20 insertion mutation-specific market research, in which 100% (3/3) of patients reported an overall negative impact of living with NSCLC. In this study, fatigue was mentioned as having the greatest negative impact on HRQoL.¹⁴

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In-depth interviews and online surveys conducted across both market research studies (2021 and 2023) included discussions on mental health for patients with EGFR Exon20 insertion mutation-positive advanced NSCLC. The interviews indicated that initial diagnosis causes high levels of stress and anxiety, reported to be heightened around the times of scans. In the 2023 study, interviews also revealed patients' anxiety regarding access to treatment for EGFR Exon20 insertion mutation-positive NSCLC. Patients also reported a reduction in self-esteem, becoming less interested in activities they once enjoyed, withdrawing socially and feeling isolated from friends and society. Key results of the 2023 market research study are summarised in Figure 5.^{13, 14}

While this market research is limited to small patient numbers due to the rarity of EGFR Exon20 insertion mutation-positive advanced NSCLC, the findings indicate the severe impact on QoL experienced by these patients due to their disease, with the emotional burden likely exacerbated by the lack of effective treatments when compared to more common types of NSCLC.

Figure 5: Summary of the impact of locally advanced or metastatic EGFR Exon20 insertion mutation-positive NSCLC on patients



Conclusions and quotes based on six interviews with four patients and 2 carers of patients with locally advanced or metastatic NSCLC with EGFR Exon20 insertion mutations. Percentage data are based on online survey among three patients and one carer of a patient with locally advanced or metastatic NSCLC with EGFR Exon20 insertion mutations.

² Scoring ≥ 6 out of 10, where 0 is no negative impact and 10 is a significant negative impact.

Abbreviations: EGFR: epidermal growth factor receptor; NSCLC: non-small cell lung cancer.

Source: Johnson & Johnson Data on File. Unmet needs in EGFR+ NSCLC Patients Market Research. (2023).¹³

Impact on caregivers/supporters

In addition to the burden on patients diagnosed with EGFR-mutated NSCLC, caregivers of patients are also shown to be negatively impacted. In the 2021 market research study, 94% of

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caregivers reported that supporting someone with EGFR-mutated NSCLC had an impact on their quality of life, having both an emotional impact and affecting their ability to participate in everyday life.¹³ In particular, the majority of caregivers felt anxious and worried (92%) as well as sad (69%) and stressed (54%) following news of their patient's diagnosis.¹³ The 2023 market research study interviewing caregivers of patients with EGFR Exon20 insertion mutation-positive NSCLC specifically revealed high time and resource burdens supporting patients with childcare, household tasks and transport requirements, with impacts on carers' own mental health and wellbeing also being reported.

Economic burden of disease

Available UK-based evidence on the economic burden of lung cancer is limited. However, available evidence supports that NSCLC is a costly disease: a 2015 study utilising administrative databases in France, Germany and England studying patients of any NSCLC mutation type reported costs of €15,787 per patient within the first year of follow up in England, based on treatment costs (accounting for €8,593 per patient) and resource use data (inpatient and outpatient costs).⁶⁶ Advanced NSCLC is also associated with a substantial cost burden to patients themselves; a cross-sectional study conducted across France, Germany and Italy in 1,030 patients with advanced NSCLC found that these patients incurred a mean annual wage loss of €2,077 and productivity losses of €1,484.⁶⁷

A recent US study (Vadagam et al. 2024) investigated healthcare resource use (HRU) and costs for patients with advanced EGFR mutated NSCLC, including a subgroup of patients with EGFR Exon20 insertion mutations specifically. The study found that, of the 13 patients with EGFR Exon20 insertion-mutation positive NSCLC, total healthcare costs were substantially higher (\$27,069) than common EGFR mutations (Exon 19 deletion: \$17,482; L858R substitutions in Exon21: \$17,763) with costs for this subgroup driven by medical service costs including hospitalisation. While the sample size for this study is limited and in a US population, findings suggest that the economic burden for patients with EGFR Exon20 insertion mutation-positive NSCLC may be more substantial than patients with more common forms of advanced NSCLC.⁶⁸

In summary, available data on patients with NSCLC demonstrates that high costs will be incurred during treatment, particularly for the treatment of adverse events, with patients also expected to experience out-of-pocket costs and productivity losses.

B.1.3.1.4 Societal perceptions of lung cancer

Patients with lung cancer experience an added burden from developing an illness that the public recognises as directly associated with smoking behaviours.²⁷ This is particularly evident in the case of patients with EGFR Exon20 insertion mutation-positive NSCLC, as this mutation disproportionately affects never-smokers.⁶ The 2021 market research study conducted by Johnson & Johnson showed that 93% of patients with EGFR-mutated NSCLC feel that people are less sympathetic to lung cancer than other cancers because it is perceived as being linked with smoking.¹³

As a result, patients may be reluctant to share their diagnosis with their employers and wider society for fear of being seen as responsible for their illness. This perceived bias against patients with lung cancer also affects interactions between patients and healthcare professionals (HCPs), with some patients reporting feeling uncomfortable communicating their symptoms, which can lead to delays in presentation, diagnosis and treatment.⁶⁹

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B.1.3.2 Clinical pathway of care

The goal of treatment in advanced NSCLC is to delay disease progression, prolong survival and maintain quality of life, with the choice of therapy depending on the presence or absence of driver mutations and factors such as disease staging and volume, and histology.⁴

As described in Table 2, patients routinely undergo genetic screening to identify the presence of driver mutations that are amenable to targeted therapy. EGFR Exon20 insertion mutations are included in the National Genomic Test Directory for cancer under the EGFR gene panel as part of routine clinical practice in the UK.²⁶ NGS is considered the most appropriate method of diagnostic testing for these patients.⁷⁰

Treatment guidelines for the management of lung cancer in the UK are provided by the NICE lung cancer diagnosis and management guidelines (NG122).⁴ While these guidelines previously included guidance for patients with EGFR Exon20 insertion mutation-positive NSCLC, this specific guidance has since been removed following the withdrawal of mobocertinib by the manufacturer in 2024, reiterating the lack of any SoC for this patient population in the UK, and exacerbating the significant unmet need in this patient population for an effective targeted treatment (see B.1.3.2.2).¹⁷

ESMO guidance published in 2021 indicated that the first-line management of patients with EGFR Exon20 insertion mutation-positive NSCLC should be similar to treatment of EGFR wild-type lung cancer (i.e., recommending platinum-based chemotherapy with pemetrexed), due to the resistance of EGFR Exon20 insertion mutations to EGFR TKIs. The addition of IO (pembrolizumab) to chemotherapy is also recommended in this guidance. At the time of this consensus, amivantamab and mobocertinib were still undergoing investigation in a first-line setting.⁷⁰ However, more recent ESMO living guidelines, published in 2023, now recommend amivantamab monotherapy for patients with EGFR Exon20 insertion-mutation positive NSCLC, after prior chemotherapy.⁷⁰ Furthermore, amivantamab in combination with carboplatin and pemetrexed is recommended for patients with EGFR Exon20 insertion mutations in the updated National Comprehensive Cancer Network (NCCN; US).⁷¹

There are a number of EGFR TKIs that are recommended by NICE (afatinib, dacomitinib, erlotinib, gefitinib and osimertinib) for the first-line treatment of EGFR-mutated NSCLC.⁴ However, these have not been recommended specifically for patients with EGFR Exon20 insertion mutations. Further, as detailed above, EGFR Exon20 insertion mutations feature *de novo* resistance to these TKI regimens, thus leading to minimal to no usage in the UK. As such, prescribing EGFR TKIs to patients with EGFR Exon20 insertion mutation-positive advanced NSCLC is not considered best practice, as confirmed by UK clinical experts.⁶⁻⁹

In the absence of UK-specific treatment guidelines or targeted treatment options available for patients with treatment naive EGFR Exon20 insertion mutations via the NHS, there is no established SoC in the UK, leading to variable practice between centres and clinicians.²²

B.1.3.2.1 Treatment pathway

As described in Table 1, there is currently no SoC for patients with EGFR Exon20 insertion mutation-positive advanced NSCLC in UK clinical practice. This is, in part, due to the absence of any formal guidance and any targeted treatments recommended specifically for these patients. In

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order to establish the treatments expected to be received by these patients in the first-line setting, multiple sources of evidence have been used in this submission:

1. An observational, population-based standing cohort study in England, using the NCRAS database: this study identified 24 patients in England with EGFR Exon20 insertion mutation-positive advanced NSCLC in the first-line setting
2. A non-interventional, retrospective, observational cohort study using the NCRAS (England), ESME (France), COTA (US) and ConcertAI (US) databases: this larger study identified █ patients with EGFR Exon20 insertion mutation-positive advanced NSCLC in the first-line setting
3. Comprehensive clinical validation of the treatment landscape for patients with EGFR Exon20 insertion mutation-positive advanced NSCLC in England and Wales provided by UK clinical experts consulted as part of three advisory boards (June 2023, March 2024 and August 2024)^{3, 5, 22, 23}

The NCRAS database study covered patients in England who were diagnosed with NSCLC between 2016 and 2021, with follow-up of patients ending in March 2023. The NCRAS data indicated that, out of 24 patients in England who had untreated EGFR Exon20 insertion mutation-positive advanced NSCLC, 54.2% (n=13) received platinum-doublet chemotherapy, 16.7% (n=4) received pembrolizumab with platinum-doublet chemotherapy, 20.8% (n=5) received pembrolizumab monotherapy and 8.3% (n=2) received an EGFR TKI. While these data are specific to England, a fundamental limitation of the results is the exceedingly small associated sample size (24 patients), which may be attributed to the rarity of the mutation, as well as the limitations associated with PCR in successfully identifying EGFR Exon20 insertions given mutation testing with NGS did not enter routine clinical practice testing until 2021.

The larger NECTAR study provides insight into first-line treatments received by patients with EGFR Exon20 insertion mutation-positive advanced NSCLC across England, France, and the US. These data indicated that █% of patients in the cohort received treatment with a platinum-based chemotherapy, █% of patients received a platinum-based chemotherapy with an IO, █% of patients received a single-agent EGFR TKI, █% of patients received a platinum-based chemotherapy with a vascular endothelial growth factor (VEGF) inhibitor, █% of patients received a single-agent IO, and the remaining █% of patients received an 'other' type of therapy regimen.³ As such, whilst clinical management is observed to vary across geographies, likely due to the lack of specific guidance or targeted therapies available for this patient population, platinum-based chemotherapy and IO with platinum-based chemotherapy emerge as two commonly used treatments within these datasets.

To supplement these RWE sources, UK clinical experts were consulted across three advisory boards. During the May 2024 advisory board, clinical experts agreed through a discussion-based consensus that platinum-based chemotherapy was received by around 70% of patients in UK clinical practice in the first-line setting, with carboplatin and pemetrexed noted as the dominant regimen. IO combination therapy was reported to be used in around 30% of patients.^{5, 22, 23}

Specifically, clinical experts stated that pembrolizumab is the only IO therapy used in combination with chemotherapy (carboplatin and pemetrexed).²²

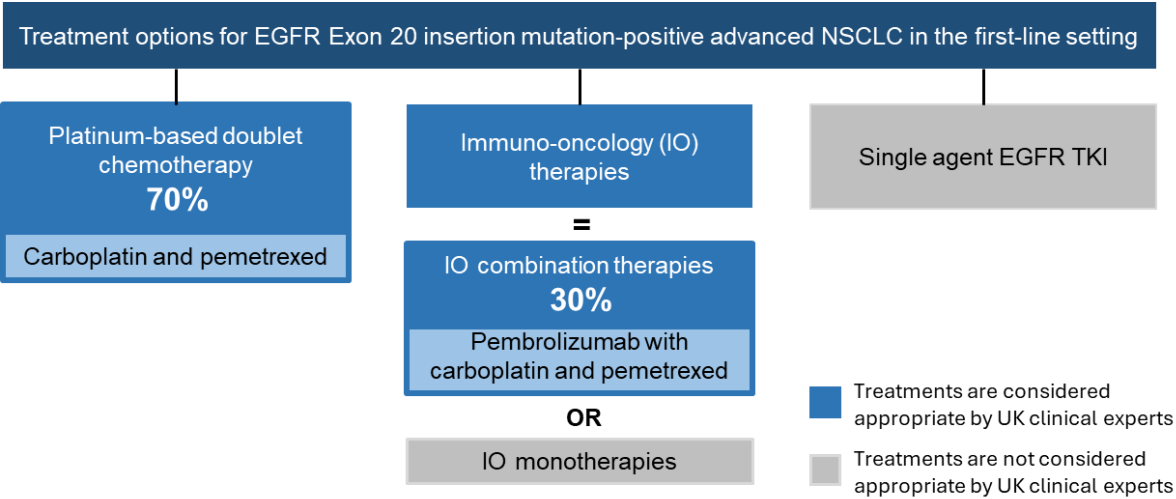
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Consistent feedback gained across the advisory board meetings indicates that IO monotherapy should not be prescribed in patients with EGFR Exon20 insertion mutations, and it is against best practice to use these treatments. The UK clinical experts explained that the motivation behind prescribing IO combination therapy is the potential added benefit of IO agents in combination with platinum-based chemotherapy (although there is a paucity of data on the efficacy of IO agents within patients with EGFR Exon20 insertion mutations), combined with the low toxicity of IOs in the EGFR Exon20 insertion mutation-positive advanced NSCLC population. Single agent IOs, without chemotherapy, should not therefore be used for this population due to a perceived lack of efficacy, though non-specialist clinicians with lesser knowledge of this specific mutation may prescribe this regimen.^{3, 5, 22, 23}

The clinical experts also confirmed that EGFR TKIs should not be used for patients with EGFR Exon20 insertion mutations, due to their established lack of efficacy in this population as described above; prescription of these treatments is also against best practice.³⁹

As such, the treatment landscape for patients with untreated, EGFR Exon20 insertion mutation-positive advanced NSCLC, informed by these evidence sources, is illustrated in Figure 6 below.

Figure 6: Current treatment options for patients with EGFR Exon20 insertion mutation-positive advanced NSCLC in UK clinical practice



Abbreviations: EGFR: epidermal growth factor receptor; IO: immuno-oncology; NCRAS: National Cancer Registration and Analysis Service; NSCLC: non-small cell lung cancer; TKI: tyrosine kinase inhibitor.
Source: Treatment percentages taken from advisory boards conducted by Johnson & Johnson.^{5, 22, 23}

In summary, the set of relevant comparators to compare the cost-effectiveness of amivantamab-chemotherapy has been primarily informed by UK clinical expert opinion from UK advisory boards and RWE from the larger NECTAR study. Considering the available evidence, platinum-based chemotherapy (carboplatin and pemetrexed) with or without IO (pembrolizumab) are considered as the relevant comparators in UK clinical practice.

However, as there is no dominant regimen, both treatments are expected to be displaced by amivantamab-chemotherapy, if recommended for use in UK clinical practice. Therefore, a weighted comparator arm within the economic model was used in this submission, with further details on this approach presented in Section B.3.2.3.

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B.1.3.2.2 Unmet need in patients with EGFR Exon20 insertion mutation-positive NSCLC

Half of patients with NSCLC present with stage IV disease at diagnosis which, regardless of mutation status, is associated with a poor prognosis.⁴⁵ As described in Section B.1.3.1, patients with EGFR Exon20 insertion mutation-positive advanced NSCLC have a poorer prognosis compared to patients with common EGFR mutations due to no effective treatment options being available for this genotype.⁶

The prognosis in patients with EGFR Exon20 insertion mutation-positive advanced NSCLC is poor; data from the NECTAR study indicate that the median OS is only 19.8 months. Additionally, the prognosis is worse compared to patients with common EGFR mutations; a US RWE study (Bazhenova et al. 2021) has reported that survival in patients with EGFR Exon20 insertion mutation-positive advanced NSCLC is worse compared to patients with more common EGFR mutations (16.2 months vs 25.5 months).^{3, 12}

As discussed in B.1.3.2.1, no NICE guidance is available for patients with EGFR Exon20 insertion mutation-positive advanced NSCLC, and currently no targeted treatments are recommended by NICE for this population, highlighting the substantial need for a new targeted and effective treatment in UK clinical practice for these patients.

Overall, an urgent unmet need exists for an efficacious, targeted therapy that can improve survival in patients with untreated EGFR Exon20 insertion mutation-positive advanced NSCLC, relieving the substantial disease burden experienced by these patients. The results from the PAPILLON Phase 3 clinical trial show amivantamab-chemotherapy addresses the unmet need in this patient population, meeting its primary endpoint by significantly improving PFS ($p < 0.0001$) as assessed by BICR, compared with chemotherapy: 11.37 months versus 6.70 months, respectively (HR: 0.40; 95% CI: 0.30-0.53).¹⁰

The value of this outcome is supported by a market research study conducted by Johnson & Johnson in 2023, which revealed that the ability to delay progression was of great importance to patients and that patients would find a new therapy regimen acceptable if it delayed progression by around five months beyond what is currently achieved with chemotherapy.¹⁴

A positive recommendation from NICE for amivantamab-chemotherapy would make this the only effective treatment specifically recommended for patients with untreated EGFR Exon20 insertion mutation-positive advanced NSCLC. This would establish a long sought SoC for patients in UK clinical practice, which in turn would transform the lives of patients and their carers. This would also narrow the gap between the clinical benefit that patients with EGFR Exon20 insertion mutation-positive advanced NSCLC can achieve compared to patients with common EGFR mutations, where efficacious treatment options are routinely available.

B.1.4 Equality considerations

There is an important equality consideration with respect to the stigma of lung cancer. Lung cancer (of all kinds) is associated with substantial stigma, for example the perception that it is in a sense 'self-inflicted' due to the public recognising the link between lung cancer and smoking.²⁷ This stigma issue is compounded when considering EGFR Exon20 insertion mutations specifically. EGFR Exon20 insertion mutations are more likely than other NSCLC mutations to be associated with women, never-smokers, and is also particularly associated with being of Asian

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ethnicity.^{7, 72} The stigma associated with lung cancer may be particularly severe for a never-smoker, and there is some evidence that symptoms of lung cancer are stigmatised in Asian communities, which could reinforce the treatment delaying behaviour seen in lung cancer more generally in this patient population.^{28, 69}

B.2 Clinical effectiveness

Clinical effectiveness summary

PAPILLON is a randomised controlled trial (RCT) that forms the principal evidence base for amivantamab-chemotherapy in untreated EGFR Exon20 insertion mutation-positive advanced NSCLC

- The PAPILLON trial is a Phase 3, randomised, open-label multicentre study that provides the main clinical evidence base for amivantamab with carboplatin and pemetrexed (hereafter referred to as 'amivantamab-chemotherapy') compared with carboplatin and pemetrexed (hereafter referred to as 'chemotherapy') in patients with untreated EGFR Exon 20 insertion mutation-positive advanced NSCLC.⁷³

The primary endpoint of PAPILLON was met, with amivantamab-chemotherapy demonstrating a clinically meaningful and statistically significant improvement in BICR-assessed PFS compared to chemotherapy. The efficacy of amivantamab-chemotherapy in this population was supported by several key secondary endpoints and patient reported outcomes

- The primary endpoint in the PAPILLON trial was PFS assessed by BICR using Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 guidelines, with secondary endpoints including OS, objective response rate (ORR), DOR, TTST, PFS2 and TTSP.⁷³
- The efficacy data for this submission are informed from the full analysis set at the 3rd May 2023 data cut-off (DCO); OS data are additionally presented for a further DCO (31st October 2023).^{21, 73}
- Results from the PAPILLON trial demonstrate that amivantamab-chemotherapy is an efficacious treatment regimen resulting in more durable responses compared to chemotherapy.⁷³
 - The primary endpoint (PFS) by BICR was met, demonstrating a 60% reduction in the risk of disease progression or death in patients in the amivantamab-chemotherapy arm compared with the chemotherapy arm: median PFS was 11.4 vs 6.7 months (HR: 0.40; 95% CI: 0.30-0.53; p<0.0001). These results were consistent with PFS assessed by investigator: 12.9 vs 6.9 months (HR, 0.38; 95% CI: 0.29-0.51; P<0.0001).
 - At the 3rd May 2023 DCO, there was a strong trend towards an OS benefit in the amivantamab-chemotherapy arm (HR=0.67 [95% CI: 0.42-1.09]; p=0.1056), despite a significant proportion of patients (65/107 [61%]) in the chemotherapy arm receiving amivantamab monotherapy after BICR-confirmed disease progression, as allowed in the study protocol, but not available through routine NHS commissioning in the second-line setting.
 - At the additional OS data cut (31st October 2023), median OS for amivantamab-chemotherapy was not reached (95% CI: 28.3-NE); median OS was 28.6 months (95% CI: 24.4-NE) for the chemotherapy treatment arm (HR=0.76 [95% CI: 0.50-1.14]; p=0.1825).²¹ At this DCO, the number of patients receiving amivantamab monotherapy after BICR-confirmed progression had increased to 78/ [redacted] (representing [redacted] of patients who experienced disease progression).²¹
 - The OS benefit observed in the PAPILLON trial is reinforced by results from the indirect treatment comparison (ITC) between amivantamab-chemotherapy (from PAPILLON) versus chemotherapy (from the NECTAR real-world evidence [RWE] study) using the average treatment effect in the treated (ATT)-weighting of individual patient level data, which estimated an OS HR of [redacted] Median OS ([redacted]) of chemotherapy in PAPILLON (following adjustment for cross-over),

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has high face validity as closely aligns with median OS () of chemotherapy in RWE (after ATT-weighting).

- At the 3rd May 2023 DCO, there was a significantly higher percentage of responders, as assessed through ORR by BICR, in the amivantamab-chemotherapy arm (111 patients [73.0%]) compared with the chemotherapy arm (72 patients [47.4%]).
- Amivantamab-chemotherapy also showed a reduced risk of second disease progression and TTSP compared with chemotherapy.
- HRQoL was comparable between the amivantamab-chemotherapy and chemotherapy arm, suggesting that the addition of amivantamab to platinum-based chemotherapy does not negatively impact patients' HRQoL.⁷⁴

Safety data from the PAPILLON trial demonstrate that amivantamab-chemotherapy is well-tolerated

- Safety data are reported for the safety population of the PAPILLON trial (amivantamab-chemotherapy: N=151; chemotherapy: N=155) at the 3rd May 2023 DCO:⁷³
 - While Grade 3 or higher treatment-emergent adverse events (TEAEs) were more commonly observed in the amivantamab-chemotherapy arm (114 patients [75.5%]) compared with the chemotherapy arm (83 patients [53.5%]), these events were primarily driven by TEAEs in line with the known safety profile of amivantamab.
 - Grade 5 (fatal) TEAEs related to study treatment were reported for three patients in the amivantamab-chemotherapy arm (cardiorespiratory arrest, COVID-19 and sepsis), and two in the chemotherapy arm (sepsis and unknown cause).
- TEAEs were manageable in both arms through treatment interruptions and dose reductions, with a low discontinuation rate of all study treatments due to AEs. Overall, amivantamab with carboplatin and pemetrexed was shown to be well-tolerated, featuring safety profiles consistent with the individual components, with no new safety signals.

In an ITC, utilising evidence from the PAPILLON trial and real-world evidence sources, amivantamab-chemotherapy was found to be superior to pembrolizumab-chemotherapy in terms of OS and TTNT

- In the absence of randomized controlled trials (RCTs) specifically evaluating pembrolizumab-chemotherapy in patients with EGFR Exon20 insertion mutation-positive advanced NSCLC, comparative data was obtained from RWE (NECTAR study).
- Since there are no head-to-head data available for amivantamab-chemotherapy versus pembrolizumab in combination with carboplatin plus pemetrexed (referred to as pembrolizumab-chemotherapy), an ITC was conducted using NECTAR study and the PAPILLON trial.
 - The average treatment effect of the treated (ATT)-weighted results demonstrated that amivantamab-chemotherapy results in a % reduction in the risk of initiating next treatment versus pembrolizumab-chemotherapy (adjusted time to next treatment [TTNT] HR: [95% CI:]; p-value<) and a statistically significant % reduction in the risk of death (OS HR: [95% CI:]; p-value<) versus pembrolizumab-chemotherapy

The results from PAPILLON and the indirect comparison illustrate that amivantamab-chemotherapy fulfils an unmet need for an efficacious and tolerable therapy for patients with EGFR Exon20 insertion mutation-positive advanced NSCLC in UK clinical practice

- The results of the Phase 3 PAPILLON trial and the ITC demonstrate that amivantamab-chemotherapy represents an efficacious and tolerable treatment option for patients with untreated EGFR Exon20 insertion mutation-positive advanced NSCLC compared with treatments currently used in UK clinical practice for this patient population. Amivantamab-

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chemotherapy is thus expected to fulfil a substantial unmet need for a targeted treatment option in this patient population, for whom no such options currently exist in UK clinical practice.

B.2.1 Identification and selection of relevant studies

A *de novo* clinical systematic literature review (SLR) was conducted in January 2021 to identify relevant evidence on clinical efficacy and safety outcomes in patients with EGFR Exon20 insertion mutation-positive advanced NSCLC. This SLR was subsequently updated in September 2021, February 2022, September 2023, March 2024, and June 2024 to ensure recently published relevant evidence has been identified.

The SLR was designed to capture data derived from RCTs, non-RCTs and observational studies, and considered baseline characteristics of patients, efficacy and safety of treatments, HRQoL and patient-reported outcomes (PRO) data as relevant outcomes. The most recent updates were conducted to identify evidence simultaneously for EGFR Exon20 insertion mutations and common EGFR mutation subgroups in addition to different treatment settings; however, results were reported separately for studies assessing treatments in the first-line setting for patients with EGFR Exon20 insertion mutations for the purposes of this submission.

The SLR was conducted according to a pre-specified protocol and performed in accordance with the methodological principles of conduct for systematic reviews as detailed in the York Centre for Reviews and Dissemination (CRD) Handbook recommended by NICE.⁷⁵

Full details of the SLR strategy, study selection and results are presented in Appendix D.

B.2.2 List of relevant clinical effectiveness evidence

Of the 91 publications reporting on 60 unique studies in the first-line setting for EGFR Exon 20 insertion mutation-positive NSCLC identified in the SLR, the PAPILLON trial was the only identified study reporting clinical evidence for amivantamab with carboplatin and pemetrexed in the patient population of interest to this submission: adult patients with untreated EGFR Exon20 insertion mutation-positive advanced NSCLC.

As such, the PAPILLON registrational trial represents the main body of evidence for amivantamab in the patient population specified in the decision problem of this submission. As the PAPILLON trial met its primary endpoint of PFS by BICR, marketing authorisation by the MHRA was granted on the 15th of July 2024 for amivantamab in combination with carboplatin and pemetrexed for the first-line treatment of adult patients with advanced NSCLC with activating EGFR Exon 20 insertion mutations.²¹

The PAPILLON trial is a Phase 3, randomised, open-label study investigating the safety and efficacy of amivantamab in combination with carboplatin and pemetrexed compared with carboplatin and pemetrexed as a treatment for patients with untreated, advanced NSCLC with EGFR Exon20 insertion mutations. An overview of the key evidence provided by the PAPILLON trial is presented in Table 3, with the methodology and results of the trial presented from Section B.2.3 onwards.

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Published results from the PAPILLON trial are available from the Zhou *et al.* publication,¹⁰ with the clinical study report (CSR; 3rd May 2023 DCO) also used to populate this submission.⁷³

Table 3: Clinical effectiveness evidence

Study	PAPILLON (NCT04538664)
Study design	Phase 3, randomised, open-label, multicentre study
Population	Adult patients (aged ≥18 years) with treatment-naïve locally advanced or metastatic NSCLC characterised by EGFR Exon20 insertion mutations
Intervention(s)	• Amivantamab ○ 1,400 mg (1,750 mg if body weight is ≥ 80 kg) by intravenous (IV) infusion once weekly from Weeks 1 to 4 ○ Week 1 – split infusion on Day 1 and Day 2 ○ Weeks 2 to 4 – infusion on Day 1 ○ 1,750 mg (2,100 mg if body weight is ≥ 80 kg) every 3 weeks starting at Week 7 onwards • Pemetrexed ○ 500 mg/m² (with vitamin supplementation) on Day 1 of each 21-day cycle ○ Given in combination with carboplatin for the first 4 cycles, and then as maintenance monotherapy until disease progression • Carboplatin ○ Carboplatin area under the curve (AUC) 5 on Day 1 of each 21-day cycle, for up to 4 cycles
Comparator(s)	Carboplatin and pemetrexed chemotherapy, administered as outlined above and as per clinical practice guidelines
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	N/A
Reported outcomes specified in the decision problem^a	<u>Primary outcome:</u> • PFS by BICR <u>Key secondary outcomes:</u> • ORR • DOR • OS • TTST • PFS after first subsequent therapy (PFS2) • TTSP

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Study	PAPILLON (NCT04538664)
	<u>Exploratory outcomes:</u> • TTD <u>Safety outcomes:</u> • Incidence and severity of AEs <u>HRQoL outcomes:</u> • EuroQol five-dimensional descriptive system (5-level version) (EQ-5D-5L) • European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC-QLQ-C30) • Patient-Reported Outcomes Measurement Information System – Physical Function (PROMIS-PF)

^a Endpoints in bold are those used to inform the cost-effectiveness model.

Abbreviations: AE: adverse event; AUC: area under the concentration-time curve; DOR: duration of response; EGFR: epidermal growth factor receptor; EORTC-QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; Exon20ins: exon 20 insertions; HRQoL: health-related quality of life; N/A: not applicable; NSCLC: non-small cell lung cancer; ORR: objective response rate; OS: overall survival; PROMIS-PF: Patient-Reported Outcomes Measurement Information System – Physical Function; PFS: progression-free survival; PFS2: PFS after subsequent therapy; TTSP: time to symptomatic progression; TTST: time to subsequent therapy.

Source: Johnson & Johnson PAPILLON CSR 2023.⁷³

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 Trial design

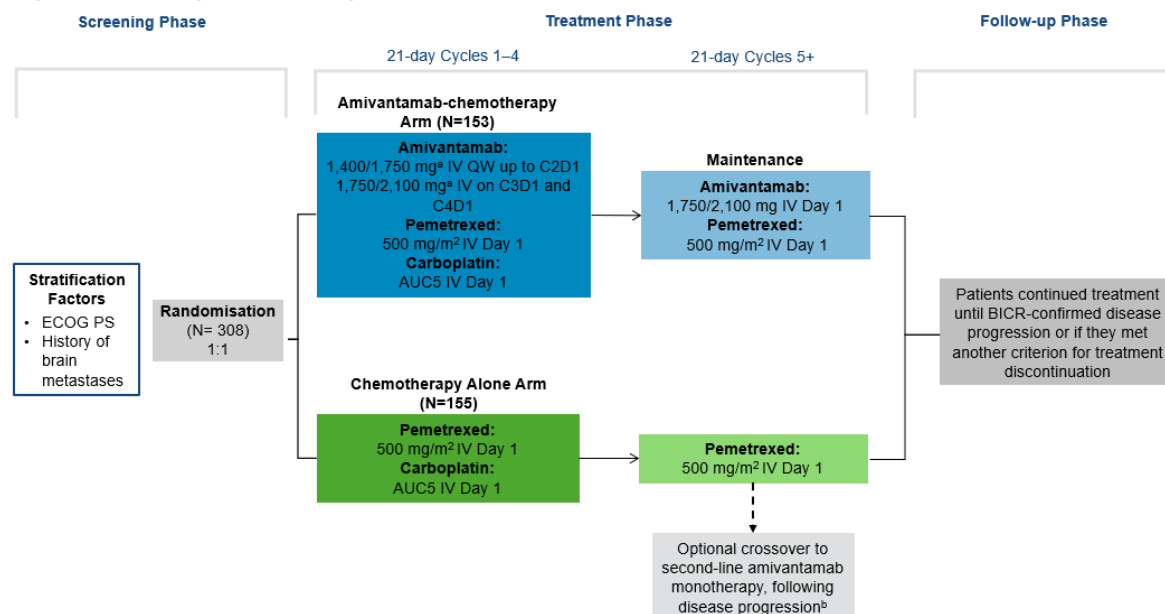
The clinical evidence base for amivantamab with carboplatin and pemetrexed as a treatment for adult patients with untreated EGFR Exon20 insertion mutation-positive advanced NSCLC is based on the registrational PAPILLON trial. The PAPILLON trial is an ongoing, randomised, open-label, multicentre, Phase 3 study which compares amivantamab in combination with carboplatin and pemetrexed (hereafter referred to as the amivantamab-chemotherapy arm) versus carboplatin with chemotherapy (the chemotherapy arm) for patients with treatment-naïve, locally advanced or metastatic EGFR Exon20 insertion mutation-positive NSCLC.

In the PAPILLON trial, patients were randomly assigned in a 1:1 ratio, based on a computer-generated randomisation schedule, to receive amivantamab-chemotherapy or chemotherapy in 21-day cycles. Randomisation was stratified according to Eastern Cooperative Oncology Group (ECOG) performance status score (0 or 1) and history of brain metastases (yes or no). Prior EGFR TKI use was removed as a stratification factor for the primary analysis as only four patients had received prior EGFR TKI monotherapy (Table 9) treatment blinding was not feasible in this trial, due to differences in administration, pre-medication requirements and safety profiles of the two regimens.^{10, 73}

The study design of the PAPILLON trial is presented in Figure 7.

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Figure 7: Design of the registrational PAPILLON trial (NCT04538664)



^a Doses are shown by body weight (<80 kg/≥80 kg).

^b Treatment crossover was only permitted following confirmation of disease progression by BICR; dosing for second-line amivantamab monotherapy is the same as in the main treatment phase of the study.

Abbreviations: AUC: area under the curve; BICR: blinded independent central review; C: Cycle; D: Day; ECOG: Eastern Cooperative Oncology Group; IV: intravenous; PS: performance status.

Source: Zhou *et al.* (2023).¹⁰

As outlined in Figure 7, the PAPILLON trial is comprised of a screening phase, a treatment phase and a follow-up phase. The screening phase was performed 28 days before randomisation, in which patients were stratified and randomly assigned to either the amivantamab-chemotherapy arm or the chemotherapy arm.

The treatment phase for each patient started at Cycle 1 Day 1 and continued in 21-day cycles until the 'end of treatment' visit (approximately 30 days after discontinuation of study treatment). Patients were permitted to discontinue study treatment upon documented radiographic (RECIST v1.1) disease progression (confirmed by BICR) or if they met another criterion for discontinuation of study treatment. Continuation of study treatment after confirmed disease progression was allowed after approval from the medical monitor, if the investigator believed the patient was deriving clinical benefit.

Patients who discontinued their assigned study treatment for any reason were followed for subsequent therapy, disease status, survival and symptomatic progression in the follow-up phase. The follow-up phase started after the 'end of treatment' visit and continued until the end of study, death, loss to follow-up, or withdrawal of consent from participation by the patient, whichever came first.

Additionally, patients randomised to the chemotherapy arm were given the option to treatment switch to receive amivantamab monotherapy (on an every three-week regimen as per the randomised treatment phase), following BICR-confirmed disease progression. [REDACTED]

[REDACTED] This treatment switch phase of the study was not randomised or controlled; however, the study assessment and procedures during the treatment switch phase were generally aligned

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with those from the randomised treatment phase. Disease assessments were, however, performed by the investigator only.⁷³ Further details on treatment switching in the PAPILLON trial are presented in Section B.2.4.3.

B.2.3.2 Trial methodology

A summary of the PAPILLON trial methodology is presented in Table 4.

Table 4: Summary of the PAPILLON trial methodology

Trial name	PAPILLON (NCT04538664)
Location	International: 131 sites across 25 countries, including three UK sites
Trial design	Phase 3, randomised, open-label, multicentre study
Population	Adult patients (aged ≥18 years) with treatment-naïve locally advanced or metastatic NSCLC with EGFR Exon20 insertion mutations
Eligibility criteria for patients	Key inclusion criteria: • Adult patients (≥18 years of age) • Histologically- or cytologically-confirmed locally advanced or metastatic, non-squamous NSCLC with documented primary EGFR Exon20 insertion mutations • Must have measurable disease according to RECIST v1.1 • An ECOG performance status of 0 or 1 • Adequate organ and bone marrow function, as assessed by laboratory measurements of haemoglobin, absolute neutrophil count, platelets, alanine aminotransferase, aspartate aminotransferase, total bilirubin and serum creatine Key exclusion criteria: • Have received prior systemic treatment for locally advanced or metastatic disease (with the exception of a few regimens outlined in the protocol)⁷⁶ • Evidence of synchronous NSCLC disease (as suggested by genetic characterisation or radiographic appearance) • Untreated or active brain metastases • History of leptomeningeal disease • A history of spinal cord compression that has not been treated definitively with surgery or radiation • Uncontrolled tumour-related pain • Medical history of ILD, including drug-induced ILD, or radiation pneumonitis • An active malignancy other than the disease being treated under the study • A history of clinically significant cardiovascular disease • Positive hepatitis B, C, or other clinically active infectious liver disease at screening • Received an investigational drug (not including anti-cancer therapy) within 6 weeks before randomisation or had major surgery within 4 weeks of randomisation • Uncontrolled inter-current illness

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	The full list of inclusion and exclusion criteria are presented in the PAPILLON protocol. ⁷⁶
Study intervention and administration	Amivantamab administered in combination with carboplatin and pemetrexed, with all components administered via IV infusion at the following doses: • Amivantamab ○ 1,400 mg (1,750 mg if body weight is $\geq$ 80 kg) by intravenous (IV) infusion once weekly from Weeks 1 to 4 ○ Week 1 – split infusion on Day 1 and Day 2 ○ Weeks 2 to 4 – infusion on Day 1 ○ 1,750 mg (2,100 mg if body weight is $\geq$ 80 kg) every 3 weeks starting at Week 7 onwards • Pemetrexed ○ 500 mg/m² (with vitamin supplementation) on Day 1 of each 21-day cycle ○ Given in combination with carboplatin for the first 4 cycles, and then as maintenance monotherapy until disease progression • Carboplatin ○ Carboplatin AUC5 on Day 1 of each 21-day cycle, for up to 4 cycles
Comparator(s)	Carboplatin and pemetrexed chemotherapy, administered as outlined above and as per clinical practice guidelines
Permitted and disallowed concomitant medication	Investigators were allowed to prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care, except for those listed as prohibited therapies (see below). Corticosteroids, folic acid and Vitamin B12, were administered concomitantly with pemetrexed according to local prescribing information or per standard local practice. Further medications allowed or disallowed before and during the study are described below: Allowed: • Symptomatic treatment of related toxicities • Prophylactic medications • Leucocyte-depleted blood transfusions at any time after randomisation Prohibited: Any chemotherapy, anti-cancer therapy, or experimental therapy (other than study treatments): • Radiotherapy to tumour lesions being assessed for tumour response prior to radiographic progression • Use of live attenuated vaccines • Use of phenytoin or fosphenytoin with carboplatin For further detail on the permitted, prohibited, or restricted concomitant medication, refer to the PAPILLON protocol.⁷⁶
Primary outcome	PFS assessed by BICR
Secondary and exploratory outcomes	Secondary outcomes assessed in the PAPILLON trial were: • ORR • DOR • OS • TTST • PFS2

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	• TTSP • EORTC-QLQ-C30 • PROMIS-PF The following exploratory outcomes were also assessed: • TTD • EQ-5D-5L A broad range of safety outcomes were analysed including: • TEAEs • TEAEs leading to death or discontinuation of any study treatment • Serious adverse event (SAEs) • Infusion-related reactions
Pre-specified subgroups	• Age: <65 versus ≥65 years and <75 versus ≥75 years • Sex: male versus female • Race: people of Asian ethnicity versus non-Asian ethnicity (patients with unknown race were not included in this subgroup analysis) • Weight: <80 kg and ≥80 kg • History of brain metastasis: yes versus no • Baseline ECOG performance status: 0 versus 1 • History of smoking: yes versus no

Abbreviations: AUC: area under the concentration-time curve; BICR: blinded independent central review; DOR: duration of response; ECOG: Eastern Cooperative Oncology Group; EGFR: epidermal growth factor receptor; EORTC-QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; Exon20ins: exon 20 insertions; HRQoL: health-related quality of life; IV: intravenous; NSCLC: non-small cell lung cancer; ORR: objective response rate; OS: overall survival; PROMIS-PF: Patient-Reported Outcomes Measurement Information System – Physical Function; PFS: progression-free survival; PFS2: progression-free survival after first subsequent therapy; RECIST: Response Evaluation Criteria in Solid Tumours; SAE: serious adverse event; TEAE: treatment-emergent adverse event; TTD: time to treatment discontinuation; TTSP: time to symptomatic progression; TTST: time to subsequent therapy.

Source: Johnson & Johnson PAPILLON CSR 2023.⁷³ Johnson & Johnson PAPILLON Clinical Trial Protocol.⁷⁶

Analysis sets

Analysis sets included in the PAPILLON trial are defined in Table 5. In this submission, efficacy results are presented for the full analysis set and are presented in Section B.2.6. Safety results are reported for the safety analysis set unless otherwise specified, with safety data summarised in Section B.2.10.

At the 3rd May 2023 DCO, the crossover analysis set consisted of a total of 65 patients that had switched treatment from the chemotherapy arm to receive amivantamab monotherapy after BICR confirmed disease progression. At the OS-specific additional DCO (31st October 2023), who had switched treatment to amivantamab monotherapy, following BICR-confirmed progression after treatment with chemotherapy, had further increased to 78 (representing ■ of the number of patients who experienced disease progression) patients.

Table 5: Primary trial populations used for the analysis of outcomes from the PAPILLON trial

Analysis set	Number analysed	Definition
Full analysis set	Amivantamab-chemotherapy: N=153 Chemotherapy: N=155	All randomised patients, classified according to their assigned treatment arm regardless of the actual treatment received
Safety analysis set	Amivantamab-chemotherapy: N=151 Chemotherapy: N=155	Randomised patients who received at least one dose of study treatment
Crossover analysis set	N=65 (3 rd May 2023 DCO) N=78 (31 st October 2023 DCO)	Patients originally randomised to the chemotherapy arm who switched to receive at least one dose of amivantamab monotherapy following BICR-confirmed disease progression
Patient-reported outcomes analysis set	NA ^a	Randomised patients who received at least one dose of study treatment and have at least one evaluable postbaseline patient-reported outcome measurement

^a Patient numbers for the patient-reported outcomes set are dependent on timepoint and specific endpoint explored in the PAPILLON trial.

Abbreviations: BICR: blinded independent central review; DCO: data cut-off; NA: not available.

Source: Johnson & Johnson PAPILLON CSR 2023 (Page 4).⁷³

Endpoint definitions

The definitions of the key primary, secondary and exploratory endpoints from the PAPILLON trial presented in this submission are outlined in Table 6 below.

Table 6: Summary of endpoint definitions from the PAPILLON trial

Endpoint	Definition
Primary endpoint	
PFS (assessed by BICR)	The time from randomisation until the date of objective disease progression (assessed by BICR [primary endpoint] and by the treating investigator) using RECIST v1.1 or death (by any cause in the absence of progression), whichever comes first
Secondary endpoints	
ORR	The percentage of patients with best response of complete response (CR) or partial response (PR), as defined by RECIST v1.1
DOR	The time from the date of first documented response (CR or PR) until the date of documented progression or death from any cause, whichever comes first
OS	The time from the date of randomisation until the date of death due to any cause
TTST ^a	The time from the date of randomisation to the start date of the subsequent anti-cancer therapy following study treatment discontinuation or death, whichever comes first
PFS2	The time from randomisation to the earliest of the progression event subsequent to that used for the primary variable PFS or death after starting the next line of treatment

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Endpoint	Definition
TTSP	The time from randomisation to documentation in the electronic case report form (eCRF) of any of the following (whichever occurs earlier): - onset of new symptoms, or, - symptom worsening, that is considered by the investigator to be related to lung cancer and requires either a change in anticancer treatment and/or clinical intervention to manage symptoms
EORTC-QLQ-C30	Measurement of cancer patients' symptoms and functioning for all cancer types
PROMIS-PF	Assessment of physical function, including upper, central, and lower extremity functions and instrumental activities of daily living
Exploratory endpoints	
TTD	The time from randomisation to discontinuation of all study treatments for any reason
EQ-5D-5L	Measurement of health state and health utility

^a A treatment switch from the carboplatin and pemetrexed arm to amivantamab monotherapy was considered as initiation of a subsequent systemic therapy.

Abbreviations: BICR: blinded independent central review; DOR: duration of response; eCRF: electronic case report form; EORTC-QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; ORR: objective response rate; OS: overall survival; PROMIS-PF: Patient-Reported Outcomes Measurement Information System – Physical Function; PFS: progression-free survival; PFS2: progression-free survival after first subsequent therapy; RECIST: Response Evaluation Criteria in Solid Tumours; TTD: time to treatment discontinuation; TTSP: time to symptomatic progression; TTST: time to subsequent therapy. **Source:** Johnson & Johnson PAPILLON CSR 2023 (Table 5, Page 40).⁷³

B.2.3.3 Baseline characteristics

The baseline demographic characteristics for patients in the amivantamab-chemotherapy arm and the chemotherapy arm are presented in Table 7. Overall, demographic and baseline characteristics were well-balanced between the two treatment arms. The median age of the amivantamab-chemotherapy arm and the chemotherapy arm was 61.0 years (range: 27–86) and 62.0 years (range: 30–92 years), respectively. Sex was broadly balanced between the treatment arms; the amivantamab-chemotherapy arm was comprised of 55.6% female patients compared to 60.0% in the chemotherapy arm. There was a slightly higher proportion of people of Asian ethnicity in the amivantamab-chemotherapy arm (64.2%) versus the chemotherapy arm (58.6%). Additionally, patients with a history of smoking were well-balanced between the two treatment arms with 42.5% of patients reporting a history of smoking in the amivantamab-chemotherapy arm and 41.3% in the chemotherapy arm.^{10, 73} Clinical validation obtained as part of the August 2024 advisory board confirmed that, overall, the two treatment arms had a good balance in baseline characteristics.^{10, 73}

The baseline characteristics seen in the PAPILLON trial were compared to UK RWE data. To do this, Johnson & Johnson conducted an observational, population-based standing cohort study in England, using the NCRAS database, to assess clinical management and outcomes in EGFR mutation-positive NSCLC. In this study, 24 patients with EGFR Exon20 insertion mutation-positive NSCLC were identified, using a selection of the eligibility criteria applied in the PAPILLON trial.¹¹ These patients had a similar mean age to both treatment arms in the

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PAPILLON trial (■■■ years); however, there were a lower proportion of patients of Asian ethnicity (■■■%).¹¹

The baseline lung cancer characteristics were generally balanced between the two treatment arms of the PAPILLON trial, as presented in Table 8. The majority of patients in the amivantamab-chemotherapy arm (151/153 [98.7%]) and the chemotherapy arm (153 [98.7%]) were diagnosed with adenocarcinoma; 133/153 (86.9%) and 121/149 (81.2%) of patients had Stage IV disease at initial diagnosis, respectively. Patients with brain metastases at screening were similar across the amivantamab-chemotherapy (35/153 [22.9%]) and chemotherapy arm (36/155 [23.2%]).^{10, 73} These disease characteristics are highly aligned with the overall EGFR mutation-positive NSCLC patient population identified in the cohort study conducted by the Company (N=■■■), with ■■■% of these patients presenting with Stage IV disease and ■■■% with adenocarcinoma.¹¹

Prior therapies received by patients in the PAPILLON trial are presented in Table 9, with the proportions of prior treatments received generally balanced across the two treatment arms. Of note, the majority of prior systemic therapies received by patients in either treatment arm were received in an adjuvant/neoadjuvant setting. Importantly, in the PAPILLON trial patients were required to have no previous treatment for EGFR Exon20 insertion mutation-positive NSCLC; brief monotherapy with an approved EGFR TKI was however allowed if a lack of response had been documented. As such, a small proportion of patients in the amivantamab-chemotherapy (1 [0.7%]) and the chemotherapy (3 [1.9%]) treatment arms had received prior treatment with EGFR TKIs. It should also be noted that due to small patient numbers (n=4), prior EGFR TKI use was removed as a stratification factor from the trial.^{10, 73}

Table 7: Summary of patient demographics and baseline characteristics; full analysis set (N=308)

Characteristic	Amivantamab-chemotherapy (N=153)	Chemotherapy (N=155)
Age, years		
Mean (SD)	59.3 (11.9)	60.0 (12.0)
Median (range)	61.0 (27–86)	62.0 (30–92)
<65, n (%)	97 (63.4)	92 (59.3)
65 to <75, n (%)	44 (28.8)	48 (31.0)
≥75, n (%)	12 (7.8)	15 (9.7)
Sex, n (%)		
Female	85 (55.6)	93 (60.0)
Male	68 (44.4)	62 (40.0)
Race, n (%)^a		
N	151	152
American Indian or Alaska Native	1 (0.7)	2 (1.3)
Asian	97 (64.2)	89 (58.6)
Black or African American	2 (1.3)	0
White	49 (32.5)	60 (39.5)

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Characteristic	Amivantamab-chemotherapy (N=153)	Chemotherapy (N=155)
Multiple ^b	1 (0.7)	0
Unknown	1 (0.7)	1 (0.7)
Weight, kg		
Mean (SD)	63.8 (14.6)	67.7 (14.0)
Median (range)	61.8 (39–127)	66.5 (37–112)
<80, n (%)	132 (86.3)	128 (82.6)
≥80, n (%)	21 (13.7)	27 (17.4)
Body mass index, kg/m²		
Mean (SD)	23.6 (4.1)	25.0 (4.6)
Median (range)	23.4 (16–39)	24.2 (16–43)
History of smoking, n (%)		
Yes	65 (42.5)	64 (41.3)
No	88 (57.5)	91 (58.7)

^a Race or ethnic group was reported by the patients. In some regions, reporting of race was not required.

^b Multiple includes one patient who selected Black or African American and White.

Abbreviations: SD: standard deviation.

Source: EMA. Rybrevant EPAR assessment report (Table 13).⁷⁷ Zhou *et al.* (2023).¹⁰

Table 8: Summary of baseline patient clinical disease characteristics; full analysis set (N=308)

Characteristic	Amivantamab-chemotherapy (N=153)	Chemotherapy (N=155)
History of brain metastasis, n (%)		
N	153	155
No	118 (77.1)	119 (76.8)
Yes	35 (22.9)	36 (23.2)
Prior EGFR TKI use, n (%)		
No	152 (99.3)	152 (98.1)
Yes	1 (0.7)	3 (1.9)
ECOG performance status, n (%)		
N	153	155
0	54 (35.3)	55 (35.5)
1	99 (64.7)	100 (64.5)
Initial diagnosis NSCLC subtype, n (%)		
N	153	155
Adenocarcinoma	151 (98.7)	153 (98.7)
Large cell carcinoma	0	1 (0.6)
Squamous cell carcinoma	0	0
Other	2 (1.3)	1 (0.6)
Histology grade at initial diagnosis, n (%)^a		
n	146	142
Poorly differentiated	24 (16.4)	17 (12.0)
Moderately differentiated	27 (18.5)	27 (19.0)

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Characteristic	Amivantamab- chemotherapy (N=153)	Chemotherapy (N=155)
Well differentiated	11 (7.5)	8 (5.6)
Other	84 (57.5)	90 (63.4)
Cancer stage at initial diagnosis, n (%)		
n	153	149
IA	2 (1.3)	4 (2.7)
IB	4 (2.6)	6 (4.0)
IIA	0	1 (0.7)
IIB	1 (0.7)	5 (3.4)
IIIA	5 (3.3)	5 (3.4)
IIIB	7 (4.6)	5 (3.4)
IIIC	1 (0.7)	2 (1.3)
IVA	62 (40.5)	54 (36.2)
IVB	71 (46.4)	67 (45.0)
Cancer stage at screening, n (%)		
N	153	155
IIIB	3 (2.0)	0
IIIC	1 (0.7)	0
IVA	67 (43.8)	70 (45.2)
IVB	82 (53.6)	85 (54.8)
Location of metastasis at screening, n (%)^b		
n	151	153
Bone	71 (47.0)	80 (52.3)
Liver	18 (11.9)	31 (20.3)
Brain	35 (23.2)	36 (23.5)
Lymph Node	102 (67.5)	114 (74.5)
Adrenal Gland	10 (6.6)	19 (12.4)
Lung	113 (74.8)	120 (78.4)
Other	71 (47.0)	64 (41.8)
Time since initial lung cancer diagnosis, months		
N	153	155
Mean (SD)	5.89 (14.5)	8.49 (18.1)
Median (range)	1.77 (0.5–80.8)	1.84 (0.6–95.9)
Time since metastatic disease diagnosis, months		
n	151	154
Mean (SD)	2.23 (3.799)	2.29 (3.088)
Median (range)	1.51 (0.2–40.0)	1.61 (0.3–30.7)

^a Other includes unknown histology grade.

^b Subjects can be counted in more than one category.

Abbreviations: Eastern Cooperative Oncology Group; EGFR: epidermal growth factor receptor; NSCLC: non-small cell lung cancer; SD: standard deviation; TKI: tyrosine kinase inhibitor.

Source: EMA. Rybrevant EPAR assessment report (Table 13 and Table 14).⁷⁷ Zhou *et al.* (2023).¹⁰

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Table 9: Prior therapies for lung cancer received by patients; safety analysis set (N=306)

Prior therapy, n (%)	Amivantamab-chemotherapy (N=151)	Chemotherapy (N=155)
Systemic therapy	8 (5.3)	14 (9.0)
Adjuvant	7 (4.5)	12 (7.9)
Neo-adjuvant	1 (0.6)	0
Palliative ^{a,c}	1 (0.6)	3 (2.0)
Radiotherapy	47 (31.1)	59 (38.1)
Cancer-related surgery ^b	151 (100.0)	155 (100.0)
EGFR TKI use	1 (0.7)	3 (1.9)

a Palliative was defined as curative/palliative/any other intent. One patient received both adjuvant and palliative therapy.

b Prior cancer-related surgery includes tumour biopsies performed for diagnosis.

c One subject received both adjuvant and palliative therapy.

Abbreviations: EGFR: epidermal growth factor receptor; TKI: tyrosine kinase inhibitor.

Source: EMA. Rybrevant EPAR assessment report (Table 15).⁷⁷ Zhou *et al.* (2023).¹⁰

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1 Statistical analysis

The statistical methods for the primary analysis for the PAPILLON trial are presented in Table 10.

Table 10: Statistical methods for the primary analysis of the PAPILLON trial

Hypothesis objective	The statistical hypothesis was that the addition of amivantamab to carboplatin and pemetrexed doublet chemotherapy would reduce the risk of either disease progression or death, as compared with carboplatin and pemetrexed, in patients with treatment-naïve, locally advanced or metastatic NSCLC characterised by EGFR Exon20 insertion mutations
Statistical analysis	Primary endpoint analysis: PFS PFS was analysed using the full analysis set. The treatment effect of the amivantamab-chemotherapy arm was compared with the chemotherapy arm based on the log rank test stratified by ECOG performance status (0 or 1) and history of brain metastases (yes or no), using the Breslow approach for handling ties. The p-value generated from the stratified log-rank test was used for the primary hypothesis testing. The HR and the corresponding 95% CI were estimated based on a stratified Cox’s regression model, using the same stratification factors as for the log-rank test, with treatment as the sole explanatory variable. Patients who did not progress or die at the time of analysis were censored at the time of the latest date of their last evaluable RECIST v1.1 assessment. If the patient progressed or died after 2 or more consecutive missed disease assessments, the patient was censored at the time of the last evaluable RECIST v1.1 assessment. If the patient had no evaluable visits or did not have baseline data, they were censored at Day 1 unless they died within 2 visits of baseline. The median PFS with 95% CI was estimated using the Kaplan-Meier (KM) method. The KM PFS curve was plotted by treatment group. Additionally, PFS rates with 95% CI were estimated by the KM method at landmark timepoints (at 6-month, 12-month, and 18-month, etc.) and reported for each treatment group. The number and percentage of patients who had a PFS event or were censored were reported and reasons for PFS event and censoring were summarised. To control the overall type I error rate for the hypotheses testing of the primary and the secondary endpoints strongly at 5%, a sequential testing strategy was used. As per the protocol, if the testing for the primary endpoint of PFS was statistically significant, the key secondary endpoints of ORR and OS would be sequentially tested, each with an overall 2-sided alpha of 0.05. Additionally, the test for ORR was conducted before the test for OS. The primary PFS endpoint was assessed by BICR. Results for PFS assessed by the treating investigator are presented in Appendix M.1.2. Secondary endpoint analysis

Company evidence submission template for amivantamab with carboplatin and pemetrexed for untreated EGFR Exon 20 insertion mutation-positive advanced non-small cell lung cancer [ID5110]

	OS was analysed using a similar methodology and model as for the primary analysis of PFS for the full analysis set. Additionally, forest plots were provided for relevant subgroups outlined in Table 4. Comparison between the two intervention groups was evaluated using the HR, with 95% CIs calculated from a Cox regression model in each subgroup. Any patient not known to have died at the time of analysis was censored based on the last recorded date on which the patient was known to be alive.⁷⁸ ORR was analysed using a logistic regression model stratified by ECOG performance status (0 or 1) and history of brain metastases (yes or no). The results of the analysis were presented in terms of an odds ratio and associated 95% profile likelihood CIs and p-value. DOR was assessed by producing a KM plot and median DOR with 95% CI calculated from the KM estimate for each treatment group. TTST and TTSP were analysed using a similar method as the primary analysis of PFS in the full analysis set. PFS2 was analysed using a similar method to the primary analysis of PFS in the full analysis set. Statistical analyses used for PRO measures and tertiary endpoints in the PAPILLON trial are outlined in the statistical analysis plan (SAP) provided alongside this submission.⁷⁸
Sample size, power calculation	As per the SAP for the PAPILLON trial, a total of 200 PFS events provides approximately 90% power to detect a HR of 0.625, corresponding to at least three months improvement in median PFS (five months for chemotherapy and eight months for the combination of amivantamab with chemotherapy) with a log-rank test (two-sided alpha=0.05) Therefore, the total sample size needed for the study was approximately 300 patients (randomised to approximately 150 patients per treatment arm). The sample size calculation takes into consideration an annual dropout rate of 5%. Assuming a 15-month recruitment period, 200 PFS events were expected to occur approximately 18 months after the first patient was randomised

Abbreviations: BICR: blinded independent central review; CI: confidence interval; CR: complete response; DOR: duration of response; ECOG: Eastern Cooperative Oncology Group; EGFR: epidermal growth factor receptor; HR: hazard ratio; KM: Kaplan-Meier; NSCLC: non-small cell lung cancer; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; PFS2: progression-free survival after first subsequent therapy; PR: partial response; PRO: patient-reported outcome; SAP: statistical analysis plan; TTSP: time to symptomatic progression; TTST: time to subsequent therapy.

Source: Johnson & Johnson PAPILLON SAP v2.⁷⁸

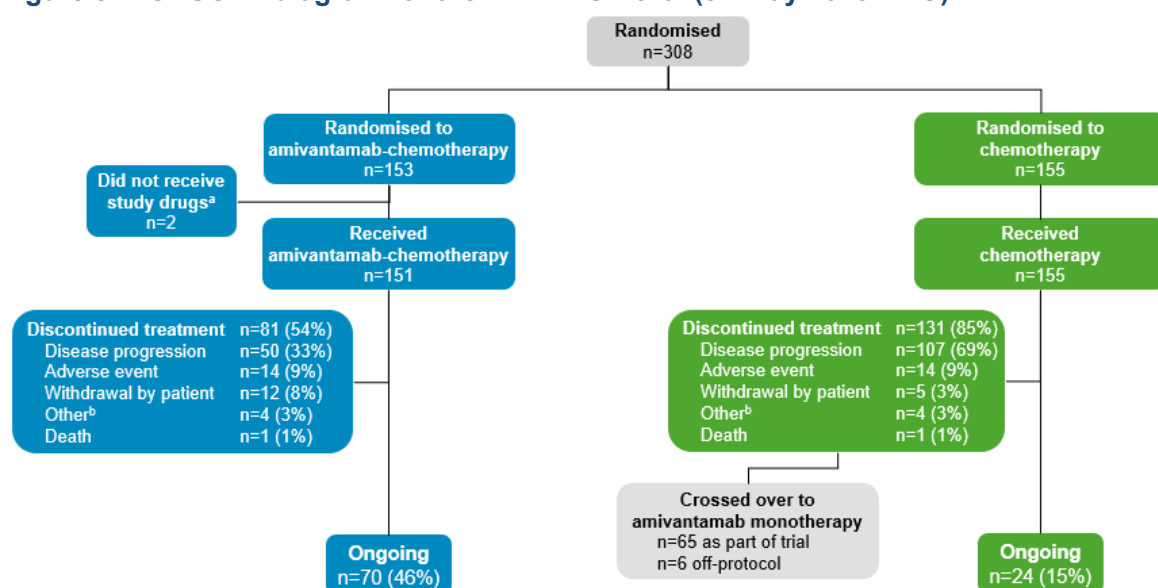
B.2.4.2 Patient flow in the PAPILLON trial

The Consolidated Standards of Reporting Trials (CONSORT) diagram for the PAPILLON trial is presented in Figure 8.

At the 3rd May 2023 DCO, a total of 153 patients were randomised into the amivantamab-chemotherapy arm and 155 patients were randomised into the chemotherapy arm. A total of 306 patients, 151 patients in the amivantamab-chemotherapy arm and 155 patients in the chemotherapy arm received at least one dose of study treatment. At this DCO, 70 patients (46.4%) and 24 patients (15.5%) remained on treatment in the amivantamab-chemotherapy and chemotherapy arms, respectively. The most common reason for discontinuation of study treatment was disease progression; occurring in 33.1% and 69.0% of patients in each treatment arm, respectively. Overall, a small number of patients (14 in each arm) discontinued all study treatment due to an AE.⁷⁷

It should be noted that at the 3rd May 2023 DCO, 65 patients in the chemotherapy treatment arm had switched to amivantamab monotherapy following BICR-confirmed disease progression at the dose specified in the trial protocol. A further 6 patients treatment switched 'off-protocol' – receiving amivantamab monotherapy outside of the trial protocol.

Figure 8: CONSORT diagram for the PAPILLON trial (3rd May 2023 DCO)



^a Both patients withdrew consent after randomisation.

^b Other includes non-compliance, other, and physician's decision (n ≤2 for all)

Abbreviations: CONSORT: Consolidated Standards of Reporting Trials; DCO: data cut-off.

Source: Adapted from Zhou *et al.* 2023.¹⁰

B.2.4.3 Treatment switching in the PAPILLON trial

Patients randomised to the chemotherapy arm were permitted to treatment switch to receive amivantamab monotherapy, following BICR-confirmed disease progression.⁷⁶ Amivantamab monotherapy was administered as per the dosing schedule for the main amivantamab treatment phase of the trial:

Company evidence submission template for amivantamab with carboplatin and pemetrexed for untreated EGFR Exon 20 insertion mutation-positive advanced non-small cell lung cancer [ID5110]

- In 21-day cycles: amivantamab 1,400 mg (1,750 mg if body weight is ≥ 80 kg) by IV infusion once weekly from Weeks 1 to 4
- 1,750 mg (2,100 mg if body weight is ≥ 80 kg) every 3 weeks starting at Week 7 onwards⁷⁹

At the 3rd May 2023 DCO, a total of 65 patients had treatment switched from the chemotherapy arm to receive amivantamab monotherapy. At the OS-specific additional DCO (31st October 2023), the number of patients who had switched to amivantamab monotherapy after treatment with chemotherapy, at the dose specified in the PAPILLON trial protocol, had further increased to 78 patients.

Efficacy results for the PAPILLON trial (presented in B.2.6) are reported for the chemotherapy treatment arm as a whole, which includes patients who treatment switched to receive amivantamab monotherapy following disease progression.

The presence of treatment switching in the PAPILLON trial is expected to confound OS results for the trial. This is evidenced by the CHRYSALIS trial for amivantamab, a Phase I study which demonstrated the benefit of amivantamab monotherapy in patients with EGFR Exon20 insertion mutation-positive NSCLC who had previously received platinum chemotherapy.⁸⁰ Therefore, the results presented for amivantamab-chemotherapy in Section B.2.6.2.3 are conservative in their estimation of treatment effect.

Amivantamab monotherapy is not recommended by NICE for the treatment of adult patients with advanced NSCLC with activating EGFR Exon20 insertion mutations, after failure of platinum-based therapy; as such, it is not available to patients in UK clinical practice via the NHS.¹⁹ As recommended by NICE Decision Support Unit (DSU) technical support document (TSD) 24, subsequent treatments used in a clinical trial that are not reflective of NHS practice should be adjusted for.⁸¹ Considering this guidance, the relatively high proportion of patients switching to amivantamab monotherapy after progression on chemotherapy, and the evidence that amivantamab provides benefit following prior platinum chemotherapy (from the CHRYSALIS trial), OS results for chemotherapy have been adjusted to account for treatment switching. This adjusts the OS data within the chemotherapy arm to reflect the survival if patients had followed UK clinical practice. This is discussed further in B.3.3.2.1.

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

The trials captured in the clinical SLR were assessed for quality using the York CRD quality assessment (QA) checklist (for RCTs) and the ROBINS-1 QA checklist (for non-RCTs). The results of these quality assessments are presented in Appendix D.3, and a summary of the quality assessment for the PAPILLON trial, according to the York CRD QA, is presented in Table 11 below. Overall, the quality assessment found PAPILLON to be a robust, high-quality trial, within minimal risk of bias.

Table 11: Quality assessment of the PAPILLON trial (NCT04538664)

Source of bias	Risk of bias
Randomisation	Low
Allocation concealment	Unclear

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Patient/care provider blinding	High
Outcome assessor blinding	Low
Balanced groups	Low
Unexpected imbalance in discontinuations	Low
More outcomes measured than reported	Low
ITT used appropriately	Unclear

Abbreviations: ITT: intention to treat.

B.2.6 Clinical effectiveness results of the relevant studies

Efficacy results from the PAPILLON trial in this submission are presented from the full analysis set, consisting of 153 patients in the amivantamab-chemotherapy arm and 155 patients in the chemotherapy arm.

Data are presented for the most recent DCO for the PAPILLON trial for all endpoints (3rd May 2023). The total median duration of follow-up across both treatment arms was 14.92 months, with a median follow-up of [REDACTED] and [REDACTED] in the amivantamab-chemotherapy arm and chemotherapy arm, respectively. For OS, data from an additional DCO (31st October 2023) are also presented alongside the 3rd May 2023 DCO data, with a total median follow-up across both treatment arms of 20.9 months (Section B.2.6.2.3). TTSP data are presented in Appendix M.1.1 for completeness.

A summary of key clinical results from the PAPILLON trial at the 3rd May 2023 DCO is presented in Table 12, with OS results presented from the additional 31st October 2023 DCO. Overall, results from the PAPILLON trial demonstrate that amivantamab-chemotherapy is an efficacious treatment for patients with EGFR Exon20 insertion mutation-positive advanced NSCLC.

Table 12: Summary of key clinical results from the PAPILLON trial

Outcome	Amivantamab-chemotherapy	Chemotherapy	Treatment difference
Median PFS, months (95% CI)	BICR: 11.37 (9.79-13.70) INV: 12.91 (11.37-16.66)	BICR: 6.70 (5.59-7.33) INV: 6.90 (6.24-8.31)	BICR HR: 0.40 (0.30-0.53) INV HR: 0.38 (0.29-0.52)
Median OS, months (95% CI) ^a	NE (28.3-NE)	28.6 (24.4-NE)	HR: 0.76 (0.50-1.14)
Median PFS2, ^b months (95% CI)	INV: NE (22.77-NE)	INV: 17.25 (13.96-21.52)	HR: 0.49 (0.32-0.76)
ORR, % (95% CI)	BICR: 73.0 (62.5-79.9) INV: [REDACTED]	BICR: 47.4 (39.2-55.6) INV: [REDACTED]	BICR OR: 2.97 (1.84-4.79) INV OR: [REDACTED]
Median DOR months (95% CI)	BICR: 10.09 (8.48-13.90) INV: 15.28 (10.87-NE)	BICR: 5.55 (4.44- 6.93) INV: 6.93 (5.55-8.15)	NR

^a OS data are presented from the additional 31st October 2023 DCO.

^b Defined as time from randomisation until the date of second objective disease progression, after initiation of subsequent anticancer therapy, based on investigator assessment (after that used for PFS) or death, whichever comes first.

Abbreviations: BICR: blinded independent central review; CI: confidence interval; DCO: data cut-off; DOR: duration of response; INV: investigator; NE: not estimable; ORR: objective response rate; OS: overall survival; PFS: progression-free survival.

Source: Zhou *et al.* 2023, Johnson & Johnson PAPILLON CSR 2023 and EMA Rybrevant EPAR assessment report. ^{10 73, 77}

B.2.6.1 Primary endpoint

Progression-free survival by BICR

Company evidence submission template for amivantamab with carboplatin and pemetrexed for untreated EGFR Exon 20 insertion mutation-positive advanced non-small cell lung cancer [ID5110]

The primary endpoint of the PAPILLON trial, PFS assessed by BICR, was met by amivantamab-chemotherapy. Following a median follow-up of 14.92 months at the 3rd May 2023 DCO, a statistically significant ($p < 0.0001$) and clinically meaningful treatment effect was observed for BICR-assessed PFS, with a 60% reduction in the risk of disease progression or death in patients receiving amivantamab-chemotherapy compared with patients receiving chemotherapy (HR: 0.40; 95% CI: 0.30-0.53). As the PAPILLON trial met its primary endpoint, the MHRA granted a license for amivantamab in combination with carboplatin and pemetrexed for the first-line treatment of adult patients with advanced NSCLC with activating EGFR Exon 20 insertion mutations.²¹

The median BICR-assessed PFS was 11.37 months (95% CI: 9.79-13.70) in the amivantamab-chemotherapy arm and 6.70 months (95% CI: 5.59-7.33) in the chemotherapy arm, as shown in Table 13. Additionally, 12- and 18-month event-free rates of 48% and 31% were observed for patients in the amivantamab-chemotherapy treatment arm, with rates of 13% and 3% observed for patients in the chemotherapy treatment arm.

A KM plot for PFS in both treatment arms is presented in Figure 9. The plot shows a distinct early separation of the treatment arms, favouring treatment with amivantamab-chemotherapy, after the second disease assessment (corresponding to the completion of the first four 21-day treatment cycles). This benefit continued throughout the maintenance phase (Cycle 5 onwards where patients received pemetrexed with or without amivantamab) as evidenced by the increased separation of the curves. By 15 months, the benefit from chemotherapy in the chemotherapy arm was no longer evident, while the amivantamab-chemotherapy curve appears to plateau, with disease control maintained in approximately one-third of patients in the amivantamab-chemotherapy arm. For completeness, investigator-assessed PFS results are further presented in Appendix M.1.2.

Table 13: Summary of PFS assessed by BICR (3rd May 2023 DCO; full analysis set)

	Amivantamab- chemotherapy (N=153)	Chemotherapy (N=155)
Event, n (%)	84 (54.9)	132 (85.2)
Censored, n (%)	69 (45.1)	23 (14.8)
Time to event (months)		
Median (95% CI)	11.37 (9.79-13.70)	6.70 (5.59-7.33)
25 th percentile (95% CI)	6.70 (5.39-7.72)	4.21 (3.48-4.40)
75 th percentile (95% CI)	NE (16.62-NE)	9.95 (8.87-11.01)
Range	0.0+, 23.6+	0.0+, 23.6+
6-month event-free rate (95% CI)	0.77 (0.69-0.83)	0.51 (0.43-0.59)
12-month event-free rate (95% CI)	0.48 (0.39-0.56)	0.13 (0.08-0.19)
18-month event-free rate (95% CI)	0.31 (0.22-0.40)	0.03 (0.01-0.09)
Treatment difference		
p-value ^a	<0.0001	
HR (95% CI) ^b	0.40 (0.30-0.53)	

^a p-value is from a log-rank test stratified by ECOG PS (0 or 1) and history of brain metastases (yes or no).

^b HR is from stratified proportional hazards model. HR <1 favors amivantamab-chemotherapy treatment.

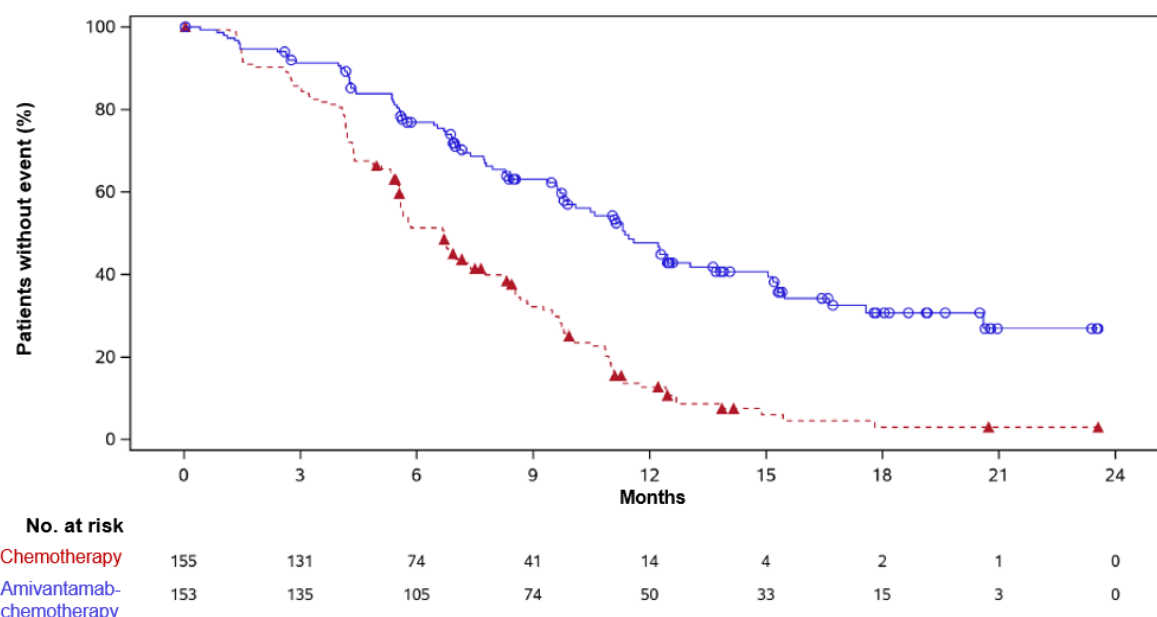
Abbreviations: BICR: blinded independent central review; CI: confidence interval; DCO: data cut-off; ECOG: Eastern Cooperative Oncology Group; HR: hazard ratio; NE: not estimable; PS: performance status.

Company evidence submission template for amivantamab with carboplatin and pemetrexed for untreated EGFR Exon 20 insertion mutation-positive advanced non-small cell lung cancer [ID5110]

Sources: Johnson & Johnson PAPILLON CSR 2023 (Table 14, Page 57)⁷³, Zhou *et al.* 2023¹⁰ and EMA Rybrevant EPAR assessment report (Table 17)

77.

Figure 9: KM plot of PFS assessed by BICR (3rd May 2023 DCO; full analysis set)



Abbreviations: BICR: blinded independent central review; DCO: data cut-off; KM: Kaplan-Meier; PFS: progression-free survival.

Source: Zhou *et al.* 2023 (Figure 1A).¹⁰

B.2.6.2 Secondary Endpoints

B.2.6.2.1 Objective response rate

As pre-specified in the SAP, ORR was assessed in patients with measurable disease at baseline and responders were defined as patients achieving either CR or PR, per RECIST v1.1 criteria. Based on BICR assessment, 152 of the 153 participants enrolled in the amivantamab-chemotherapy arm and 152 of the 155 participants enrolled in the chemotherapy arm had measurable disease at baseline and were included in the analysis of ORR.

At the 3rd May 2023 DCO, ORR as assessed by BICR showed a significantly higher proportion ($p < 0.0001$) of responders in the amivantamab-chemotherapy arm (111 patients [73.0%]) compared with the chemotherapy arm (72 patients [47.4%]), yielding an odds ratio of 2.97 (95% CI: 1.84-4.79), as presented in Table 14. Of note, a higher proportion of patients in the amivantamab-chemotherapy arm achieved a PR or better as the best response (69.1%) compared with the chemotherapy arm (46.7%). Additionally, there were fewer patients in the amivantamab-chemotherapy with progressive disease compared with the chemotherapy arm; 2.6% and 10.5%, respectively.

Company evidence submission template for amivantamab with carboplatin and pemetrexed for untreated EGFR Exon 20 insertion mutation-positive advanced non-small cell lung cancer [ID5110]

Table 14: Summary of ORR based on RECIST v1.1 criteria in patients with measurable disease at baseline by BICR (3rd May 2023 DCO; full analysis set)

	Amivantamab- chemotherapy (N=153)	Chemotherapy (N=155)
Number of patients with measurable disease at baseline	152	152
ORR, n (%)	111 (73.0)	72 (47.4)
95% CI	62.5-79.9	39.2-55.6
Treatment difference		
p-value ^a	<0.0001	
Odds ratio (95% CI) ^b	2.97 (1.84-4.79)	
BOR, n (%)		
CR	6 (3.9)	1 (0.7)
PR	105 (69.1)	71 (46.7)
SD	29 (19.1)	62 (40.8)
PD	4 (2.6)	16 (10.5)
NE	8 (5.3)	2 (1.3)

^a p-value is from a logistic regression model stratified by ECOG PS (0 or 1) and history of brain metastases (yes or no).

^b Odds ratio >1 favours amivantamab-chemotherapy treatment.

Note: CR and PR do not have to be confirmed. Percent of Responder is based on the number of subjects with measurable disease at baseline

Abbreviations: BICR: blinded independent central review; BOR: best overall response; CI: confidence interval CR: complete response; DCO: data cut-off; ECOG: Eastern Cooperative Oncology Group; NE: not estimable; ORR: objective response rate; PR: partial response; PS: performance status; RECIST: Response Evaluation Criteria in Solid Tumours; SD: stable disease.

Sources: EMA. Rybrevant EPAR assessment report (Table 19)⁷⁷ and Zhou *et al.* 2023.¹⁰

B.2.6.2.2 Duration of response

Among the confirmed responding patients at the 3rd May 2023 DCO, approximately three times as many patients maintained their response in the amivantamab-chemotherapy arm compared with the chemotherapy arm (49.0% versus 18.2%). Correspondingly, median DOR was doubled in the amivantamab-chemotherapy arm; 10.09 months (95% CI: 8.48-13.90), compared with 5.55 months (95% CI: 4.44-6.93) in the chemotherapy arm (Table 15). The 12- and 18-month event-free rates were 45% and 35%, respectively for patients receiving amivantamab-chemotherapy compared with 11% and 5% for patients receiving chemotherapy. This indicates that amivantamab-chemotherapy results in more durable responses in patients when compared with chemotherapy.

Table 15: Summary of DOR in confirmed responders based on patients with measurable disease at baseline by BICR (3rd May 2023 DCO; full analysis set)

	Amivantamab- chemotherapy (N=153)	Chemotherapy (N=155)
Number of patients with measurable disease at baseline	152	152
Event, n (%)	52 (51.0)	45 (81.8)
Censored, n (%)	50 (49.0)	10 (18.2)
Time to event (months)		
Median (95% CI)	10.09 (8.48-13.90)	5.55 (4.44-6.93)
25th percentile (95% CI)	6.54 (5.39-8.21)	4.17 (2.86-4.44)
75th percentile (95% CI)	NE (15.21-NE)	8.94 (6.93-11.47)
Range	1.4+, 22.3+	1.3+, 22.4+
6-month event-free rate (95% CI)	0.77 (0.67-0.85)	0.44 (0.30-0.56)
12-month event-free rate (95% CI)	0.45 (0.34-0.55)	0.11 (0.03-0.23)
18-month event-free rate (95% CI)	0.35 (0.24-0.47)	0.05 (0.01-0.19)

+ censored observation

Abbreviations: BICR: blinded independent central review; CI: confidence interval; DCO: data cut-off; DOR: duration of response; NE: not estimable.

Source: EMA. Rybrevant EPAR assessment report (Table 20)⁷⁷ and Zhou *et al.* 2023.¹⁰

B.2.6.2.3 Overall survival

There have been two DCOs for the OS data in the PAPILLON trial: 3rd May 2023 and 31st October 2023. Data from the additional DCO (31st October 2023) were used to inform the cost-effectiveness analysis (Section B.3.3).

For completeness, data at both DCOs are presented in the submission. At the 3rd May DCO, there were 28 OS events in the amivantamab-chemotherapy arm and 42 in the chemotherapy arm, as presented in Table 16. There was a strong trend towards improved survival in the amivantamab-chemotherapy arm, despite 65 patients in the chemotherapy arm receiving amivantamab monotherapy after BICR-confirmed disease progression (HR: 0.67 [95% CI: 0.42-1.09]; p=0.1056). The OS rate at 18 months and 24 months was 74% and 72%, respectively, for patients in the amivantamab-chemotherapy arm versus 68% and 54%, respectively for patients treated with chemotherapy.⁷⁷

The KM plot for OS at the 3rd May 2023 DCO is presented in Figure 10. The KM plot also demonstrates a strong trend towards improved survival in the amivantamab-chemotherapy arm.

Table 16: Summary of OS (3rd May 2023 DCO; full analysis set)

	Amivantamab- chemotherapy (N=153)	Chemotherapy (N=155)
Event, n (%)	28 (18.3)	42 (27.1)
Censored, n (%)	125 (81.7)	113 (72.9)
Time to event (months)		
Median (95% CI)	NE (NE-NE)	24.38 (22.08-NE)
25th percentile (95% CI)	16.85 (13.96-NE)	13.67 (11.10-18.37)
75th percentile (95% CI)	NE (NE-NE)	25.49 (24.38-NE)
Range	0.3+, 27.0+	0.4, 26.9+
6-month event-free rate (95% CI)	0.94 (0.89-0.97)	0.97 (0.92-0.99)
12-month event-free rate (95% CI)	0.86 (0.79-0.91)	0.82 (0.74-0.87)
18-month event-free rate (95% CI)	0.74 (0.64-0.82)	0.68 (0.58-0.76)
24-month event-free rate (95% CI)	0.72 (0.61-0.81)	0.54 (0.37-0.68)
Treatment difference		
p-value ^a	0.1056	
HR (95% CI) ^b	0.67 (0.42-1.09)	

^a p-value is from a log-rank test.

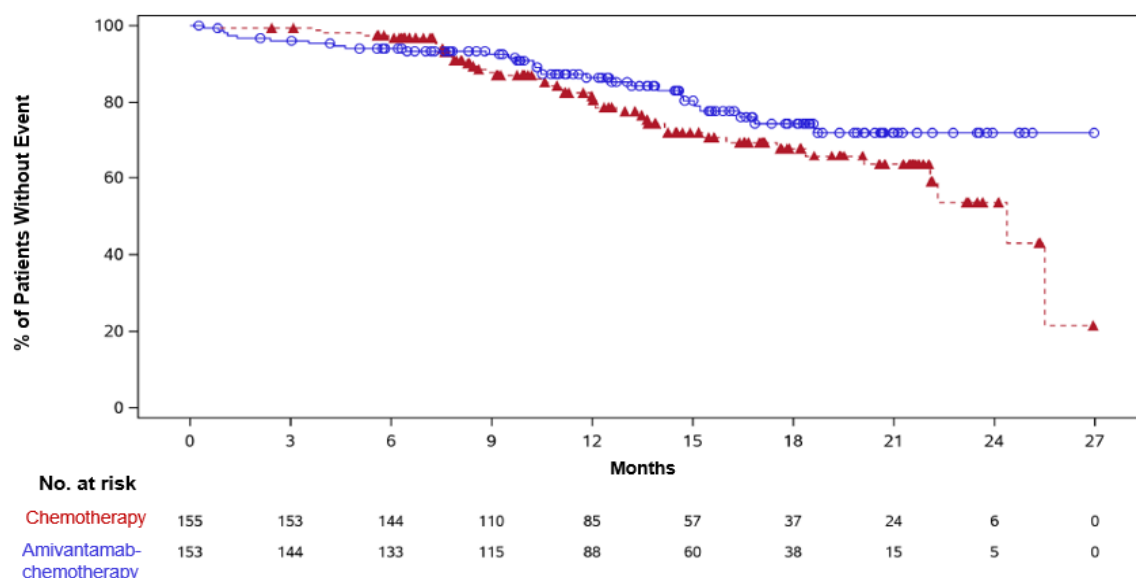
^b HR is from stratified proportional hazards model. HR <1 favors amivantamab-chemotherapy treatment.

+ censored observation

Abbreviations: CI: confidence interval; DCO: data cut-off; HR: hazard ratio; NE: not estimable; OS: overall survival.

Sources: EMA Rybrevant EPAR assessment report (Table 21)⁷⁷ and Johnson & Johnson PAPILLON CSR 2023 (Table 20, Page 71)⁷³, Zhou *et al.* 2023.¹⁰

Figure 10: KM plot of overall survival (3rd May 2023 DCO; full analysis set)



Abbreviations: DCO: data cut-off; KM: Kaplan-Meier.

Source: Zhou *et al.* 2023.¹⁰

Company evidence submission template for amivantamab with carboplatin and pemetrexed for untreated EGFR Exon 20 insertion mutation-positive advanced non-small cell lung cancer [ID5110]

At the 31st October 2023 DCO, the total median duration of follow-up across both treatment arms was 20.9 months. In total there were 40 OS events in the amivantamab-chemotherapy arm and 52 in the chemotherapy arm, as presented in Table 17. There continued to be a strong trend towards improved survival in the amivantamab-chemotherapy arm with a 24% reduction in the risk of death (HR: 0.76 [95% CI: 0.50-1.14]; $p=0.1825$) despite 78 patients (representing █ of patents who experienced disease progression) in the chemotherapy-arm receiving amivantamab monotherapy after BICR-confirmed disease progression.

A KM plot for OS at the 31st October 2023 DCO is further presented in Figure 11.

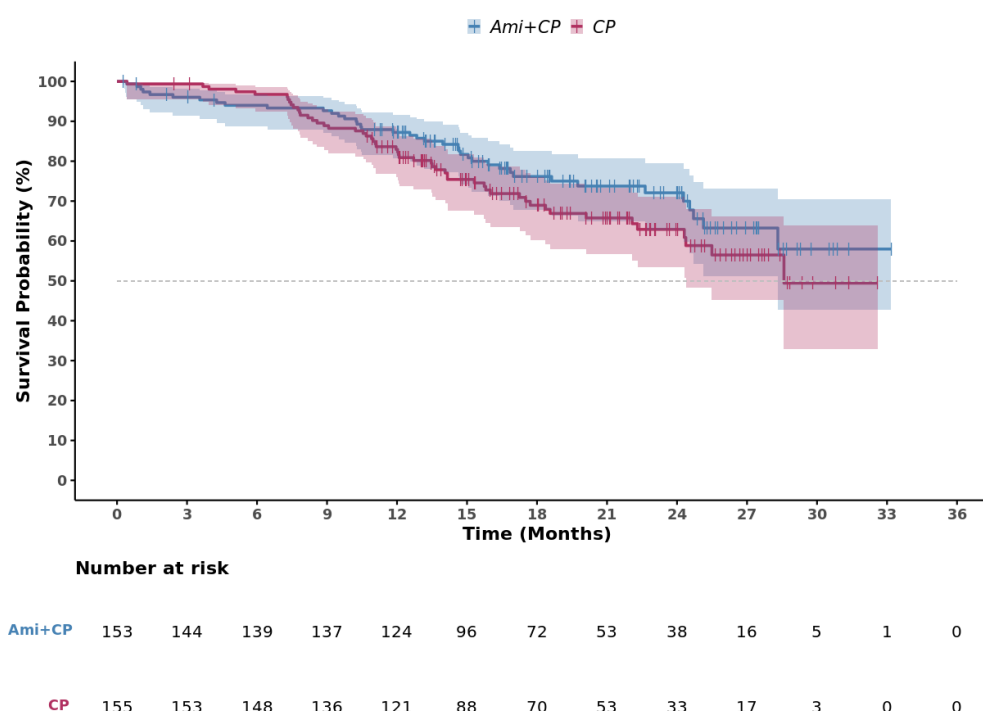
Table 17: Summary of overall survival (31st October 2023; full analysis set)

	Amivantamab- chemotherapy (N=153)	Chemotherapy (N=155)
Event, n (%)	40 (26.1)	52 (33.5)
Time to event (months)		
Median (95% CI)	NE (28.3-NE)	28.6 (24.4-NE)
Treatment difference		
p-value	0.1825	
HR (95% CI), p value	0.76 (0.50-1.14, $p=0.1825$)	

Abbreviations: CI: confidence interval; DCO: data cut-off; HR: hazard ratio; NE: not estimable.

Source: Amivantamab SmPC 2024.²¹

Figure 11: KM plot of overall survival (31st October 2023 DCO; full analysis set)



Abbreviations: ACP: amivantamab in combination with carboplatin and pemetrexed; CP: carboplatin and pemetrexed; DCO: data cut-off; KM: Kaplan-Meier.

Source: Amivantamab SmPC 2024.²¹

Company evidence submission template for amivantamab with carboplatin and pemetrexed for untreated EGFR Exon 20 insertion mutation-positive advanced non-small cell lung cancer [ID5110]

Given that, at the 31st October DCO, █% of patients in the chemotherapy arm who experienced disease progression (78 out of █) received subsequent treatment with amivantamab monotherapy (not UK clinical practice), treatment switching adjustment was explored to mitigate any potential confounding from subsequent amivantamab on the OS results. The IPCW method of adjusting for treatment switching was considered the most relevant; the methods and results of this adjustment are presented in Section B.3.3.2.1.

B.2.6.2.4 Time to subsequent therapy

A substantially higher proportion of patients in the amivantamab-chemotherapy arm had not initiated subsequent systemic therapy compared with the chemotherapy arm at the 3rd May 2023 DCO (62.1% versus 29.7%, respectively). Furthermore, the median time to initiation of any subsequent anti-cancer therapy was of longer duration in the amivantamab-chemotherapy arm (17.71 months [95% CI: 13.67-NE]) compared with the chemotherapy arm (9.89 months [95% CI: 8.57-11.07]). This resulted in a HR of 0.35 (95% CI: 0.25-0.49; nominal p<0.0001), demonstrating the durability of clinical benefit offered by amivantamab-chemotherapy in prolonging time until patients require a subsequent therapy versus chemotherapy.⁸² This is also supported by the event-free rates observed for these patients; at 18 months, 86% of patients in the chemotherapy arm had initiated subsequent therapy compared with 51% in the amivantamab-chemotherapy arm. A summary of TTST is presented in Table 18 with the associated KM plot presented in Figure 12.

Table 18: Summary of time to subsequent systemic anti-cancer therapy (3rd May 2023 DCO; full analysis set)

	Amivantamab-chemotherapy (N=153)	Chemotherapy (N=155)
Event, n (%)	58 (37.9)	109 (70.3)
Censored, n (%)	95 (62.1)	46 (29.7)
Time to event (months)		
Median (95% CI)	17.71 (13.67-NE)	9.89 (8.57-11.07)
25th percentile (95% CI)	10.18 (8.18-12.65)	6.34 (5.36-7.39)
75th percentile (95% CI)	NE (23.26-NE)	13.47 (12.02-15.44)
Range	0.3+, 27.0+	0.4, 25.4+
6-month event-free rate (95% CI)	0.90 (0.84-0.94)	0.79 (0.72-0.85)
12-month event-free rate (95% CI)	0.68 (0.59-0.76)	0.36 (0.27-0.44)
18-month event-free rate (95% CI)	0.49 (0.39-0.59)	0.14 (0.07-0.23)
24-month event-free rate (95% CI)	0.37 (0.21-0.53)	0.05 (0.01-0.13)
Treatment difference		
Nominal p-value ^a	<0.0001	
HR (95% CI) ^b	0.35 (0.25-0.49)	

^a p-value is from a log-rank test stratified by ECOG PS (0 or 1) and history of brain metastases (yes or no).

^b HR is from stratified proportional hazards model. HR <1 favors amivantamab-chemotherapy treatment.

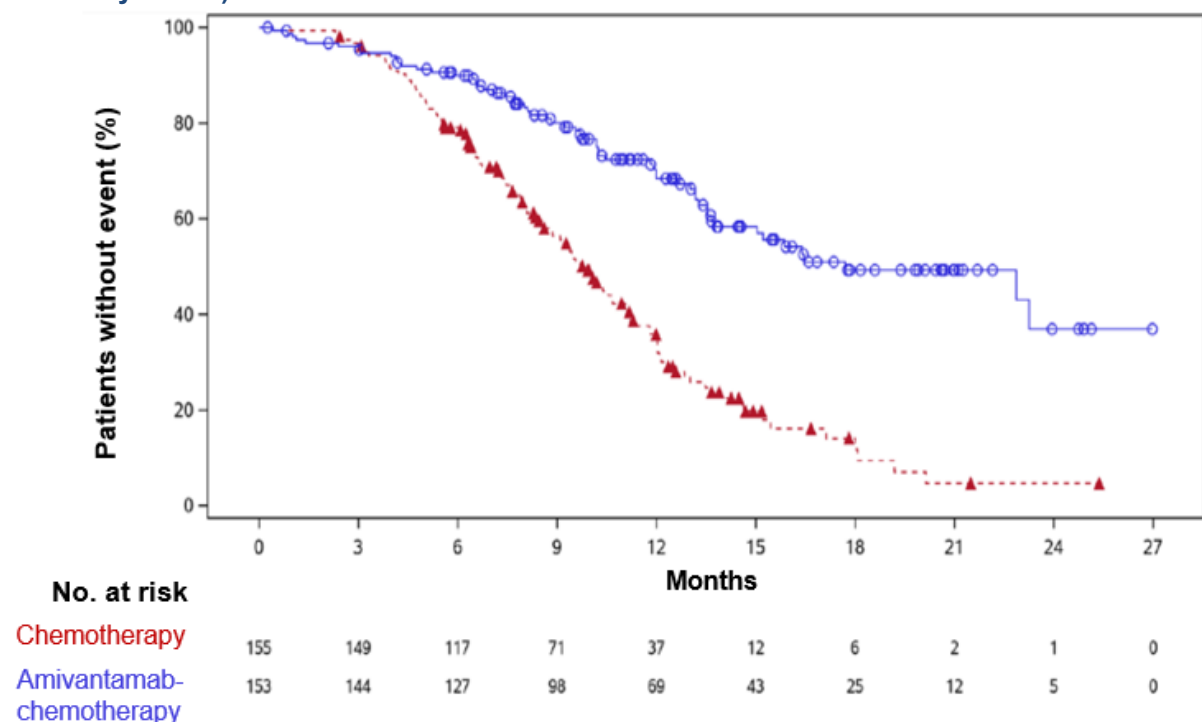
+ censored observation

Abbreviations: CI: confidence interval; DCO: data cut-off; ECOG: Eastern Cooperative Oncology Group; HR: hazard ratio; NE: not estimable; PS: performance status.

Source: EMA Rybrevant EPAR assessment report (Table 25)⁷⁷, Johnson & Johnson PAPILLON CSR 2023 (Table 21, Page 73)⁷³ and Felip *et al* 2024.⁸²

Company evidence submission template for amivantamab with carboplatin and pemetrexed for untreated EGFR Exon 20 insertion mutation-positive advanced non-small cell lung cancer [ID5110]

Figure 12: KM plot of time to subsequent systemic anti-cancer therapy (3rd May 2023 DCO; full analysis set)



Abbreviations: DCO: data cut-off; KM: Kaplan-Meier.

Source: EMA Rybrevant EPAR assessment report ⁷⁷, Johnson & Johnson PAPILLON CSR 2023 (Figure 7, Page 75)⁷³ and Felip *et al* 2024.⁸²

B.2.6.2.5 PFS after first subsequent therapy

At the 3rd May 2023 DCO, a higher proportion of patients had experienced progression after first subsequent therapy (PFS2) in the chemotherapy arm (39.4%) compared with amivantamab-chemotherapy arm (21.6%). Despite 65 patients in the chemotherapy arm treatment switching to receive amivantamab monotherapy as the first systemic subsequent therapy received at the 3rd May 2023 DCO, PFS2 analysis showed a 51% reduction in the risk of second disease progression or death in the amivantamab-chemotherapy arm compared with the chemotherapy arm (HR: 0.49 [95% CI: 0.32-0.76; nominal p=0.0010]).⁸² These results therefore suggest that receipt of amivantamab-chemotherapy at first line also confers a benefit in delaying patients' subsequent progression. These data further support the expected prolongation of OS in this patient population upon treatment with amivantamab-chemotherapy, in the current absence of mature OS data.

The median PFS2 was 17.25 months in the chemotherapy arm and not estimable in the amivantamab-chemotherapy arm. The PFS2 event-free rate at 18 and 24 months was 67% and 57% respectively for the amivantamab-chemotherapy arm compared with 46%, and 35% respectively for the chemotherapy arm, as summarised in Table 19. The associated Kaplan-Meier plot for PFS2 is presented in Figure 13.⁸²

Table 19: Summary of PFS2 (3rd May 2023 DCO; full analysis set)

	Amivantamab- chemotherapy (N=153)	Chemotherapy (N=155)
Event, n (%)	33 (21.6)	61 (39.4)
Censored, n (%)	120 (78.4)	94 (60.6)
Time to event (months)		
Median (95% CI)	NE (22.77-NE)	17.25 (13.96-21.52)
25th percentile (95% CI)	14.98 (13.67-18.63)	10.68 (8.87-12.06)
75th percentile (95% CI)	NE (NE-NE)	24.38 (21.52-NE)
Range	0.0+, 24.9+	0.0+, 26.9+
6-month event-free rate (95% CI)	0.94 (0.89-0.97)	0.95 (0.91-0.98)
12-month event-free rate (95% CI)	0.86 (0.79-0.91)	0.69 (0.60-0.77)
18-month event-free rate (95% CI)	0.67 (0.55-0.76)	0.46 (0.35-0.57)
24-month event-free rate (95% CI)	0.57 (0.39-0.72)	0.35 (0.23-0.48)
Treatment difference		
Nominal p-value ^a	0.0010	
HR (95% CI) ^b	0.49 (0.32-0.76)	

^a p-value is from a log-rank test stratified by ECOG PS (0 or 1) and history of brain metastases (yes or no).

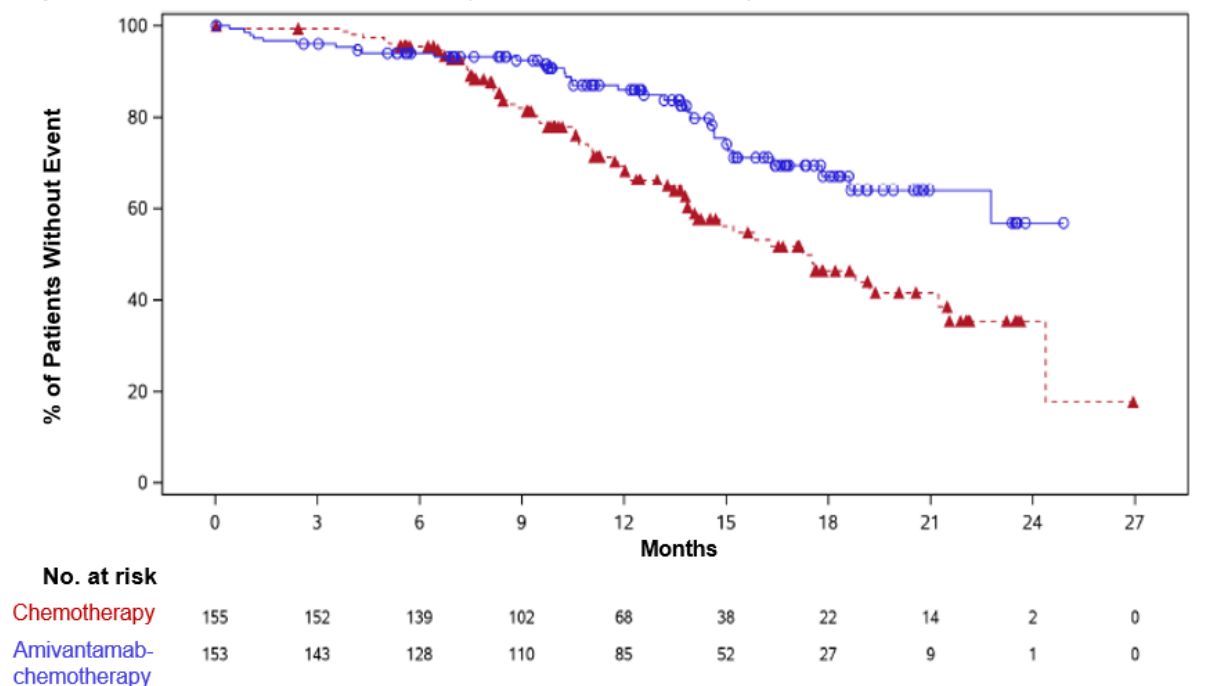
^b HR is from stratified proportional hazards model. HR <1 favors amivantamab-chemotherapy treatment.

+ censored observation

Abbreviations: CI: confidence interval; DCO: data cut-off; ECOG: Eastern Cooperative Oncology Group; HR: hazard ratio; NE: not estimable; PFS2: progression-free survival after first subsequent therapy; PS: performance status.

Sources: EMA Rybrevant EPAR assessment report (Table 26)⁷⁷, Johnson & Johnson PAPILLON CSR 2023 (Table 22, Page 76)⁷³ and Felip *et al* 2024.⁸²

Figure 13: KM plot of PFS2 (3rd May 2023 DCO; full analysis set)



Abbreviations: DCO: data cut-off; KM: Kaplan-Meier; PFS2: progression-free survival after first subsequent therapy.

Source: EMA Rybrevant EPAR assessment report (Figure 13)⁷⁷, Johnson & Johnson PAPILLON CSR 2023 (Figure 8, Page 77)⁷³ and Felip *et al* 2024.⁸²

B.2.6.2.6 Time to treatment discontinuation

TTD was investigated as an exploratory endpoint in the PAPILLON trial. At the 3rd May DCO, there was approximately three times as many patients in the amivantamab-chemotherapy arm who were continuing treatment compared with the chemotherapy arm (70 versus 24), as presented in Table 20. Additionally, a significant ($p < 0.0001$) prolongation in the median TTD was observed in the amivantamab-chemotherapy arm; 13.17 months (95% CI: 11.76-15.24), compared with 7.46 months (95% CI: 6.97-8.38) in the chemotherapy arm (HR: 0.38; 95% CI: 0.28-0.51). At 18 months, 35% of patients were still on active treatment in the amivantamab-chemotherapy arm compared with 5% of patients in the chemotherapy arm; these data are consistent with the BICR-assessed 18-month PFS and DOR.⁸² Carboplatin was given for a maximum of four cycles while pemetrexed was administered based on disease progression.

Table 20: Summary of TTD (3rd May 2023 DCO; full analysis set)

	Amivantamab- chemotherapy (N=153)	Chemotherapy (N=155)
Event, n (%)	83 (54.2)	131 (84.5)
Censored, n (%)	70 (45.8)	24 (15.5)
Time to event (months)		
Median (95% CI)	13.17 (11.76-15.24)	7.46 (6.97-8.38)
25th percentile (95% CI)	8.02 (6.28-9.56)	5.13 (4.27-5.85)
75th percentile (95% CI)	22.34 (18.40-NE)	11.14 (9.99-12.29)
Range	0.3, 27.0+	0.4, 25.4+
6-month event-free rate (95% CI)	0.84 (0.77-0.89)	0.66 (0.58-0.73)
12-month event-free rate (95% CI)	0.58 (0.49-0.66)	0.21 (0.15-0.29)
18-month event-free rate (95% CI)	0.35 (0.26-0.45)	0.05 (0.02-0.11)
24-month event-free rate (95% CI)	0.23 (0.13-0.35)	0.03 (0.01-0.08)
Treatment difference		
p-value ^a	<0.0001	
HR (95% CI) ^b	0.38 (0.28-0.51)	

^a p-value is from a log-rank test stratified by ECOG PS (0 or 1) and history of brain metastases (yes or no).

^b HR is from stratified proportional hazards model. HR <1 favors amivantamab-chemotherapy treatment.

+ censored observation

Abbreviations: CI: confidence interval; DCO: data cut-off; ECOG: Eastern Cooperative Oncology Group; HR: hazard ratio; NE: not estimable; PS: performance status; TTD: time to treatment discontinuation.

Source: EMA Rybrevant EPAR assessment report (Table 28)⁷⁷, Johnson & Johnson PAPILLON CSR 2023 (Table 24, Page 80)⁷³ and Felip *et al* 2024.⁸²

B.2.6.3 HRQoL Endpoints

As outlined in Table 6 in Section B.2.3.2, three PRO measures were reported in the PAPILLON trial, EORTC-QLQ-C30, PROMIS-PF, and EQ-5D-5L. For brevity, only EORTC-QLQ-C30 results (global health status and physical functioning) and EQ-5D-5L utility scores are presented in this submission; all data are published from the full analysis set at the 3rd May 2023 DCO.⁷³

B.2.6.3.1 EORTC-QLQ-C30

EORTC-QLQ-C30 measures functioning of cancer patients for all cancer types, including 30 items.⁷⁸ All scale and item scores have been linearly transformed to be in the range of 0–100, where a higher score represents a better level of functioning.⁷⁸ The change in score from baseline over time was analysed using mixed-effects model for repeated measures (MMRM).⁷⁸

EORTC-QLQ-C30 scores indicated that a larger proportion of patients in the amivantamab-chemotherapy arm had improved/stable global health status and physical functioning at 6- and 12-months versus patients in the chemotherapy arm, with 54% of patients in the amivantamab-chemotherapy arm reporting improved/stable global health status versus 43% in the chemotherapy arm at 6 months ($p = 0.064$), with this difference increasing at 12 months (36% versus 13% for amivantamab-chemotherapy versus chemotherapy, $P < 0.0001$).^{73, 83} Additionally, a higher proportion of patients in the amivantamab-chemotherapy arm reported improved / stable physical functioning compared with the chemotherapy arm at 6-months (57% vs 42%, $P = 0.008$) and 12-months (28% vs 14%, $P = 0.014$).⁸³

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These results were consistent across the role, emotional, cognitive and social functioning scales. Additionally, more patients in the amivantamab-chemotherapy arm reported an absence of symptoms compared with the chemotherapy arm.

Typically, adding more drugs into a treatment regimen increases toxicity, thereby reducing patients' HRQoL; however, EORTC-QLQ-C30 scores for global health status and physical functioning were broadly consistent between the two treatment arms at each key timepoint in the PAPILLON trial. Therefore, the fact that HRQoL is maintained upon addition of amivantamab demonstrates that amivantamab does not have substantial negative impacts on the HRQoL of patients. Changes in EORTC-QLQ-C30 global health status scores from baseline across the two treatment arms at key trial timepoints are presented in Table 21 and Figure 14, with physical functioning scores presented in Table 22 and Figure 15.

Table 21: Analysis of EORTC-QLQ-C30 global health status scores (3rd May 2023 DCO; full analysis set)

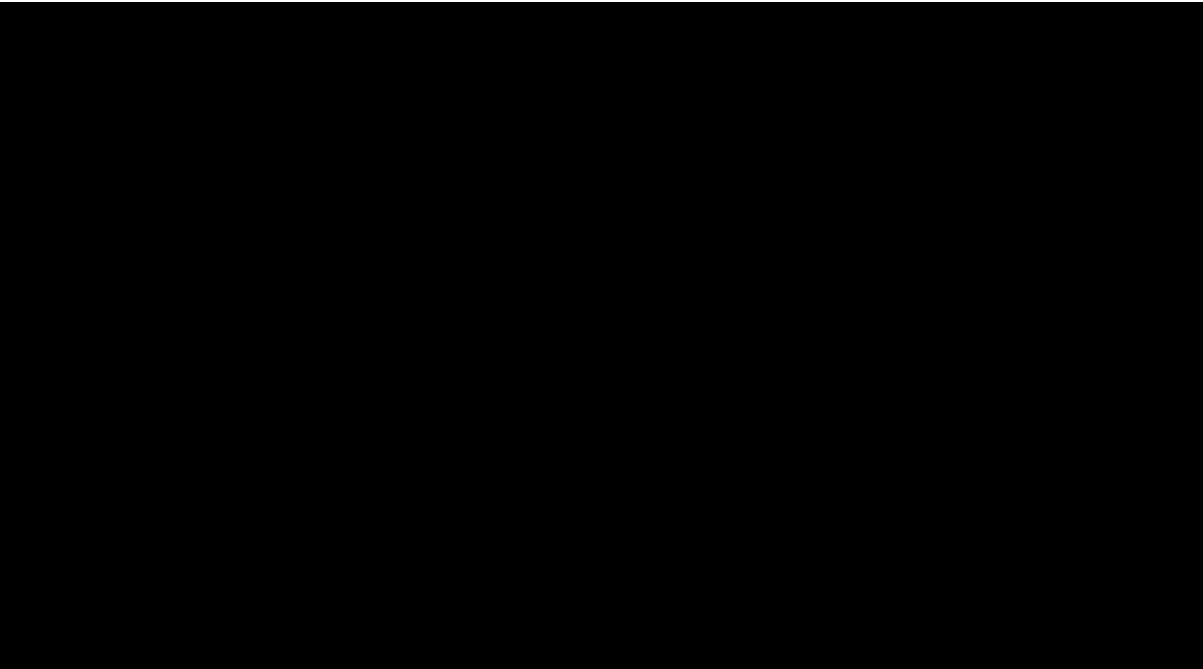
Global health status	Amivantamab- chemotherapy (N=153)	Chemotherapy (N=155)
Baseline		
n	■	■
Mean (SD)	■	■
Initiation of maintenance phase (Cycle 5 Day 1)		
n	■	■
Mean (SD)	■	■
Mean change from baseline	■	■
End of treatment		
n	■	■
Mean (SD)	■	■
Mean change from baseline	■	■

n for measured value is the number of patients with a non-missing value at the specified time point.

Abbreviations: DCO: data cut-off; EORTC-QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; SD: standard deviation.

Source: Johnson & Johnson PAPILLON HRQoL Data 2023 (TPROQLQ02).⁷⁴

Figure 14: Change from baseline of EORTC-QLQ-C30 global health status/quality of life score over time (3rd May 2023 DCO; full analysis set)



Note: Patient numbers at risk are informed by the availability of data at each study visit; blank values for chemotherapy are attributed to no available data at C31D1 and C33D1

Abbreviations: C: cycle; D: day; DCO: data cut-off; EORTC-QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; GHS: global health score; QoL: quality of life; SE: standard error.

Source: Johnson & Johnson PAPILLON HRQoL Data 2023 (GPROQL01).⁷⁴

Table 22: Analysis of EORTC-QLQ-C30 physical functioning scores (3rd May 2023 DCO; full analysis set)

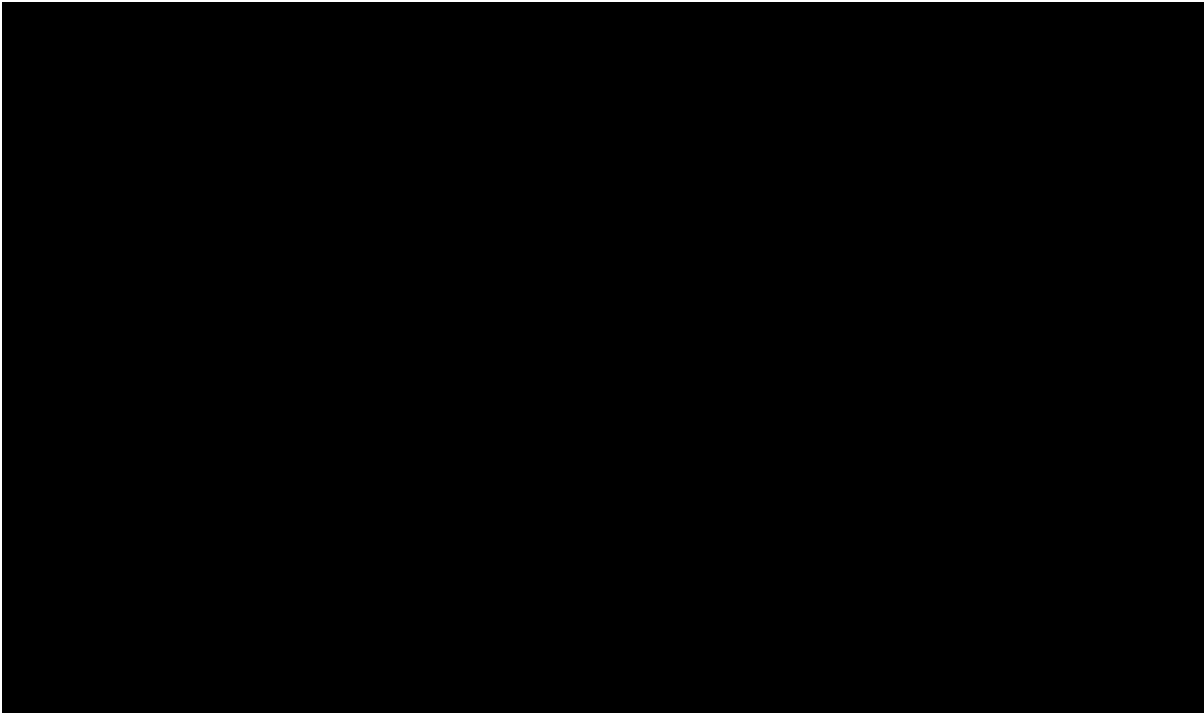
Physical functioning	Amivantamab- chemotherapy (N=153)	Chemotherapy (N=155)
Baseline		
n		
Mean (SD)		
Initiation of maintenance phase (Cycle 5 Day 1)		
n		
Mean (SD)		
Mean change from baseline		
End of treatment		
n		
Mean (SD)		
Mean change from baseline		

n for measured value is the number of patients with a non-missing value at the specified time point.

Abbreviations: DCO: data cut-off; EORTC-QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; SD: standard deviation.

Source: Johnson & Johnson PAPILLON HRQoL Data 2023 (TPROQLQ02).⁷⁴

Figure 15: Change from baseline of EORTC-QLQ-C30 physical functioning score over time (3rd May 2023 DCO; full analysis set)



Note: Patient numbers at risk are informed by the availability of data at each study visit; blank values for chemotherapy are attributed to no available data at C31D1 and C33D1
Abbreviations: C: cycle; D: day; DCO: data cut-off; EORTC-QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; SE: standard error.
Source: Johnson & Johnson PAPILLON HRQoL Data 2023 (GPROQLQ01).⁷⁴

B.2.6.3.2 EQ-5D-5L

EQ-5D-5L was an exploratory endpoint in the PAPILLON trial. EQ-5D-5L is a five-item questionnaire that assesses five domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The scores for the five dimensions are used to compute a single utility score ranging from 0–1 representing the general health status of the individual (but allows for values less than 0 by UK scoring algorithm).⁷⁸ The change in utility score from baseline over time was analysed using MMRM.⁷⁸ Randomised patients who received at least one dose of study treatment and had at least one evaluable post-baseline measurement were included in the analysis.⁷⁸

As with EORTC-QLQ-C30 scores, EQ-5D-5L utility scores were broadly consistent between the two treatment arms at each key timepoint in the trial (baseline, start of maintenance phase and end of treatment), further indicating that the addition of amivantamab does not negatively impact the HRQoL of patients. Changes in EQ-5D-5L utility scores from baseline across the two treatment arms are presented in Table 23 and Figure 16.

Table 23: Analysis of EQ-5D-5L utility scores (3rd May 2023 DCO; full analysis set)

Utility score	Amivantamab- chemotherapy (N=153)	Chemotherapy (N=155)
Baseline		
n	■	■

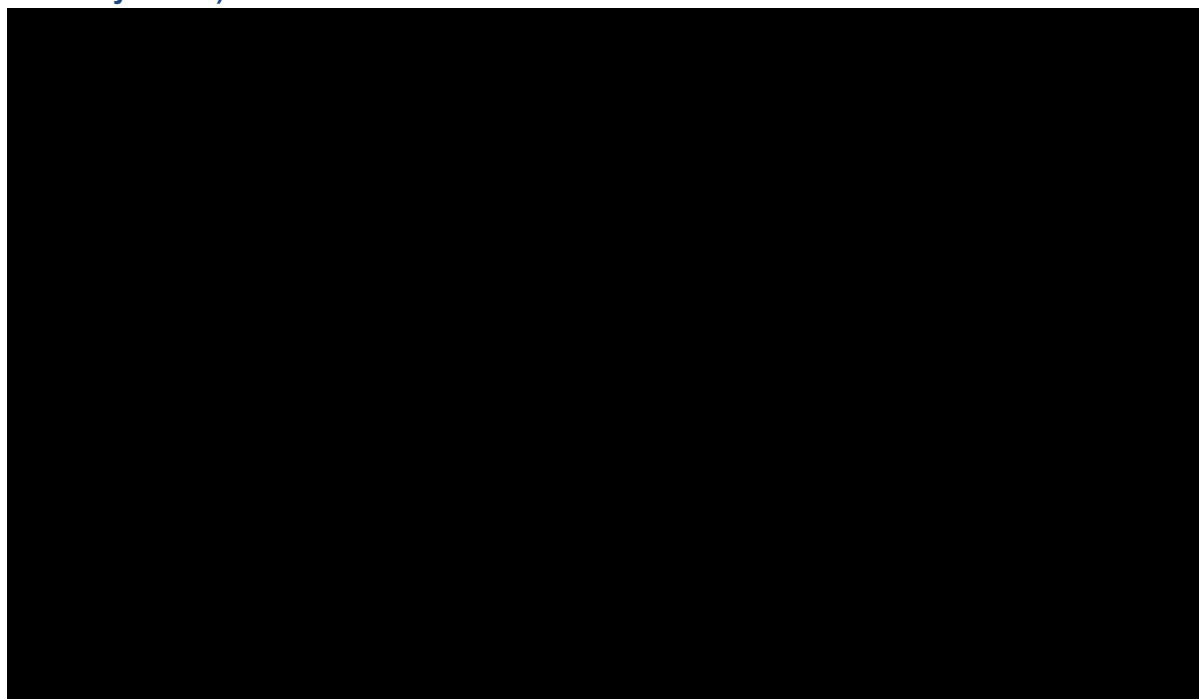
Utility score	Amivantamab- chemotherapy (N=153)	Chemotherapy (N=155)
Mean (SD) utility	██████	██████
Initiation of maintenance phase (Cycle 5 Day 1)		
n	██	██
Mean (SD) utility	██████	██████
Mean change from baseline	██	██
End of treatment		
n	██	██
Mean (SD) utility	██████	██████
Mean change from baseline	██	██

n for measured value is the number of patients with a non-missing value at the specified time point.

Abbreviations: DCO: data cut-off; SD: standard deviation.

Source: Johnson & Johnson PAPILLON HRQoL Data 2023 (TPROEQ02).⁷⁴

Figure 16: Change from baseline of EQ-5D-5L utility score over time (3rd May 2023 DCO; full analysis set)



Note: Patient numbers at risk are informed by the availability of data at each study visit; blank values for chemotherapy are attributed to no available data at C31D1 and C33D1

Abbreviations: C: cycle; DCO: data cut-off; D: day; SE: standard error.

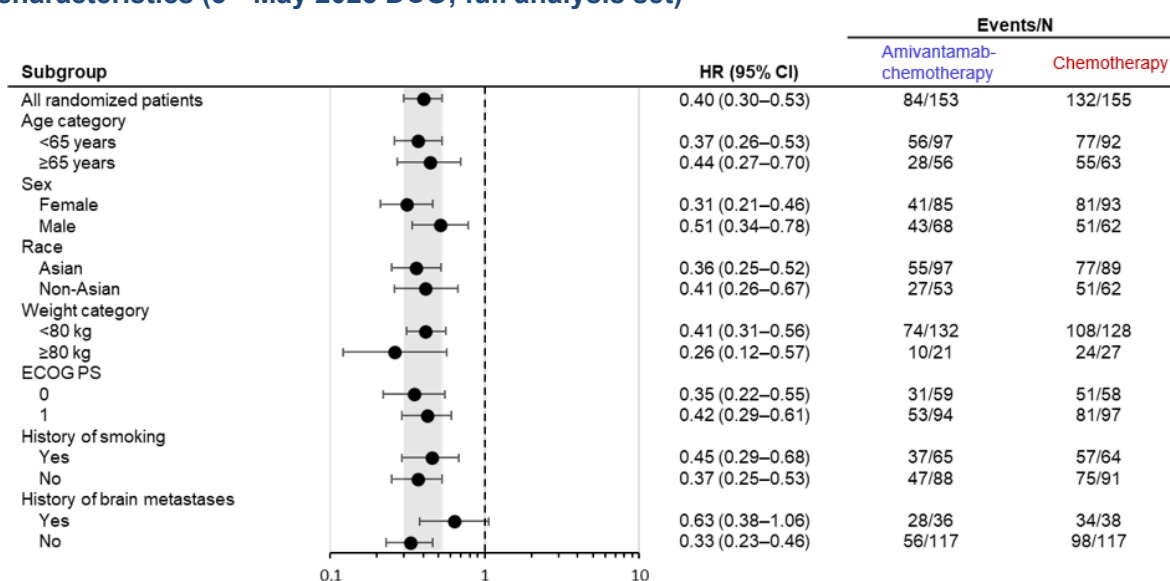
Source: Johnson & Johnson PAPILLON HRQoL Data 2023 (GPROEQ02).⁷⁴

B.2.7 Subgroup analysis

PFS assessed by BICR was analysed according to baseline disease characteristics, with the corresponding forest plot presented in Figure 17. A consistent benefit with amivantamab-chemotherapy was observed across all pre-specified subgroups. Of note, the treatment benefit was identified to be independent of ethnicity (people of Asian ethnicity versus non-Asian ethnicity) and age.

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Figure 17: Forest plot of BICR-assessed PFS for subgroups defined by baseline disease characteristics (3rd May 2023 DCO; full analysis set)



Abbreviations: BICR: blinded independent central review; CI: confidence interval; DCO: data cut-off; ECOG: Eastern Cooperative Oncology Group; HR: hazard ratio; PFS: progression-free survival; PS: performance status.

Source: Zhou *et al.* 2023 (Figure 1C).¹⁰

B.2.8 Meta-analysis

The PAPILLON trial was the only trial identified evaluating amivantamab-chemotherapy in this setting. As such, no meta-analysis was conducted as part of this submission.

B.2.9 Indirect and mixed treatment comparisons

Through the use of RWE and comprehensive clinical input gained across multiple advisory boards, the treatments that are observed to be typically prescribed in UK clinical practice, are platinum-based chemotherapy with or without IO therapy (pembrolizumab).^{3, 22}

Therefore, relevant comparators to amivantamab-chemotherapy in this submission are chemotherapy (carboplatin and pemetrexed) and pembrolizumab-chemotherapy (pembrolizumab with carboplatin and pemetrexed).⁷⁰ Whilst the PAPILLON trial provides head-to-head comparative evidence for amivantamab-chemotherapy versus chemotherapy, the clinical SLR update performed in June 2024 indicates that there are no head-to-head clinical trials for amivantamab-chemotherapy versus pembrolizumab-chemotherapy in patients with advanced NSCLC with EGFR Exon20 insertion mutations. This clinical SLR is detailed in Section B.2.1.

As such, an ITC was required to estimate the comparative efficacy of amivantamab-chemotherapy versus pembrolizumab-chemotherapy. In the absence of clinical trials for pembrolizumab-chemotherapy in EGFR Exon20 insertion mutation-positive advanced NSCLC, several sources of RWE were pooled in order to estimate the comparative efficacy of amivantamab-chemotherapy versus this treatment.

Company evidence submission template for amivantamab with carboplatin and pemetrexed for untreated EGFR Exon 20 insertion mutation-positive advanced non-small cell lung cancer [ID5110]

B.2.9.1 Selection of evidence sources

Clinical SLR

As detailed in Section B.2.1 and Appendix D, a *de novo* clinical SLR was conducted in January 2021 to identify relevant clinical evidence and safety outcomes in patients with EGFR Exon20 insertion mutation-positive advanced NSCLC, in line with the indication for amivantamab-chemotherapy. This SLR was subsequently updated in September 2021, February 2022, September 2023, March 2024 and June 2024 to ensure all recently published relevant evidence had been identified. A total of 60 unique studies reported in 91 records investigating treatment in the first-line setting for EGFR Exon20 insertion mutation-positive advanced NSCLC were included in the SLR.⁸⁴

Of the studies identified in the SLR, the PAPILLON trial was the only Phase 3 RCT identified in the indication of interest investigating amivantamab-chemotherapy versus relevant comparators in this submission (considered as chemotherapy and pembrolizumab-chemotherapy); no other Phase 2/3 RCTs were identified comparing amivantamab-chemotherapy to relevant comparators in UK clinical practice (Appendix D.1.3).

Selection of RWE databases

No RCTs were identified in the clinical SLR update providing clinical evidence on pembrolizumab-chemotherapy within patients with EGFR Exon20 insertion mutations. While several observational studies reporting results for the population of interest (patients with EGFR Exon20 insertion mutations) investigating IO combination therapies were identified in the clinical SLR update (Bazhenova et al. 2021, Girard et al. 2022 and Ou 2023; Appendix D.1.3), each study was limited to one database and thus featured particularly limited sample sizes. As such, the ITCs presented in this submission were conducted within a non-interventional, retrospective observational cohort study investigating first-line treatments in patients with EGFR Exon20 insertion mutation-positive advanced NSCLC across multiple databases: the NECTAR study.³

The primary objective of the NECTAR study was to understand and describe the current use of first-line treatments for patients with EGFR Exon20 insertion mutation-positive advanced NSCLC, and the associated outcomes of these treatments. The secondary objective was to evaluate the effectiveness of amivantamab-chemotherapy compared with treatment classes used in the real-world setting, through conducting ITCs between PAPILLON RCT data and the pooled RWE.

The NECTAR study identified and assessed potential RWE sources using a systematic and methodologically robust approach guided by the NICE RWE framework published in 2022.⁸⁵ An SLR in EGFR Exon20 insertion mutation-positive NSCLC (the March 2024 update of the clinical SLR) and a European RWE source landscaping assessment in advanced NSCLC were conducted to identify all available European data sources for patients with EGFR Exon20 insertion mutation-positive NSCLC, utilising the search strategy presented in Table 24 below. The search strategy ensured that the relevant patient population and relevant evidence were captured in the searches with appropriate prioritisation of evidence; the strategy was informed through expert consultation to ensure all potential data sources were captured. The majority of observational studies identified in the SLR were excluded using this search strategy, leaving three ongoing structured EU databases/ registers as potential sources to inform the ITC (see Figure 18). These three sources progressed to the next step of the database selection process.

Company evidence submission template for amivantamab with carboplatin and pemetrexed for untreated EGFR Exon 20 insertion mutation-positive advanced non-small cell lung cancer [ID5110]

Prior to study initiation, feasibility assessments for the US databases ConcertAI and COTA were conducted. These assessments considered the sample size of the patient populations with EGFR Exon20 insertion mutation-positive NSCLC that aligned with the PAPILLON trial criteria, the availability of key prognostic factors at baseline and the sample size of populations by type of first-line treatment. Both databases were subsequently included in the ITC, with further details provided in Section B.2.9.1.

Table 24: RWE search, relevance assessment and prioritisation criteria for inclusion in the NECTAR study

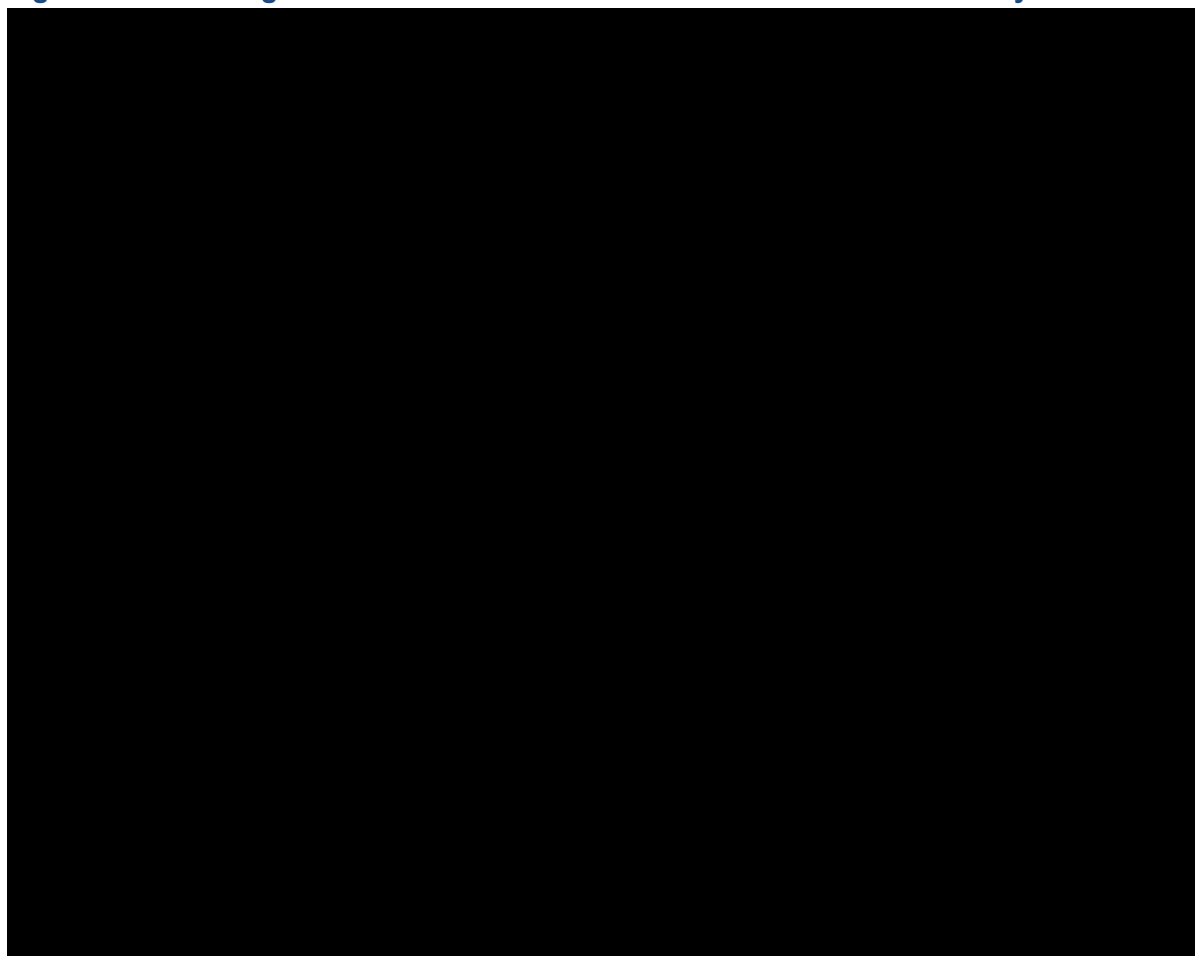
Criteria	Considerations
Data source search criteria	• RWE source • Includes patients in Europe • A structured register or database • Includes patients with EGFR Exon20 insertion mutated NSCLC • Ongoing data collection • Captures longitudinal treatment and outcomes
NECTAR relevance assessment	• Number of patients • Data collection period • Advanced EGFR Exon20 insertion mutated NSCLC • Patient demographics • Clinical characteristics • Treatment information • Outcomes • Follow-up • Industry data access • EGFR mutations and EGFR Exon20 insertion publications

Abbreviations: EGFR: epidermal growth factor receptor; NSCLC: non-small cell lung cancer; RWE: real world evidence.

Source: Johnson & Johnson Data on File. RWD selection report. 2024.⁸⁶

Overall, the EGFR Exon20 insertion mutation-positive NSCLC SLR identified 88 studies, with the advanced NSCLC RWE landscaping assessment identifying 133 data sources. All potential evidence sources were screened based on the data source search criteria (Table 25), with 14 data sources subsequently identified as suitable candidates for the NECTAR study. A flow diagram illustrating rationale for exclusion of evidence is presented in Figure 18.

Figure 18: Flow diagram for evidence sources included in the NECTAR study



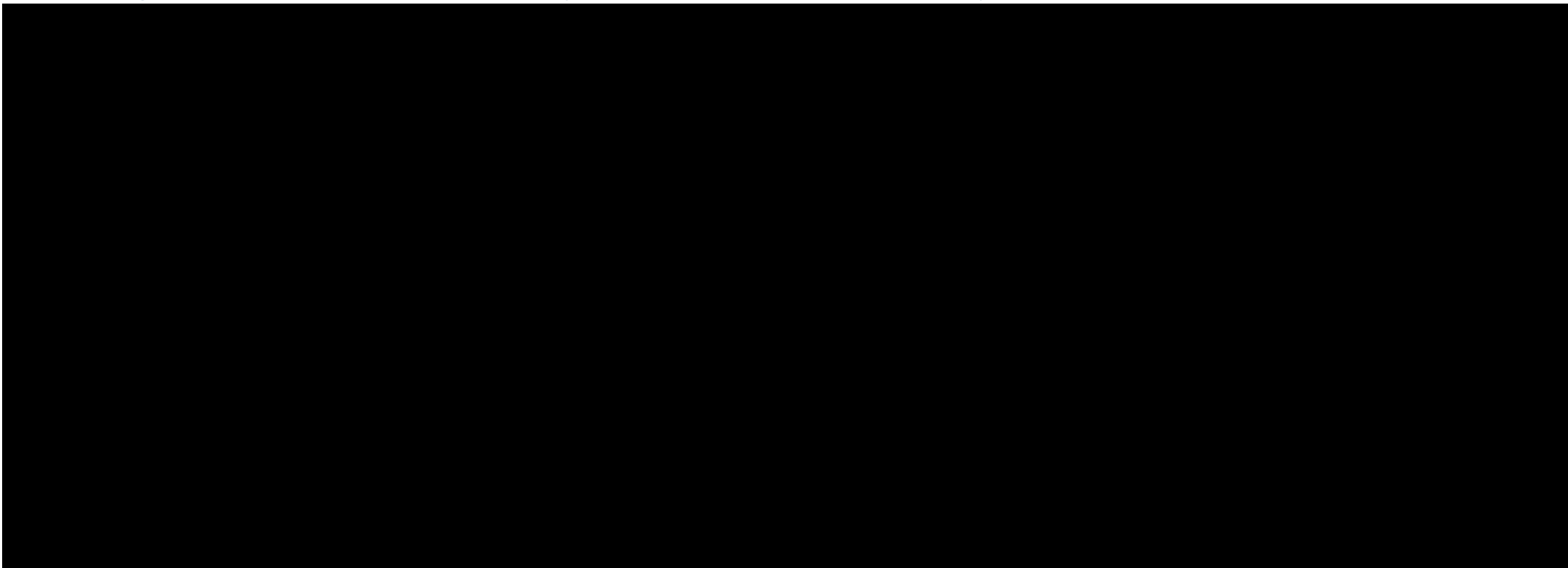
Note: The 'exon20ins systematic literature review' refers to the SLR which was conducted for patients with EGFR mutations (for both common EGFR mutations and EGFR Exon 20 insertion mutations) with results reported separately for studies in patients with EGFR Exon20 insertion mutations specifically.

Abbreviations: aNSCLC: advanced non-small cell lung cancer; EMEA: Johnson & Johnson Europe, Middle East and Africa; EU: European Union; RWD: real-world data.

The 14 potential evidence sources were assessed against the NECTAR study relevance criteria (Table 24), with a summary assessment of these sources are provided in Figure 19.

Overall, the NCRAS; England, ESME (France) and Network Genomic Medicine (Germany) databases were considered highly relevant, as they included patients over a sufficient period of time and had associated publications. Ultimately, the NCRAS and ESME databases were selected as the European databases for inclusion in the ITC through further considerations such as operational aspects impacting the feasibility of study execution. These European databases were combined with the US databases (COTA and ConcertAI) to provide the complete evidence base for pembrolizumab-chemotherapy. Further details on each of these databases are provided in Section B.2.9.1.

Figure 19: Relevance assessment and summary of evidence sources for the NECTAR study



Abbreviations: EGFR: epidermal growth factor receptor; ex20 ins: EGFR Exon20 insertion mutations NSCLC: non-small cell lung cancer; SACT: systemic anti-cancer therapy.

B.2.9.2 Sources included in the ITC

In total, four RWE databases were utilised in the NECTAR study: NCRAS, Epidemiological Strategy and Medical Economics (ESME), COTA and ConcertAI. The systematic identification of the databases is explored in more detail in Section B.2.9.1.

NCRAS is a population-based cancer registry covering England, which contains detailed and quality assured diagnostic and pathologic data for all people living in England diagnosed with malignant and pre-malignant neoplasms since 1971.^{87, 88} This database is linked to sources such as the Somatic Molecular Dataset (SMD), Systemic Anti-Cancer Therapy dataset (SACT), Cancer Outcomes and Services Dataset (COSD) and Hospital Episode Statistics (HES) datasets. Overall, the database covers around 500,000 patients per year.³

ESME is a multicentre, real-world database using a retrospective data collection process from medical centres in France. The ESME dataset contains three data platforms, one of which is in metastatic NSCLC and is therefore relevant to this submission: The French Epidemio-Strategy and Medical Economics Advanced or Metastatic Lung Cancer Data Platform (ESME-LC). This is a longitudinal database derived from routine care electronic health records for advanced and metastatic lung cancer patients treated at 36 participating centres across France⁸⁹ The ESME-LC database includes around 26,000 advanced and metastatic lung cancer patients.³

The COTA and ConcertAI databases are both US datasets. The COTA database provides detailed real-world oncology patient data, including patients with NSCLC and confirmed EGFR Exon20ins mutations from 5 unique sites of care across the US.⁹⁰ Additionally, the ConcertAI database sources clinical data from multiple partnerships spanning a broad range of US geographies.⁹¹ Inclusion of patients from the US databases was considered suitable as there were no notable differences in observed demographics and baseline characteristics between patients included in the US databases versus the European databases, with inclusion of the US data enriching this real-world evidence source.

B.2.9.3 Feasibility assessment

A feasibility assessment of the four databases was performed to determine their suitability for informing an ITC, with a summary of findings provided below.

Design of evidence sources

A summary of key characteristics of the data sources considered for use in the ITC are summarised in Table 25.

The PAPILLON trial is a multi-centre trial conducted across 25 countries with three UK sites, whereas the RWE databases are country-specific. Overall, the data sources span from 2012–2023, with the ESME RWE providing the longest median duration of follow-up of 51.5 months. Each database provided individual patient-level data (IPD), which could be used to inform the ITC. The only caveat was that IPD from the ESME database remained indirectly accessible for the study duration. The source data for ESME remained external throughout the study, but Johnson & Johnson developed analytical programmes which were shared with the RWE source to ensure the analyses were conducted in line with the other RWE sources. Implications on the

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availability of data from the ESME database are discussed further in the methodology for the ITCs (see below).

Table 25: Evidence sources used in the ITC

Data Source	Country	Design	Period (years)	Median follow-up (months)	Data available
PAPILLON	Multi-centre	RCT	██████	14.6 (PFS) ^a , 20.9 (OS) ^b	IPD
NCRAS	UK	RWE	2016–2022	27.2	IPD
ESME	France	RWE	██████	██	IPD; indirectly accessible
COTA	US	RWE	█	██	IPD
ConcertAI	US	RWE	██████	██	IPD

^a Median follow-up (months) for amivantamab-chemotherapy at the 3rd May 2023 DCO.

^b Median follow-up (months) at the 31st October 2023 DCO.

Abbreviations: DCO: data cut-off; IPD: individual patient data; ITC: indirect treatment comparison; NCRAS: National Cancer Registration and Analysis Service; OS: overall survival; PFS: progression free survival; RCT: randomised controlled trial; RWE: real-world evidence; UK: United Kingdom; US: United States.

Eligibility criteria

The population of interest in this submission is patients with EGFR Exon20 insertion mutation-positive advanced NSCLC.

The PAPILLON trial had a pre-defined eligibility criteria, which are presented in Section B.2.3.1. In order to more closely align the pooled patient population from the RWE databases with the PAPILLON trial, additional eligibility criteria were applied to each RWE data source. The eligibility criteria for the RWE data sources are presented in Table 26.

Following the application of this eligibility criteria, N=██ patients were included from the pooled RWE sources. Patient characteristics following the application of these criteria are presented in the following section.

Table 26: Eligibility criteria for RWE data sources

Eligibility criteria for patients in the RWE data sources	• Adult patients (≥18 years of age) • Histologic confirmation of non-squamous advanced NSCLC^a • EGFR Exon20 insertion mutation diagnosis before 30 days after the start of first-line treatment • No record of other malignancy in the 24 months before advanced NSCLC diagnosis • Received first-line treatment, following advanced NSCLC diagnosis • Record of ECOG performance status of 0 or 1 at the time of first-line treatment in the advanced NSCLC phase, with patients with missing ECOG performance status included

^a Includes patients diagnosed with Stage IIIB, IIIC, IV, IV-A, or IV-B NSCLC, or diagnosed with early-stage NSCLC and subsequently developed recurrent or progressive disease

Abbreviations: ECOG: Eastern Cooperative Oncology Group; EGFR: epidermal growth factor receptor; NSCLC: non-small cell lung cancer; RWE: real-world evidence.

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Patient characteristics

Key demographic and baseline patient characteristics for each of the RWE databases, following the application of the inclusion and exclusion criteria, are presented in Table 27. These data are presented alongside demographic and baseline characteristics of the amivantamab-chemotherapy arm of the PAPILLON trial for means of comparison. Characteristics are also summarised for the total pooled RWE population (N=■).

Key baseline characteristics for the pooled RWE by relevant treatment arm for the ITC (i.e., pembrolizumab-chemotherapy) are provided in Section B.2.9.5.

Table 27: Demographics and baseline patients characteristics from the PAPILLON trial and RWE databases

Characteristic, n (%)	PAPILLON (ACP)	Overall RWE	ESME	NCRAS	ConcertAI	COTA
N	153	■	■	23	■	■
Sex						
Female	85 (55.6)	■	■	16 (69.6)	■	■
Male	68 (44.4)	■	■	7 (30.4)	■	■
ECOG performance status^a						
0	54 (35.3)	■	■	10 (43.5)	■	■
1	99 (64.7)	■	■	13 (56.5)	■	■
Missing	0 (0.0)	■	■	-	■	■
Smoking status						
Current or prior smoker	65 (42.5)	■	■	0 (0.0)	■	■
No smoking history	88 (57.5)	■	■	0 (0.0)	■	■
Missing	0 (0.0)	■	■	23 (100)	■	■
Metastatic site						
Adrenal glands						
No	NR	■	■	21 (91.3)	■	■
Yes	■	■	■	2 (8.7)	■	■
Bone						
No	NR	■	■	19 (82.6)	■	■
Yes	■	■	■	4 (17.4)	■	■
Brain						
No	■	■	■	23 (100)	■	■
Yes	■	■	■	0	■	■
Liver						
No	135 (88.2)	■	■	19 (82.6)	■	■
Yes	■	■	■	4 (17.4)	■	■
Lymph nodes						
No	NR	■	■	12 (52.2)	■	■

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Characteristic, n (%)	PAPILLON (ACP)	Overall RWE	ESME	NCRAS	ConcertAI	COTA
Yes				11 (47.8)		
Number of metastatic locations (CT)						
0	NR			0		
1	NR			5 (21.7)		
2	NR			10 (43.5)		
3	NR			5 (21.7)		
4	NR			1 (4.3)		
5	NR			2 (8.7)		
6	NR			0 (0.0)		
7	NR			0 (0.0)		

Abbreviations: ACP: amivantamab chemotherapy; CT: computed tomography; ECOG: Eastern Cooperative Oncology Group; ESME: Epidemiological Strategy and Medical Economics; NCRAS: National Cancer Registration and Analysis Service; RWD: real-world data.

Comparators

The PAPILLON trial provides direct evidence for amivantamab-chemotherapy versus chemotherapy. In this context, chemotherapy refers only to platinum-based chemotherapy consisting of carboplatin and pemetrexed, which is the predominant regimen used in UK clinical practice, as confirmed by clinical experts in advisory boards conducted in June 2023, May 2024 and August 2024.^{5, 22, 23}

The NCRAS, ESME, COTA and ConcertAI databases informing the NECTAR study provided clinical evidence for patients receiving pembrolizumab-chemotherapy treatment regimens, for which the 'chemotherapy' component of the regimen comprised a variety of different platinum-based chemotherapy regimens, aside from carboplatin and pemetrexed. However, all patients captured in this treatment arm received the same IO treatment, pembrolizumab.

Owing to the rarity of patients with EGFR Exon20 insertion mutations, it was necessary to pool individual regimens into an overall treatment class for 'platinum chemotherapy + IO' within the ITC in order to maximise the sample size and ensure a robust analysis. The 'platinum chemotherapy + IO' treatment class in the NECTAR study was assumed to reflect pembrolizumab-chemotherapy, which was a defensible assumption given that ■ of patients within this treatment class received pembrolizumab in combination with carboplatin plus pemetrexed.

Outcomes

The endpoints of interest to the ITC were OS and TTNT. PFS was not able to be assessed as the exact date of progression was not available from the RWE sources. Outcome definitions were aligned between the PAPILLON trial and RWE sources:

- **OS:** the time between the index date and death from any cause. Patients still alive at the end of the study period were censored at the study end date. For patients who were alive or for whom vital status was unknown, this interval was censored at the date the patient was last known to be alive

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- **TTNT:** the time between the index date and the start date of subsequent treatment or death, whichever came first. Patients alive without a record of subsequent therapy were censored at the date of last contact. This was included as an outcome of interest instead of PFS, as the RWE datasets could not capture systematic progressive disease data or RECIST v1.1 criteria. Additionally, the lack of exact disease progression dates captured from pooled RWE meant that PFS could not be estimated accurately, resulting in the need to include an alternative disease progression estimate such as TTNT.

Summary of the feasibility assessment

No other Phase 3 RCTs investigating amivantamab-chemotherapy versus relevant comparators in patients with locally advanced or metastatic EGFR Exon20 insertion mutation-positive NSCLC were identified, other than the PAPILLON trial, in the clinical SLR. Furthermore, no clinical studies investigating pembrolizumab-chemotherapy in the EGFR Exon20 insertion mutation-positive advanced NSCLC study were identified. As such, clinical evidence for pembrolizumab-chemotherapy was generated by pooling RWE from two European and two US databases. Each database produced IPD that could inform the ITC analysis.

The databases were selected through feasibility assessments and systematic searches, providing a total pooled population of N=█ patients with EGFR Exon20 insertion mutation-positive advanced NSCLC following the exclusion of patients who did not align with key eligibility criteria for the PAPILLON trial. The implementation of this criteria resulted in a pooled patient population with broadly generalisable characteristics to the PAPILLON trial without population adjustment, with some imbalances in ECOG scores and locations of metastasis between the patient populations.

The key outcomes assessed in the ITC were OS and TTNT, which were required to inform the cost-effectiveness analysis for amivantamab-chemotherapy versus pembrolizumab-chemotherapy.

B.2.9.4 Methodology for the indirect treatment comparisons

Patient populations included in the analysis

IPD available for all patients in the amivantamab-chemotherapy arm of the PAPILLON trial (N=153) were used in the ITC. The index date for patients in the PAPILLON trial was the date that the first dose of amivantamab was received. IPD from the RWE sources was pooled for comparison of patient baseline characteristics, first-line treatments and outcomes. The pooled dataset was subsequently stratified by first-line treatment received by patients (with N=█ patients receiving pembrolizumab-chemotherapy in the dataset). The study index date for the RWE databases was the date of initiation of first-line treatment for advanced NSCLC with a confirmed EGFR Exon20 insertion mutation.

For the PAPILLON trial and the RWE databases, the last available date of follow up was the last encounter/contact date, last enrolment date, or continuous enrolment end date (if applicable), or the DCO date, whichever took place the earliest.

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Identification and adjustment of prognostic variables

Patients included in the pooled RWE, who received pembrolizumab-chemotherapy in the first-line setting, were re-weighted to provide a similar distribution of confounders (characteristics that may be considered as prognostic factors) compared to the amivantamab-chemotherapy arm of the PAPILLON trial.

Potential prognostic factors in advanced NSCLC were identified and ranked based on a SLR and expert validation conducted in 2021. Further details on this exercise may be found in the accompanying report submitted within the reference pack.⁹² The full list of factors considered for adjustment in the analysis, in rank order, was:

1. [REDACTED]
2. [REDACTED]
3. [REDACTED]
4. [REDACTED]
5. [REDACTED]
6. [REDACTED]
7. [REDACTED]
8. [REDACTED]

A 'Missing' category was included for variables, where needed. Variables with high numbers of missing values or that lead to lack of convergence of the propensity score (PS) model (see below) were not included in the adjustment. An advisory board consisting of clinical experts in NSCLC and EGFR Exon20 insertion mutations concluded that the selected variables were sufficient for adjustment.²²

Propensity score weighting

PSs are used in ITCs to adjust for clinically important and prognostic characteristics between the patient populations being compared, as imbalances in these characteristics may influence patient outcomes. Specifically, PSs are the probability (likelihood) of each patient receiving a particular treatment conditional on their observed baseline covariates.⁹³ Once PSs are derived for each patient, patients in either population can then be matched or weighted based upon their PSs.

For the ITCs, PSs were estimated using logistic regression. A binary treatment variable was chosen as the dependent variable, which is the variable being predicted. The identified prognostic factors were included as explanatory variables, which are factors that are used to predict the dependent variable. Covariates were included in the logistic regression model in order of the ranking described above. Adding these covariates into the model was also dependent on data availability and level of missing data from the data sources.

The estimated PSs were used to derive weights for each patient using estimand-specific weighting formulas. Specifically, the PSs were converted to 'average treatment effect of the Company evidence submission template for amivantamab with carboplatin and pemetrexed for untreated EGFR Exon 20 insertion mutation-positive advanced non-small cell lung cancer [ID5110]

treated (ATT) inverse probability weights'. This approach was chosen over other available approaches (such as average treatment effect [ATE] or average treatment effect among the overlap population [ATO]) as IPD were available from the RWE data sources. As such, patients in the amivantamab-chemotherapy arm of the PAPILLON trial received a weight of 1 (i.e., remained unchanged), while patients in the comparator arm were reweighted by a factor of $PS/(1-PS)$ which estimates the treatment effect in the amivantamab-chemotherapy arm.^{94, 95}

To maintain the original sample size for both of the adjusted populations and to reflect the associated uncertainty, ATT weights were multiplied by the ratio of the original sample size versus the sum of the ATT weights, making the sum of these recalculated weights equal to the original sample size.

Estimating treatment effect

An unbiased treatment effect was then estimated using a multivariable model, which included all of the relevant prognostic variables (listed above) as covariates together with the treatment indicator. Multivariable analyses were performed using the prognostic variables as covariates in the regression model (Cox regression for time to event endpoints). Each factor was assessed separately (they were included in the model together with treatment) as well as including all covariates in a multivariable model to assess the outcomes. The same set of covariates considered for PS methods were included/adjusted for in the outcome regression modelling, after assessing the impact of missingness in the prognostic factors.

Time-to-event endpoints explored in these ITCs were summarised for amivantamab-chemotherapy and pembrolizumab-chemotherapy treatment arms using the total number and percentage of patients experiencing events (TTNT and OS) and the number and percentage of censored patients. KM estimates were produced and presented with summary statistics such as the median time to event (with a 95% CI, when estimable). Additionally, HRs with corresponding 95% CIs were reported, estimated from a weighted Cox proportional hazards model with treatment as the only covariate.

B.2.9.5 Results of the indirect treatment comparisons

B.2.9.5.1 Adjustment of baseline characteristics

Adjustment of baseline characteristics

Due to IPD from the ESME trial being indirectly accessible, the amivantamab-chemotherapy arm and the pembrolizumab-chemotherapy indirectly accessible population (ESME) were reweighted separately to the pembrolizumab-chemotherapy directly accessible population (NCRAS, COTA and ConcertAI), with the outcomes then pooled between the two separate analyses.

The unadjusted and ATT-adjusted baseline characteristics for the amivantamab-chemotherapy arm of the PAPILLON trial and the pembrolizumab-chemotherapy directly accessible population (NCRAS, COTA and ConcertAI) are presented in Table 28. Following adjustment, all variables were broadly aligned between the two treatment groups, with some residual imbalance in the proportion of patients with brain metastases.

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The unadjusted and ATT-adjusted baseline characteristics for the amivantamab-chemotherapy arm of the PAPILLON trial and the pembrolizumab-chemotherapy indirectly accessible population (ESME) are presented in Table 29. Following adjustment, all variables were well aligned.

The distribution of PS weights for both the directly accessible and indirectly accessible patient population are presented in Figure 15 and Figure 16, Appendix O.2.

Table 28: Unadjusted and ATT-adjusted baseline characteristics for patients in the amivantamab-chemotherapy arm and directly accessible pembrolizumab-chemotherapy population (NCRAS, ConcertAI and COTA)

Variable, n (%)	PC-IO Unadjusted	ACP Unadjusted	SMD Unadjusted	PC-IO Adjusted	ACP Adjusted	SMD Adjusted
Total, n	■	■		■	■	
ECOG performance status						
0	■	■	■	■	■	■
1	■	■		■	■	
Missing	■	■		■	■	
Metastatic site brain						
No	■	■	■	■	■	■
Yes	■	■		■	■	
Metastatic site liver						
No	■	■	■	■	■	■
Yes	■	■		■	■	
Age groups (cut-off=65 years)						
≤65 years	■	■	■	■	■	■
>65 years	■	■		■	■	

Abbreviations: ACP: amivantamab-chemotherapy; ATT: average treatment effect in the treated; ECOG: Eastern Cooperative Oncology Group; IPD: individual patient-level data; NCRAS: National Cancer Registration and Analysis Service; PC-IO; platinum chemotherapy-immune-oncology; SMD: standardised mean difference.

Table 29: Unadjusted and ATT-adjusted baseline characteristics for patients in the amivantamab-chemotherapy arm and indirectly accessible pembrolizumab-chemotherapy population (ESME)

Variable, n (%)	PC-IO Unadjusted	ACP Unadjusted	SMD Unadjusted	PC-IO Adjusted	ACP Adjusted	SMD Adjusted
Total, n	■	■	■	■	■	■
ECOG performance status						
0	■	■	■	■	■	■
1	■	■		■	■	
Missing	■	■		■	■	
Metastatic site brain						
No	■	■	■	■	■	■
Yes	■	■		■	■	
Metastatic site liver						

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Variable, n (%)	PC-IO Unadjusted	ACP Unadjusted	SMD Unadjusted	PC-IO Adjusted	ACP Adjusted	SMD Adjusted
No	████████	████████	■	████████	████████	■
Yes	██████	████████		████████	████████	
Age groups (cut-off=65 years)						
≤65 years	████████	████████	■	████████	████████	■
>65 years	████████	████████		████████	████████	

Abbreviations: ACP: amivantamab-chemotherapy; ATT: average treatment effect in the treated; ECOG: Eastern Cooperative Oncology Group; IPD: individual patient-level data; NCRAS: National Cancer Registration and Analysis Service; PC-IO; platinum chemotherapy–immune-oncology; SMD: standardised mean difference.

Results

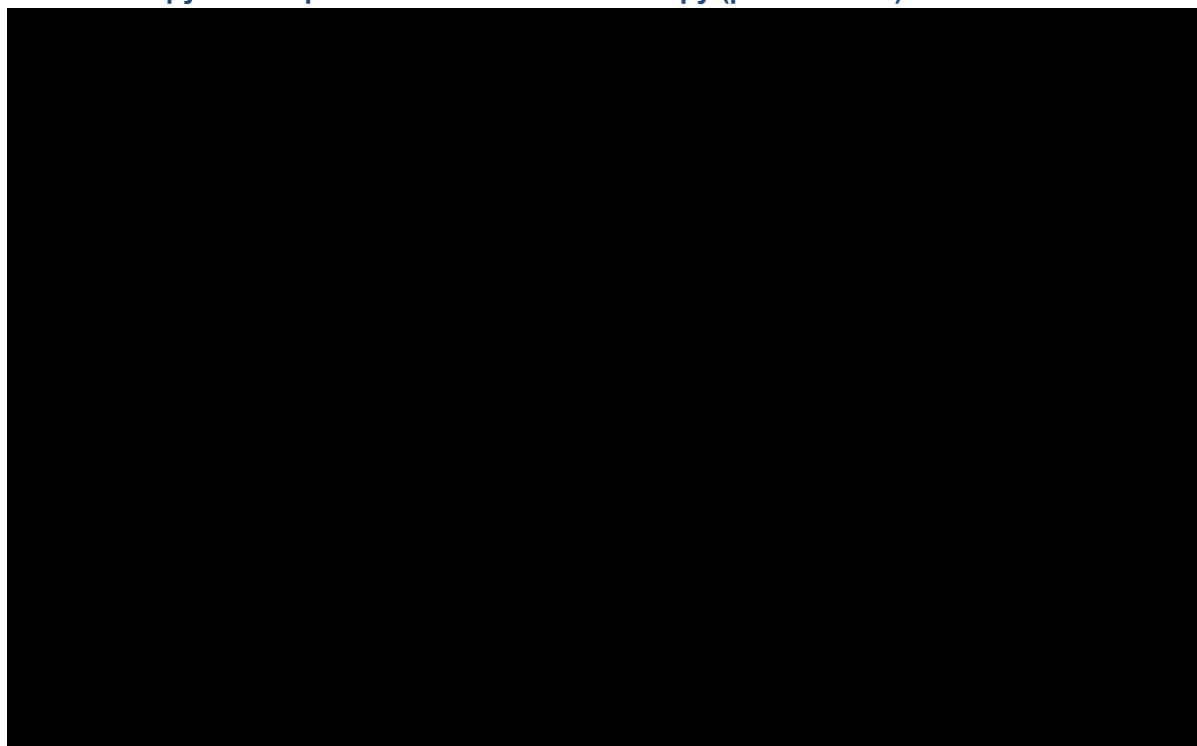
Time to next treatment

Unadjusted and ATT-adjusted TTNT KM curves for amivantamab-chemotherapy and the pooled pembrolizumab-chemotherapy population (NCRAS, ESME, COTA, ConcertAI) are presented in

Figure 20.

Weighting improved the treatment effect of amivantamab-chemotherapy versus pembrolizumab-chemotherapy. The adjusted analysis demonstrates that amivantamab–chemotherapy results in a [REDACTED]% reduction in the risk of initiating next treatment versus pembrolizumab-chemotherapy (adjusted TTNT HR: [REDACTED] [95% CI: [REDACTED]-[REDACTED]; Wald p-value<[REDACTED]). Furthermore, median TTNT for amivantamab–chemotherapy was substantially longer ([REDACTED] months [95% CI: [REDACTED]-[REDACTED]]) than pembrolizumab-chemotherapy ([REDACTED] months [95% CI: [REDACTED]-[REDACTED]]).

Figure 20: Unweighted and ATT-weighted TTNT KM curves for amivantamab-chemotherapy versus pembrolizumab-chemotherapy (pooled RWE)



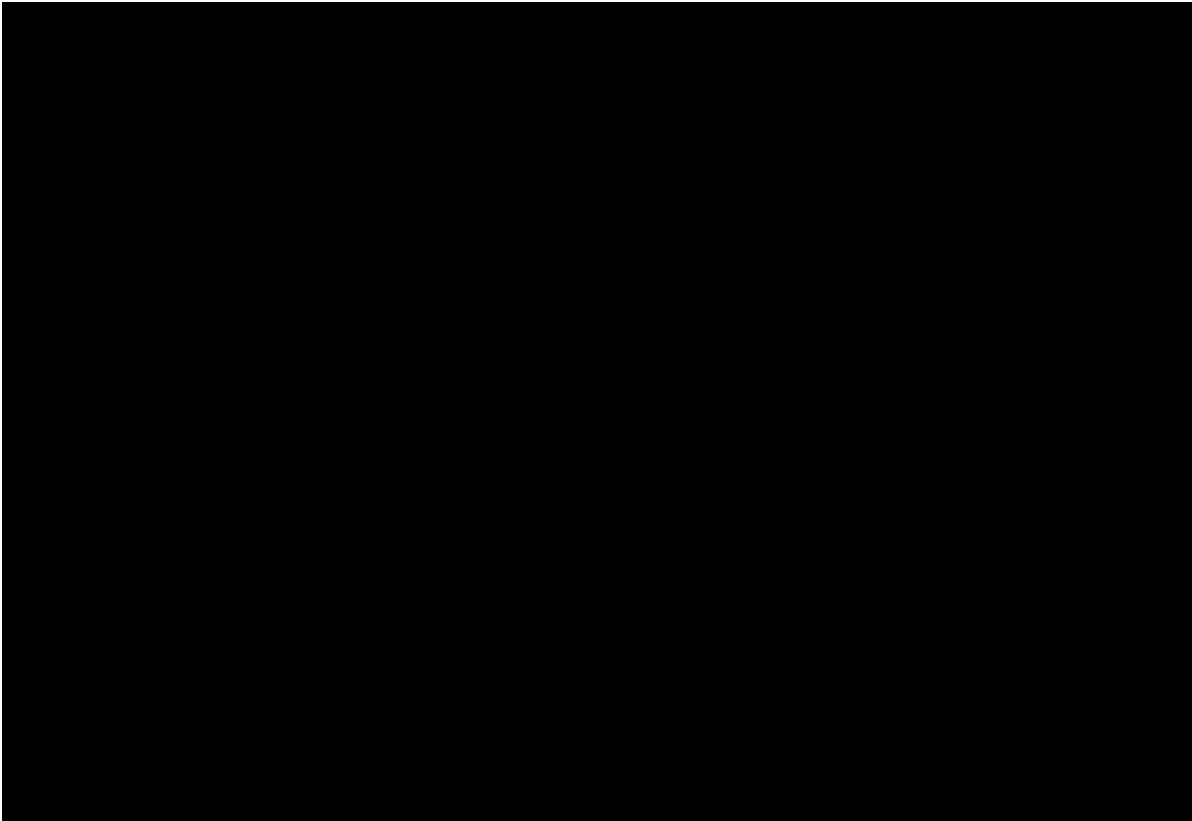
Abbreviations: ACP: amivantamab-chemotherapy; ATT: average treatment effect in the treated; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; ESME: Epidemiological Strategy and Medical Economics; HR: hazard ratio; IO: immunotherapy; NA: not applicable; NCRAS: National Cancer Registration and Analysis Service; TTNT: time to next treatment.

Overall survival

Unadjusted and ATT-adjusted OS KM curves for amivantamab-chemotherapy and the pooled pembrolizumab-chemotherapy population (NCRAS, ESME, COTA, ConcertAI) are presented in Figure 21. Importantly, OS data for amivantamab was informed by the most recent 31st October 2023 DCO of the PAPILLON trial providing further survival data.

The ITC results demonstrate that amivantamab–chemotherapy results in a statistically significant █% reduction in the risk of death versus pembrolizumab-chemotherapy ATT-adjusted (OS HR: █ [95% CI: █-█]; Wald p-value=█). In the adjusted analysis, median OS for amivantamab–chemotherapy was █ (95% CI: █-█); however, median OS █ in the pembrolizumab-chemotherapy treatment arm (█ months [95% CI: █-█]).

Figure 21: Unweighted and ATT-weighted OS KM curves for amivantamab-chemotherapy versus pembrolizumab-chemotherapy (pooled RWE)



Abbreviations: ACP: amivantamab-chemotherapy; ATT: average treatment effect in the treated; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; ESME: Epidemiological Strategy and Medical Economics; HR: hazard ratio; IO: immunotherapy; NA: not applicable; NCRAS: National Cancer Registration and Analysis Service; OS: overall survival.

Summary

A summary of unadjusted and ATT-weighted efficacy outcomes for amivantamab-chemotherapy versus pembrolizumab-chemotherapy are presented in Table 30. The results demonstrated that amivantamab–chemotherapy resulted in a statistically significant improvement for both unadjusted and adjusted TTNT and OS compared to pembrolizumab-chemotherapy. These results strongly support the treatment benefit amivantamab–chemotherapy would provide to patients, while also demonstrating the lack of efficacy that currently available treatments have in the EGFR Exon20 insertion mutation-positive advanced NSCLC population.

Table 30: Summary of ITC results for amivantamab-chemotherapy versus pembrolizumab-chemotherapy

Outcome	Unadjusted analysis			ATT-adjusted analysis		
	Median, months (95% CI)	HR (95% CI)	Wald p-value	Median, months (95% CI)	HR (95% CI)	Wald p-value
TTNT						
Amivantamab-chemotherapy						

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Pembrolizumab-chemotherapy						
OS						
Amivantamab-chemotherapy						
Pembrolizumab-chemotherapy						

Abbreviations: ACP: amivantamab-chemotherapy; ATT: average treatment effect in the treated; CI: confidence interval; HR: hazard ratio; ITC: indirect treatment comparison; OS: overall survival; TTNT: time to next treatment.

B.2.9.6 Uncertainties in the indirect and mixed treatment comparisons

ITCs were conducted as part of the NECTAR study for amivantamab-chemotherapy versus pembrolizumab-chemotherapy, in the absence of head-to-head clinical data. As no clinical trials were identified investigating pembrolizumab-chemotherapy specifically in patients with untreated, EGFR Exon20 insertion mutation-positive advanced NSCLC, the clinical efficacy for this treatment was informed by pooled RWE from the NCRAS (England), ESME (France), COTA (US) and ConcertAI (US) databases.

The most appropriate European databases were selected through a systematic search and prioritisation framework guided by the NICE RWE framework, and were combined with two US based databases, following a feasibility assessment, to create a pooled patient population of sufficiently robust size (N=■) for analysis.⁸⁵ The pooled population was then separated by first-line treatment, and an ITC was conducted to estimate the comparative efficacy of amivantamab-chemotherapy versus pembrolizumab-chemotherapy in the first-line setting.

The availability of IPD from the PAPILLON trial and each database permitted ATT-weighting via the calculation of PSs when sample sizes in the RWE treatment groups were sufficient. In the comparison for amivantamab-chemotherapy versus pembrolizumab-chemotherapy, following adjustment, key baseline characteristics were well balanced between the amivantamab-chemotherapy and pembrolizumab-chemotherapy (directly and indirectly accessible populations) population. Key results of the ITC indicate the greatly improved efficacy of amivantamab-chemotherapy versus pembrolizumab-chemotherapy in this patient population, with amivantamab-chemotherapy reducing the risk of initiation of next treatment and death by ■% and ■%, respectively. All results for this analysis (OS and TTNT) were ■.

While these results are greatly promising for amivantamab-chemotherapy, there are inherent limitations to ITCs and the RWE used to inform the comparative efficacy of amivantamab-chemotherapy and pembrolizumab-chemotherapy. Pooling the RWE provided robust sample sizes and allowed inclusion of patients across a broad range of geographies, similar to the setting of the multi-centre PAPILLON trial. However, data collection methods are expected to vary between the controlled environment of the PAPILLON trial and the RWE databases. For example, longer intervals between visits in the RWE is anticipated to bias estimates of TTNT in favour of pembrolizumab-chemotherapy. Additionally, previous studies have indicated that missing deaths in RWE may lead to overestimations of OS.⁹⁶ However, these limitations only serve to bias results against amivantamab-chemotherapy, and therefore the ITC results may be conservative.

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It should also be noted that patients were included in the RWE dataset for the ITC for amivantamab-chemotherapy versus pembrolizumab-chemotherapy if they received pembrolizumab in addition to different types of platinum chemotherapy regimens. In this submission, the only relevant platinum chemotherapy regimen is assumed to be carboplatin with pemetrexed, confirmed to be the predominant chemotherapy regimen used in this patient population in UK clinical practice by clinical experts consulted across multiple advisory boards.^{5, 22, 23} The assumption that the efficacy of pembrolizumab in combination with these varied chemotherapy regimens is representative of pembrolizumab in combination with carboplatin with pemetrexed was considered appropriate given that [REDACTED] of patients within this treatment class were receiving pembrolizumab with carboplatin plus pemetrexed.

A wide range of potentially prognostic factors were considered for adjustment in the comparison between amivantamab-chemotherapy and pembrolizumab-chemotherapy, based on previous systematic searches and expert validation in NSCLC. However, as with all non-randomised comparisons, bias due to residual confounding may still exist and should be acknowledged.

Despite the limitations acknowledged above, many of which are unavoidable and associated with the low patient numbers associated with EGFR Exon20 insertion mutation-positive advanced NSCLC, the ITCs made use of the most robust clinical data available for amivantamab-chemotherapy and pembrolizumab-chemotherapy. OS and TTNT results are promising and consistently show substantial evidence in favour of the superior efficacy of amivantamab-chemotherapy over pembrolizumab-chemotherapy in patients with EGFR Exon20 insertion mutation-positive advanced NSCLC.

B.2.10 Adverse reactions

Safety results from the PAPILLON trial are presented from the 3rd May 2023 DCO. Results are presented from the safety analysis set, defined as randomised patients who received at least one dose of study treatment; 151 patients in the amivantamab-chemotherapy arm and 155 patients in the chemotherapy arm.

B.2.10.1 Treatment exposure

B.2.10.1.1 Treatment disposition

At the 3rd May 2023 DCO, 70 patients (46.4%) in the amivantamab-chemotherapy arm and 24 patients (15.5%) in the chemotherapy arm remained on treatment. The most common reason for discontinuation of study treatment was progressive disease, with a smaller proportion of discontinuation due to progressive disease seen in the amivantamab-chemotherapy arm relative to the chemotherapy arm (33.1% versus 69.0%, respectively). Overall, a small and equal number of patients (14 patients in each arm, translating to 9.3% in the amivantamab-chemotherapy arm and 9.0% in the chemotherapy arm) discontinued all study treatment due to an AE, as shown in Table 31. In the amivantamab-chemotherapy arm, the most common TEAEs leading to discontinuation of any study treatment was pneumonitis which occurred in 4 patients (2.6%) and the most common TEAE leading to discontinuation of any study treatment in the chemotherapy arm was thrombocytopenia (3 patients [1.9%]).¹⁰

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In terms of discontinuation rates, the addition of amivantamab to chemotherapy did not significantly differ from chemotherapy alone, except in cases when discontinuation occurred due to disease progression.

Table 31: Summary of treatment disposition (3rd May 2023 DCO; safety analysis set)

Event, n (%)	Amivantamab- chemotherapy (N=151)	Chemotherapy (N=155)
Treatment disposition		
Patients ongoing	70 (46.4)	24 (15.5)
Discontinued all study treatment	81 (53.6)	131 (84.5)
Reason for discontinuation^a		
Progressive disease	50 (33.1)	107 (69.0)
AE	14 (9.3)	14 (9.0)
AE (COVID-19 related) ^b	2 (1.3)	0
Refused further study treatment	12 (7.9)	5 (3.2)
Non-compliance with study drug	1 (0.7)	2 (1.3)
Death	1 (0.7)	1 (0.6)
Physician decision	1 (0.7)	0
Other	2 (1.3)	2 (1.3)

^a The reason for discontinuation for all study treatment is the reason of discontinuation for the last study treatment received.

^b AEs that are considered COVID-19 related (associated) are based on events that code to a COVID-19 MedDRA term and events that are identified via the COVID-19 Case of AEs form.

Abbreviations: AE: adverse event; DCO: data cut-off.

Source: EMA Rybrevant EPAR assessment report (Table 10)⁷⁷

B.2.10.1.2 Treatment exposure

The median duration of treatment in the amivantamab-chemotherapy arm was 9.72 months (comprised of a median of 9.26 months [range: 0.0–26.9] for amivantamab, 2.14 months [range: 0.0–3.8] for carboplatin, and 8.34 months [range: 0.0–24.9] for pemetrexed). The median duration of treatment in the chemotherapy arm was 6.74 months (comprised of a median of 2.14 months [range: 0.0–3.9] for carboplatin and 6.74 months [range: 0.0–25.3] for pemetrexed). The exposure to pemetrexed in the amivantamab-chemotherapy arm was also numerically higher than in the chemotherapy arm. A summary of duration on study treatment is presented in Table 32.

Patients in the amivantamab-chemotherapy arm received a median of █ treatment cycles, with █ patients (█%) receiving 14 or more treatment cycles, and █ patient receiving █ cycles. Patients in the chemotherapy arm received a median of █ treatment cycles, with █ patients (█%) receiving ten or more treatment cycles, and █ patient receiving █ cycles.

Table 32: Summary of duration of study treatment (3rd May 2023 DCO; safety analysis set)

	Amivantamab- chemotherapy (N=151)	Chemotherapy (N=155)
Duration of study treatment, months		
Mean (SD)	██████	██████
Median	9.72	6.74

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Range	0.1–26.9	0.0–25.3
Duration of study treatment, n (%)		
<6 months	██████	██████
6 –<12 months	██████	██████
≥12 months	██████	██████

Abbreviations: DCO: data cut-off; SD: standard deviation.

Source: Johnson & Johnson PAPILLON CSR 2023 (Table 13, Page 54).⁷³

The relative dose intensity (RDI), which is the ratio of actual versus expected doses for amivantamab, pemetrexed and carboplatin are presented in Table 33 .

Table 33: RDI of study treatment

Component	Dose	Treatment duration	RDI (%)
Amivantamab	1,400 mg	<80kg patients: 4 weeks (up to C2D1)	██████
Amivantamab	1,750 mg	≥80kg patients: 4 weeks (up to C2D1)	██████
Amivantamab	1,750 mg	<80kg patients: until progression	██████
Amivantamab	2,100 mg	≥80kg patients: until progression	██████
Pemetrexed	500 mg/m ²	Until progression	██████
Carboplatin	AUC 5	4 cycles	██████

Relative dose intensity (%) is calculated as the ratio of total actually received dose versus total expected dose.

Abbreviations: AUC: area under the curve; C: Cycle; D: Day; RDI: relative dose intensity.

Source: calculated based on Johnson & Johnson PAPILLON CSR 2023 (Table 13, page 55).⁷³

B.2.10.2 Adverse events

B.2.10.2.1 Overview of treatment-emergent adverse events

An overall summary of TEAEs for the safety population in the PAPILLON trial at the 3rd May 2023 DCO is presented in Table 34. In both treatment arms, most patients experienced at least one AE; 100% of patients in the amivantamab-chemotherapy arm and 98.1% of patients in the chemotherapy arm. Overall, the safety profile of amivantamab-chemotherapy was consistent with the established safety profile of the individual components.

Grade 3 or higher TEAEs were observed with a higher incidence in the amivantamab-chemotherapy arm (114 [75.5%]) compared with the chemotherapy arm (83 [53.5%]).¹⁰ These were primarily driven by TEAEs known to be associated with EGFR inhibition (rash/dermatitis acneiform, stomatitis, and paronychia) and MET inhibition (hypoalbuminemia and peripheral oedema). Additionally, the higher incidence of grade 3 or higher TEAEs in the amivantamab-chemotherapy arm could partly be attributed to the longer time on treatment resulting in greater exposure to the drug. Incidence of SAEs was comparable between the two treatment arms, experienced by 56 patients (37.1%) and 48 patients (31.0%) in the amivantamab-chemotherapy and chemotherapy arms, respectively. Overall, TEAEs were manageable in both treatment arms with treatment interruptions and dose reductions.

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Table 34: Overall summary of TEAEs (3rd May 2023 DCO; safety analysis set)

Event, n (%)	Amivantamab- chemotherapy (N=151)	Chemotherapy (N=155)
Patients with ≥1 AE	151 (100.0)	152 (98.1)
Related AEs ^a	151 (100.0)	146 (94.2)
AEs leading to death^b	7 (4.6)	4 (2.6)
Related AEs leading to death ^{a,b}	3 (2.0)	2 (1.3)
Serious AEs^c	56 (37.1)	48 (31.0)
Related serious AEs ^a	36 (23.8)	16 (10.3)
AEs leading to discontinuation of any study agent	36 (23.8)	16 (10.3)
AEs leading to discontinuation of amivantamab	17 (11.3)	N/A
Related AEs to amivantamab ^a	10 (6.6)	N/A
AEs leading to dose reduction of any study agent	73 (48.3)	35 (22.6)
AEs leading to dose reduction of amivantamab	54 (35.8)	N/A
Related AEs to amivantamab ^a	54 (35.8)	N/A
AEs leading to dose interruption of any study agent^d	104 (68.9)	56 (36.1)
AEs leading to dose interruption of amivantamab	97 (64.2)	N/A
Related AEs to amivantamab ^{a, d}	63 (41.7)	N/A
Grade ≥3 AEs^e	114 (75.5)	83 (53.5)
Related grade ≥3 AEs ^a	100 (66.2)	57 (36.8)
Grade 1	██████	██████
Grade 2	██████	██████
Grade 3	██████	██████
Grade 4	██████	██████
Grade 5	██████	██████

^a An AE is assessed by the investigator as related to the study treatment.

^b AEs leading to death are based on AE outcome of Fatal. Per protocol, all deaths within 30 days of last dose were required to have an associated AE reported, even if due to progressive disease.

^c SAEs were defined in the PAPILLON trial protocol as any untoward medical occurrence that, at any dose, results in death, is life-threatening, causes or prolongs hospitalisation (exceptions apply), results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect, is a suspected transmission of any infectious agent via a medicinal product or is Medically Important.⁷⁹

^d Excludes infusion related reactions.

^e Grade 3 TEAEs were defined in the PAPILLON trial protocol as severe or medically significant but not immediately life-threatening; causing or prolonging hospitalisation, disabling or limiting self-care activities of daily living.⁷⁶

Abbreviations: AE: adverse event; DCO: data cut-off; TEAE: treatment-emergent adverse event.

Sources: Johnson & Johnson PAPILLON CSR 2023 (Table 25, Page 83)⁷³ and Zhou *et al* 2023.¹⁰

B.2.10.2.2 Common TEAEs by preferred term

TEAEs observed with a frequency of at least 5% in either treatment arm are presented in Table 35. The most frequently reported TEAEs (≥ 15% of patients in any arm) were generally in line with the well-established safety profile of the individual treatment components. Common TEAEs

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associated with the EGFR inhibition activity of amivantamab included rash and dermatitis acneiform (53.6%), paronychia (56.3%), stomatitis (25.2%) and diarrhoea (20.5%) and were more frequently observed in the amivantamab-chemotherapy arm compared with the chemotherapy arm. Common TEAEs associated with MET inhibition activity of amivantamab included hypoalbuminemia (41.1%) and peripheral oedema (29.8%), which were observed more frequently in the amivantamab-chemotherapy arm compared to the chemotherapy arm; 9.7% and 10.3%, respectively.

Table 35: Number of patients with TEAEs with a frequency of at least 5% in any treatment group by system organ class and preferred term (3rd May 2023 DCO; safety analysis set)

Event, n (%)	Amivantamab- chemotherapy (N=151)	Chemotherapy (N=155)
Patients with 1 or more AEs	151 (100.0)	152 (98.1)
Skin and subcutaneous tissue disorders		
Rash	81 (53.6)	12 (7.7)
Dermatitis acneiform	47 (31.1)	5 (3.2)
Dry skin		
Alopecia		
Pruritus		
Skin ulcer		
Erythema		
Gastrointestinal disorders		
Constipation	60 (39.7)	47 (30.3)
Nausea	55 (36.4)	65 (41.9)
Stomatitis	38 (25.2)	9 (5.8)
Vomiting	32 (21.2)	29 (18.7)
Diarrhoea	31 (20.5)	20 (12.9)
Haemorrhoids		
Mouth ulceration		
Abdominal pain		
Gingival bleeding		
Abdominal distension		
Abdominal pain upper		
Infections and infestations		
Paronychia	85 (56.3)	0
COVID-19	36 (23.8)	21 (13.5)
Pneumonia		
Conjunctivitis		
Upper respiratory tract infection		
Urinary tract infection		
Metabolism and nutrition disorders		
Hypoalbuminaemia	62 (41.1)	15 (9.7)

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Event, n (%)	Amivantamab- chemotherapy (N=151)	Chemotherapy (N=155)
Decreased appetite	54 (35.8)	43 (27.7)
Hypokalaemia	32 (21.2)	13 (8.4)
Hypomagnesaemia	██████	██████
Hypocalcaemia	██████	██████
Hyponatraemia	██████	██████
Hypophosphataemia	██████	██████
Hypoproteinaemia	██████	██████
Hyperglycaemia	██████	██████
Hyperkalaemia	██████	█
Blood and lymphatic system disorders	██████	██████
Neutropenia	89 (58.9)	70 (45.2)
Anaemia	76 (50.3)	85 (54.8)
Leukopenia	57 (37.7)	50 (32.3)
Thrombocytopenia	55 (36.4)	46 (29.7)
Lymphopenia	██████	██████
General disorders and administration site conditions	██████	██████
Oedema peripheral	45 (29.8)	16 (10.3)
Asthenia	30 (19.9)	29 (18.7)
Pyrexia	24 (15.9)	9 (5.8)
Fatigue	23 (15.2)	32 (20.6)
Malaise	██████	██████
Mucosal inflammation	██████	██████
Oedema	██████	██████
Investigations	██████	██████
Alanine aminotransferase increased	50 (33.1)	56 (36.1)
Aspartate aminotransferase increased	47 (31.1)	51 (32.9)
Gamma-glutamyltransferase increased	21 (13.9)	26 (16.8)
Weight decreased	██████	██████
Blood alkaline phosphatase increased	██████	██████
Blood lactate dehydrogenase increased	██████	██████
Blood creatinine increased	██████	██████
Injury, poisoning and procedural complications	██████	██████
Infusion related reaction	63 (41.7)	2 (1.3)

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Event, n (%)	Amivantamab- chemotherapy (N=151)	Chemotherapy (N=155)
Respiratory, thoracic and mediastinal disorders		
Cough	21 (13.9)	24 (15.5)
Dyspnoea		
Pulmonary embolism		
Productive cough		
Pleural effusion		
Nervous system disorders		
Dizziness		
Dysgeusia		
Headache		
Musculoskeletal and connective tissue disorders		
Back pain		
Arthralgia		
Myalgia		
Eye disorders		
Lacrimation increased		
Vascular disorders		
Deep vein thrombosis		
Hypertension		
Hepatobiliary disorders		
Hyperbilirubinaemia		
Psychiatric disorders		
Insomnia		

Patients were counted only once for any given event, regardless of the number of times they actually experienced the event. AEs were coded using MedDRA Version 25.0.

Abbreviations: AE: adverse event; DCO: data cut-off; TEAE: treatment-emergent adverse event.

Source: Johnson & Johnson PAPILLON CSR 2023 (Table 26, Page 85)⁷³ and Zhou *et al* 2023.¹⁰

B.2.10.2.3 Grade 3 or higher TEAEs

Grade ≥ 3 TEAEs were reported in 114 patients (75.5%) in the amivantamab-chemotherapy arm and 83 patients (53.5%) in the chemotherapy arm at the 3rd May 2023 DCO, as summarised in Table 36.¹⁰ Out of the patients who experienced a Grade ≥ 3 TEAE, 56.3% of patients in the amivantamab-chemotherapy arm and 41.9% of patients in the chemotherapy arm experienced a maximum severity grade of Grade 3. 14.6% and 4.6% of patients in the amivantamab-chemotherapy arm compared with 9.0% and 2.6% of patients in the chemotherapy arm experienced a maximum severity grade of Grade 4 and Grade 5 events, respectively.⁷⁷

The most frequently reported Grade ≥ 3 TEAEs in both treatment arms were haematologic AEs (neutropenia, leukopenia, anaemia, and thrombocytopenia), which are known to be associated with chemotherapy. The frequency of haematologic Grade ≥ 3 TEAEs were generally comparable between the two treatment arms, with the exception of transient neutropenia, whereby a slightly

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more pronounced decrease in neutrophil count was observed in the amivantamab-chemotherapy arm compared with the chemotherapy arm at Cycle 1 Day 8. Despite this transient increase in neutropenia in the amivantamab-chemotherapy arm, most of these neutropenia events were non-serious.

Grade ≥ 3 TEAEs considered related to study treatment were reported in 100 patients (66.2%) in the amivantamab-chemotherapy arm and 57 patients (36.8%) in the chemotherapy arm.¹⁰

Table 36: Number of patients with Grade ≥ 3 TEAEs with frequency of at least 5% in any treatment group by system organ class and preferred term (3rd May 2023 DCO; safety analysis set)

Event, n (%)	Amivantamab-chemotherapy (N=151)	Chemotherapy (N=155)
Patients with 1 or more Grade ≥ 3 AEs	114 (75.5)	83 (53.5)
Blood and lymphatic system disorders	58 (38.4)	52 (33.5)
Neutropenia	50 (33.1)	35 (22.6)
Leukopenia	17 (11.3)	5 (3.2)
Anaemia	16 (10.6)	19 (12.3)
Thrombocytopenia	15 (9.9)	16 (10.3)
Infections and infestations	31 (20.5)	11 (7.1)
Paronychia	10 (6.6)	0
Skin and subcutaneous tissue disorders	28 (18.5)	0
Rash	17 (11.3)	0
Metabolism and nutrition disorders	23 (15.2)	7 (4.5)
Hypokalaemia	13 (8.6)	2 (1.3)
General disorders and administration site conditions	14 (9.3)	9 (5.8)
Asthenia	8 (5.3)	4 (2.6)

Grade 3 TEAEs were defined in the PAPILLON trial protocol as severe or medically significant but not immediately life-threatening; causing or prolonging hospitalisation, disabling or limiting self-care activities of daily living.⁷⁶ Patients were counted only once for any given event, regardless of the number of times they actually experienced the event. AEs were coded using MedDRA Version 25.0.

Abbreviations: AE: adverse event; DCO: data cut-off; TEAE: treatment-emergent adverse event.

Source: EMA Rybrevant EPAR assessment report (Table 38)⁷⁷

B.2.10.2.4 Serious adverse events

SAEs have been defined in the PAPILLON trial protocol as per the definition published by the International Council for Harmonization (ICH) and European Union Guidelines on Pharmacovigilance for Medicinal Products for Human Use. These are any untoward medical occurrences that, at any dose results in death, is life-threatening, requires inpatient hospitalization (or prolongation of an existing hospitalization), persistent or significant disability/incapacity, is a congenital anomaly/birth defect, is a suspected transmission of any infectious agent via a medicinal product, is medically important.

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The overall incidence of SAEs was comparable between treatment arms with SAEs reported in 56 patients (37.1%) in the amivantamab-chemotherapy arm and 48 patients (31.0%) in the chemotherapy arm. The most frequently reported SAEs (reported in $\geq 2\%$ of patients in any of the arms) were pneumonia (4.0% in the amivantamab-chemotherapy arm versus 2.6% in the chemotherapy arm), COVID-19 (2.0% in the amivantamab-chemotherapy arm versus 0.6% in the chemotherapy arm), vomiting (2.0% in the amivantamab-chemotherapy arm versus 0.6% in the chemotherapy arm) and pneumonitis (2.6% in the amivantamab-chemotherapy arm versus 0% in the chemotherapy arm).¹⁰ The vast majority of these SAEs were experienced by a small proportion of patients ($\leq 4\%$ of patients in each arm). Haematological SAEs, which correlate to the known chemotherapy safety profile, occurred at a low and generally comparable frequency in both treatment arms. The only exception was anaemia, which had a higher incidence in the chemotherapy arm compared with the amivantamab-chemotherapy arm; 3.9% versus 0.7%, respectively.

In line with the established safety profile of amivantamab, pneumonitis (4 patients [2.6%]) as well as rash and dermatitis acneiform (2 patients each [1.3%]) were reported in the amivantamab-chemotherapy arm only.

A summary of the SAEs observed in the PAPILLON trial are presented in Table 37.

Table 37: Number of patients with treatment-emergent SAEs by system organ class and preferred term (3rd May 2023 DCO; safety analysis set)

Event, n (%)	Amivantamab-chemotherapy (N=151)	Chemotherapy (N=155)
Patients with 1 or more SAEs	56 (37.1)	48 (31.0)
Infections and infestations	18 (11.9)	10 (6.5)
Pneumonia	6 (4.0)	4 (2.6)
COVID-19	3 (2.0)	1 (0.6)
Cellulitis	2 (1.3)	1 (0.6)
Rash pustular	2 (1.3)	0
Skin infection	2 (1.3)	0
COVID-19 pneumonia	1 (0.7)	0
Infection	1 (0.7)	0
Pneumonia viral	1 (0.7)	0
Postoperative wound infection	1 (0.7)	1 (0.6)
Sepsis	1 (0.7)	1 (0.6)
Appendicitis	0	1 (0.6)
Enterocolitis infectious	0	1 (0.6)
Gastrointestinal disorders	10 (6.6)	4 (2.6)
Vomiting	3 (2.0)	1 (0.6)
Diarrhoea	2 (1.3)	1 (0.6)
Abdominal pain	1 (0.7)	0
Cheilitis	1 (0.7)	0
Duodenitis	1 (0.7)	0

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Event, n (%)	Amivantamab- chemotherapy (N=151)	Chemotherapy (N=155)
Enterocolitis	1 (0.7)	0
Lower gastrointestinal haemorrhage	1 (0.7)	0
Ascites	0	1 (0.6)
Gastrointestinal haemorrhage	0	1 (0.6)
Respiratory, thoracic and mediastinal disorders	8 (5.3)	14 (9.0)
Pneumonitis	4 (2.6)	0
Pulmonary embolism	4 (2.6)	4 (2.6)
Dyspnoea	1 (0.7)	5 (3.2)
Haemoptysis	1 (0.7)	1 (0.6)
Pleural effusion	1 (0.7)	5 (3.2)
Hypoxia	0	1 (0.6)
Metabolism and nutrition disorders	6 (4.0)	5 (3.2)
Hypokalaemia	3 (2.0)	1 (0.6)
Decreased appetite	1 (0.7)	0
Dehydration	1 (0.7)	0
Hypomagnesaemia	1 (0.7)	0
Hyponatraemia	1 (0.7)	1 (0.6)
Hypophagia	1 (0.7)	1 (0.6)
Hyperglycaemia	0	1 (0.6)
Malnutrition	0	1 (0.6)
Blood and lymphatic system disorders	5 (3.3)	11 (7.1)
Thrombocytopenia	3 (2.0)	5 (3.2)
Neutropenia	2 (1.3)	0
Anaemia	1 (0.7)	6 (3.9)
Febrile neutropenia	1 (0.7)	3 (1.9)
Leukopenia	1 (0.7)	0
Myelosuppression	0	1 (0.6)
Skin and subcutaneous tissue disorders	5 (3.3)	0
Dermatitis acneiform	2 (1.3)	0
Rash	2 (1.3)	0
Rash maculo-papular	1 (0.7)	0
Nervous system disorders	4 (2.6)	5 (3.2)
Cerebrovascular accident	1 (0.7)	0
Encephalopathy	1 (0.7)	0
Myoclonic epilepsy	1 (0.7)	0
Transient ischaemic attack	1 (0.7)	0
Depressed level of consciousness	0	1 (0.6)

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Event, n (%)	Amivantamab- chemotherapy (N=151)	Chemotherapy (N=155)
Dysarthria	0	1 (0.6)
Headache	0	1 (0.6)
Lacunar infarction	0	1 (0.6)
Syncope	0	1 (0.6)
Vertebrobasilar insufficiency	0	1 (0.6)
General disorders and administration site conditions	3 (2.0)	6 (3.9)
Asthenia	2 (1.3)	1 (0.6)
Death	1 (0.7)	1 (0.6)
Fatigue	0	1 (0.6)
General physical health deterioration	0	1 (0.6)
Influenza like illness	0	1 (0.6)
Pain	0	1 (0.6)
Investigations	3 (2.0)	2 (1.3)
Alanine aminotransferase increased	1 (0.7)	1 (0.6)
Blood creatinine increased	1 (0.7)	1 (0.6)
C-reactive protein increased	1 (0.7)	0
Aspartate aminotransferase increased	0	1 (0.6)
Injury, poisoning and procedural complications	2 (1.3)	2 (1.3)
Infusion related reaction	1 (0.7)	0
Lumbar vertebral fracture	1 (0.7)	0
Femur fracture	0	1 (0.6)
Incisional hernia	0	1 (0.6)
Musculoskeletal and connective tissue disorders	2 (1.3)	4 (2.6)
Back pain	1 (0.7)	0
Myalgia	1 (0.7)	0
Arthralgia	0	1 (0.6)
Bone pain	0	1 (0.6)
Pain in extremity	0	1 (0.6)
Pathological fracture	0	1 (0.6)
Reproductive system and breast disorders	2 (1.3)	0
Endometrial thickening	1 (0.7)	0
Ovarian mass	1 (0.7)	0
Cardiac disorders	1 (0.7)	2 (1.3)
Cardio-respiratory arrest	1 (0.7)	0
Acute myocardial infarction	0	1 (0.6)

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Event, n (%)	Amivantamab-chemotherapy (N=151)	Chemotherapy (N=155)
Pericardial effusion	0	1 (0.6)
Hepatobiliary disorders	1 (0.7)	1 (0.6)
Biliary obstruction	1 (0.7)	0
Cholecystitis acute	1 (0.7%)	0
Jaundice cholestatic	0	1 (0.6)
Immune system disorders	1 (0.7%)	0
Contrast media reaction	1 (0.7%)	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (0.7%)	1 (0.6)
Prostate cancer	1 (0.7%)	0
Cancer pain	0	1 (0.6)
Renal and urinary disorders	1 (0.7%)	0
Acute kidney injury	1 (0.7%)	0
Ear and labyrinth disorders	0	1 (0.6)
Hypoacusis	0	1 (0.6)

SAEs were defined in the PAPILLON trial protocol as any untoward medical occurrence that, at any dose, results in death, or is life-threatening, or causes or prolongs hospitalisation (exceptions apply), or results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect, is a suspected transmission of any infectious agent via a medicinal product or is Medically Important.⁷⁶

Patients were counted only once for any given event, regardless of the number of times they actually experienced the event. AEs were coded using MedDRA Version 25.0.

Abbreviations: DCO: data cut-off; SAE: serious adverse event.

Source: EMA Rybrevant EPAR assessment report (Table 43)⁷⁷

B.2.10.2.5 Deaths

A summary of deaths that occurred at any time during the PAPILLON trial up until the 3rd May 2023 DCO in the full analysis patient population is presented in Table 38. At the DCO, 28 patients (18.3%) in the amivantamab-chemotherapy arm and 42 patients (27.1%) in the chemotherapy arm died during the study. Progressive disease was the most frequent cause of death in both treatment arms; 20 (13.1%) and 30 patients (19.4%) in the amivantamab-chemotherapy and chemotherapy arm, respectively.¹⁰

Per the study protocol, all deaths within 30 days of the last treatment dose were required to have an associated AE reported, even if due to progressive disease. These TEAEs are summarised in Table 39. An in-depth review of the TEAEs in the 7 patients (4.6%) in the amivantamab-chemotherapy arm and the 4 patients (2.6%) in the chemotherapy arm suggests no new safety signals.¹⁰

Table 38: Summary of death and cause of death (3rd May 2023 DCO; full analysis set)

Event, n (%)	Amivantamab-chemotherapy (N=151)	Chemotherapy (N=155)
Deaths during study^a	28 (18.3)	42 (27.1)
Progressive disease	20 (13.1)	30 (19.4)

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Event, n (%)	Amivantamab- chemotherapy (N=151)	Chemotherapy (N=155)
AE	4 (2.6)	9 (5.8)
Other	2 (1.3)	3 (1.9)
COVID-19	2 (1.3)	0
Deaths within 30 days of last dose^{a,b}	7 (4.6)	7 (4.5)
AE	3 (2.0)	4 (2.6)
Progressive disease	1 (0.7)	2 (1.3)
COVID-19	2 (1.3)	0
Other	1 (0.7)	1 (0.6)
Deaths within 30 days of last dose (main study)^{b,c}	7 (4.6)	4 (2.6)
AE	3 (2.0)	2 (1.3)
COVID-19	2 (1.3)	0
Other	1 (0.7)	1 (0.6)
Progressive disease	1 (0.7)	1 (0.6)

^a Subjects who died during the treatment switch phase are included.

^b Subjects who died within 30 days will be counted in deaths during study as well.

^c Subjects who died during the treatment switch phase are excluded.

Abbreviations: AE: adverse event; DCO: data cut-off.

Source: Zhou *et al* 2024. ¹⁰

Table 39: Number of patients with TEAEs leading to death by system organ class and preferred term (3rd May 2023 DCO; safety analysis set)

Event, n (%)	Amivantamab- chemotherapy (N=151)	Chemotherapy (N=155)
Patients with 1 or more AEs leading to death	7 (4.6)	4 (2.6)
Infections and infestations	4 (2.6)	1 (0.6)
COVID-19	1 (0.7)	0
COVID-19 pneumonia	1 (0.7)	0
Pneumonia	1 (0.7)	0
Sepsis	1 (0.7)	1 (0.6)
Cardiac disorders	1 (0.7)	1 (0.6)
Cardio-respiratory arrest	1 (0.7)	0
Acute myocardial infarction	0	1 (0.6)
General disorders and administration site conditions	1 (0.7)	1 (0.6)
Death	1 (0.7)	1 (0.6)
Nervous system disorders	1 (0.7)	0
Cerebrovascular accident	1 (0.7)	0
Respiratory, thoracic and mediastinal disorders	0	1 (0.6)
Dyspnoea	0	1 (0.6)

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Patients were counted only once for any given event, regardless of the number of times they actually experienced the event. AEs were coded using MedDRA Version 25.0.

Abbreviations: AE: adverse event; DCO: data cut-off; TEAE: treatment-emergent adverse event.

Source: EMA Rybrevant EPAR assessment report (Table 45)^{10, 77}

B.2.10.2.6 AEs of special interest

Adverse events of special interest (AESIs) were prospectively identified based upon the identified safety profile of amivantamab; predefined AESIs per the protocol were rash, infusion-related reactions and pneumonitis/interstitial lung disease.⁷⁶

There were no new AESIs identified during the course of the PAPILLON trial. Overall, 139 patients (92.1%) in the amivantamab-chemotherapy arm and 30 patients (19.4%) in the chemotherapy arm had at least one AESI.⁷⁷ As expected, all the prospectively identified AESIs, which are known to be associated with amivantamab, were reported at a higher frequency in the amivantamab-chemotherapy arm than in the chemotherapy arm, providing reason for the differences in incidence between treatment arms for TEAEs (specifically Grade ≥ 3 TEAEs) and dose modifications.

B.2.10.2.7 Infusion-related reactions

In line with the well-established safety profile of amivantamab, infusion-related reactions (IRRs) were one of the most frequently occurring TEAEs in the amivantamab-chemotherapy arm; reported in 63 patients (41.7%) compared with 2 patients (1.3%) in the chemotherapy arm. Most of the IRR events were Grade 1 or 2, with only 2 patients in the amivantamab-chemotherapy arm (1.3%) experiencing Grade 3 IRR and no patients experiencing a Grade 4 or 5 IRR.¹⁰

B.2.11 Ongoing studies

The PAPILLON trial is ongoing, with the final analysis anticipated in [REDACTED].

As mentioned in Table 2, the clinical trial programme PALOMA is assessing the safety and feasibility of a SC amivantamab formulation in advanced solid malignancies, including NSCLC.^{33,}

⁹⁷ The programme comprises two trials:

- The Phase 2, open-label PALOMA-2 trial is specifically assessing SC amivantamab in combination with carboplatin and pemetrexed as a first-line option for patients with EGFR Exon20 insertion mutation-positive advanced NSCLC.⁹⁷
- The Phase 3 PALOMA-3 trial assessing SC amivantamab versus IV amivantamab, both in combination with lazertinib, in patients with EGFR-mutated (Exon19 deletion or Exon 21 L858R substitution mutations) advanced NSCLC has shown a five-fold reduction in reported IRRs with the SC formulation compared with the IV formulation; 13% and 66%, respectively.⁹⁸ The SC formulation also demonstrated a non-inferior ORR and led to longer median DOR, PFS and OS.⁹⁸ The SC formulation of amivantamab for the patient population of interest in this submission is anticipated to be launched in the UK in [REDACTED].⁹⁹

In addition to the PALOMA trial programme, the SKIPPIrr trial is a Phase 2, open label trial investigating the use of premedication to reduce infusion-related reactions (IRRs) associated with amivantamab.¹⁰⁰ Data presented at the World Conference on Lung Cancer (WCLC) 2024 showed that prophylaxis with 8-mg oral dexamethasone resulted in a meaningful reduction in the incidence of IRRs and is an effective strategy to reduce IRRs.¹⁰¹

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B.2.12 Interpretation of clinical effectiveness and safety evidence

B.2.12.1 Principal findings from the clinical evidence base

Patients with EGFR Exon20 insertion mutation-positive advanced NSCLC face a critical lack of effective treatment options available via the NHS in UK clinical practice, leading to suboptimal survival outcomes

RWE and clinical opinion obtained across multiple advisory boards conducted by Johnson & Johnson indicate that, in the absence of targeted treatments, patients with EGFR Exon20 insertion mutation-positive advanced NSCLC receive treatments such as platinum-based chemotherapy with and without IO in clinical practice which are also used for patients without sensitising EGFR mutations.^{5, 22, 23} Some patients may also receive IO monotherapy or EGFR TKIs, though this is considered against best practice by UK clinical experts given the lack of efficacy of each treatments observed in this patient population.²²

Survival in the EGFR Exon 20 insertion mutation-positive advanced NSCLC population is therefore poor, and is also worse compared to the common EGFR mutated NSCLC population due to the comparative lack of efficacious treatment options, evidenced by the Bazhenova 2021 RWE study (reporting a median OS of 16.2 months versus 25.5 months for patients with EGFR Exon20 insertion mutations versus common EGFR mutations in the first-line setting).¹² As such, there is a critical unmet need in this patient population due to the discrepancy in survival outcomes observed between patients with EGFR mutated NSCLC. Prolongment of time progression and achieving stable disease has been identified as key areas of unmet need in these patients during market research conducted by Johnson & Johnson.

Results from the PAPILLON trial demonstrate that amivantamab-chemotherapy is an efficacious treatment for these patients versus carboplatin and pemetrexed, a relevant comparator in UK clinical practice

The primary clinical and safety evidence base for amivantamab with carboplatin and pemetrexed ('amivantamab-chemotherapy') as a treatment for adult patients with untreated EGFR Exon20 insertion mutation-positive advanced NSCLC is informed by the PAPILLON trial. In the Phase 3 PAPILLON trial, patients were randomised 1:1 to receive amivantamab-chemotherapy combination or chemotherapy, with efficacy and safety endpoints compared between the two treatment arms.

The PAPILLON trial demonstrated the ability of amivantamab-chemotherapy to improve survival outcomes for patients by meeting its primary endpoint: PFS by BICR. After a median follow-up of 14.92 months, a statistically significant ($p < 0.0001$) and clinically meaningful improvement in PFS was observed, translating to a 60% reduction in the risk of disease progression or death in patients receiving amivantamab-chemotherapy combination compared with those receiving chemotherapy (HR: 0.40; 95% CI: 0.30-0.53).¹⁰

The secondary endpoints from the PAPILLON trial provide strong supporting evidence of the superiority of amivantamab-chemotherapy versus chemotherapy:

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- At the 3rd May 2023 DCO, a significantly higher proportion of patients ($p < 0.0001$) responded to treatment in the amivantamab-chemotherapy arm (111 patients [73.0%]) compared with the chemotherapy arm (72 patients [47.4%]), as assessed by BICR.
- Additionally, the median DOR was doubled in the amivantamab-chemotherapy arm, reaching 10.09 months (95% CI: 8.48-13.90) compared with 5.55 months (95% CI: 4.44-6.93) in the chemotherapy arm
- Median OS was not reached in the amivantamab-chemotherapy arm at either the 3rd May 2023 and 31st October 2023 DCO; however, there was a strong trend towards improved OS in the amivantamab-chemotherapy arm compared with the chemotherapy arm, with an HR of 0.76 (95% CI: 0.50-1.14; $p = 0.1825$) at the 31st October 2023 DCO (follow-up of 20.9 months)
 - This strong trend was observed despite a total of 78 patients in the chemotherapy arm treatment switching to receive amivantamab monotherapy in the 31st October DCO.¹⁰²
 - The strong trend towards improved survival is expected to translate into a long-term survival benefit for patients with EGFR Exon20 insertion mutation-positive advanced NSCLC. This would reflect the long-term benefit observed for amivantamab monotherapy after platinum chemotherapy in the CHRYSALIS trial where, 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).⁴³

Overall, amivantamab-chemotherapy has been shown to significantly improve PFS as well as achieve a more durable response compared with chemotherapy. This enables patients to maintain their level of HRQoL for a longer period of time, which is highly valued by patients and their families as evidenced by in-depth interviews and online surveys conducted in the patient population of interest by Johnson & Johnson.¹⁴ These results are further supported by the observed prolonged PFS2, whereby first-line amivantamab-chemotherapy appears to delay further progression following subsequent therapy.

Ultimately, a strong trend towards improved OS was observed for patients who received amivantamab-chemotherapy versus chemotherapy, despite the permitted treatment switching from the chemotherapy arm to amivantamab monotherapy. This treatment switching confounds the results and leads to an unrealistic OS estimate of chemotherapy, as amivantamab monotherapy is not available in routine clinical practice in the UK. Following treatment switch adjustment via IPCW (see Section B.3.3.2.1 for further details) the true survival benefit achieved through treatment with amivantamab-chemotherapy versus chemotherapy (adjusted OS HR: [REDACTED] [95% CI: [REDACTED]-[REDACTED]]) can be determined. The strong trend towards improved survival is expected to translate into a long-term benefit for patients. This is supported by the long-term benefit of amivantamab monotherapy observed in the CHRYSALIS trial where, at a median follow-up of 19.2 months, the median OS of amivantamab monotherapy in patients with EGFR Exon20 insertion mutation-positive advanced NSCLC who had received prior platinum chemotherapy was 23 months (95% CI, 18.5-29.5).⁴³

The OS benefit observed in the PAPILLON trial is reinforced by results from the ITC between amivantamab-chemotherapy (from PAPILLON) versus chemotherapy (from the NECTAR study) using the ATT-weighting of individual patient level data, which estimated an OS HR of [REDACTED] ([REDACTED]). Median OS ([REDACTED]) of chemotherapy in PAPILLON (following adjustment for

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cross-over), has high face validity as closely aligns with median OS (████████) of chemotherapy in RWE (after ATT-weighting).

Impacts on EQ-5D-5L utility scores at the start of maintenance phase and end of treatment time points were comparable between the amivantamab-chemotherapy and chemotherapy arms. Adding more medicines into a treatment regimen typically increases toxicity and reduces patients' HRQoL; however, the fact that HRQoL is maintained upon addition of amivantamab suggests that the addition of amivantamab does not negatively impact patients HRQoL. Additionally, EORTC-QLQ-C30 scores indicated that a larger proportion of patients in the amivantamab-chemotherapy arm reported improved/stable functioning or an absence of symptoms compared with the chemotherapy arm.⁸³

In addition to demonstrating a superior efficacy versus chemotherapy, amivantamab-chemotherapy is shown to be a tolerable treatment option with a positive risk/benefit ratio

Overall, amivantamab-chemotherapy was shown to be well-tolerated, with the safety profiles consistent with each individual treatment component. Grade 3 or higher TEAEs were observed with a higher incidence in the amivantamab-chemotherapy arm (114 [75.5%]) compared with the chemotherapy arm (83 [53.5%]); however, these were primarily driven by TEAEs known to be associated with EGFR inhibition. Additionally, the higher incidence of grade 3 or higher TEAEs within the amivantamab-chemotherapy arm could partly be attributed to the longer time of treatment resulting in greater exposure to this drug combination. Furthermore, overall discontinuation rates in the two study arms were similar (9.3% of patients in the amivantamab-chemotherapy arm versus 9.0% of patients in the chemotherapy arm). In general, TEAEs were considered manageable in both treatment arms with appropriate treatment interruptions and dose reductions, with no new safety signals or concerns.¹⁰

Findings from the ITCs conducted for amivantamab-chemotherapy versus pembrolizumab-chemotherapy provide supportive evidence for the efficacy of amivantamab in this patient population

No direct evidence was identified for amivantamab-chemotherapy versus pembrolizumab-chemotherapy in the population of interest to this submission. As such, an ITC was conducted using clinical data from the PAPILLON trial and pooled RWE gathered across the NCRAS (England), ESME (France), COTA (US) and ConcertAI (US) databases as part of the NECTAR study.³

The patient populations in the NECTAR study were ATT-weighted to ensure that key baseline characteristics aligned with the PAPILLON trial, with prognostic factors identified through an SLR and expert validation exercises. As accurate data on the date of progression were not available for all RWE databases, TTNT was used as a key endpoint in the ITC in place of PFS. Further information on how these results were incorporated into the economic model is provided in Section B.3.3.2.5.

Following adjustment, patient characteristics were well-balanced. Results of the ITC demonstrate that amivantamab-chemotherapy results in a ██████████% reduction in the risk of initiating next treatment versus platinum chemotherapy+IO (adjusted TTNT HR: █████ [95% CI: █████-████; p-value █████]) and a statistically significant █████% reduction in the risk of death (OS HR: █████ [95% CI: █████-████; p-value █████]).

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Though there are limitations to utilising RWE in indirect comparisons, as outlined in Section B.2.9.6, the consistency of results across all endpoints (including statistical significance) and the magnitude of the treatment benefit estimated by these results demonstrates the superiority of amivantamab-chemotherapy versus pembrolizumab-chemotherapy in patients with untreated EGFR Exon20 insertion mutation-positive advanced NSCLC. The results from the ITC vs pembrolizumab-chemotherapy can be considered robust given the similarity between the OS HR of amivantamab-chemotherapy vs chemotherapy from the PAPILLON trial (direct comparison after IPCW-adjustment for subsequent amivantamab monotherapy) and the OS HR of amivantamab-chemotherapy vs chemotherapy from the NECTAR study (ITC after ATT-weighting of RWE data). This is further described in section B.3.3.2.1.

B.2.12.2 Strengths and limitations of the evidence base

Internal and external validity

The clinical evidence presented in this submission has been derived from an SLR conducted in accordance with the high-quality standards required by NICE as well as standards set forth in other established guidelines, including PRISMA and the Cochrane handbook. The clinical SLR identified the pivotal clinical trial, PAPILLON, as the primary evidence source for amivantamab in combination with carboplatin and pemetrexed in the population of interest to this submission: adult patients with untreated EGFR Exon20 insertion mutation-positive advanced NSCLC. The results of the quality assessment of the PAPILLON trial demonstrated that it is a methodologically robust and well-reported trial, with results considered to be of low risk of bias in the majority of categories (Table 11).

The PAPILLON trial considered a wide range of endpoints (PFS, ORR, DOR, OS, TTST, PFS2 and TTSP) that are clinically relevant to patients with untreated EGFR Exon20 insertion mutation-positive advanced NSCLC and reflect outcomes assessed in prior appraisals of therapies within both EGFR mutation-positive and wild-type advanced NSCLC.^{17, 19}

Limitations

The SLR did not identify any studies directly comparing amivantamab-chemotherapy versus pembrolizumab-chemotherapy. Therefore, an ITC was required to estimate the comparative efficacy of amivantamab-chemotherapy versus pembrolizumab-chemotherapy. This ITC was methodologically robust, utilising RWE (in the absence of data available from RCTs) that was systematically identified through a methodology aligned with the NICE RWE framework. The ITC adjusted for available patient baseline characteristics to minimise imbalances between the PAPILLON trial and the pooled RWE population which may have influenced efficacy outcomes.³

OS data from the PAPILLON trial was relatively immature, with median OS not reached in the amivantamab-chemotherapy arm at either the 3rd May 2023 or the 31st October 2023 DCO. Median OS was however reached in the chemotherapy treatment arm at the May 2023 DCO (24.38 months) and the October 2023 DCO (28.6 months). A strong trend towards improved survival was observed in patients receiving amivantamab-chemotherapy versus chemotherapy, despite treatment switching to amivantamab monotherapy, with splitting and widening of the KM curves observed (as shown in Figure 10 and Figure 11).^{10, 21} Surrogate efficacy endpoints, such as PFS (Section B.2.6.1) and PFS2 (Section B.2.6.2.5), support the survival benefit expected for patients receiving amivantamab-chemotherapy versus chemotherapy.

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The PAPILLON trial allowed patients in the chemotherapy arm to receive amivantamab monotherapy, following BICR-confirmed disease progression. At the 31st October 2023 DCO, 78/ (%) patients had received subsequent amivantamab monotherapy following BICR-confirmed disease progression. Amivantamab monotherapy is not currently recommended by NICE and is not therefore available on the NHS for patients with EGFR Exon20 insertion mutation positive NSCLC who have progressed following first-line therapy.¹⁹ As recommended by the NICE DSU TSD 24, subsequent treatments used in a clinical trial that are not reflective of NHS practice should be adjusted for.⁸¹ Considering this guidance and the evidence that amivantamab monotherapy provides benefit following prior platinum chemotherapy, OS results for chemotherapy have been adjusted for to ensure the efficacy data were reflective of UK clinical practice. The treatment switching methods explored included two-stage estimation (TSE), rank preserving structural failure time (RPSFT) and inverse probability of censoring weight (IPCW). Following adjustment via IPCW, recommended by experts during the August 2024 advisory board with UK clinical experts, the strong survival benefit provided by amivantamab-chemotherapy versus chemotherapy becomes evident.²²

Conclusions

The registrational Phase 3 PAPILLON trial is a robust and well-reported trial, with the results demonstrating that amivantamab-chemotherapy improves survival, achieves higher, more durable response rates and prolongs the time until disease progression compared with chemotherapy in adult patients with EGFR Exon20 insertion mutation-positive advanced NSCLC. The PAPILLON trial met its primary endpoint, given amivantamab-chemotherapy demonstrated a statistically significant and clinically meaningful improvement in BICR-assessed PFS over chemotherapy (11.37 months vs 6.70 months, HR: 0.40, 95% CI: 0.30-0.53, $p < 0.0001$).¹⁰ Furthermore, amivantamab-chemotherapy has a tolerable and manageable safety profile, with the safety profiles consistent with the individual treatment components. The data available for amivantamab-chemotherapy provide strong evidence to suggest it can extend PFS and TTSP, thus maintaining patients' HRQoL for longer, until disease progression. In conclusion, amivantamab-chemotherapy fulfils a substantial unmet need for a targeted treatment option in patients with EGFR Exon20 insertion mutation-positive advanced NSCLC, for whom no such options currently exist in UK clinical practice.

B.3 Cost effectiveness

A *de novo* economic model assessed the cost-effectiveness of amivantamab-chemotherapy versus a weighted comparator of chemotherapy and pembrolizumab-chemotherapy, which are the relevant treatments prescribed to patients with EGFR Exon20 insertion mutation-positive advanced NSCLC in the UK

- A *de novo* cost-effectiveness model (CEM) was developed to assess the cost-effectiveness of amivantamab in combination with carboplatin and pemetrexed (amivantamab-chemotherapy) for the treatment of patients with EGFR Exon20 insertion mutation-positive advanced NSCLC.
- The model adopted a partitioned survival model (PSM) approach with three health states: progression-free, progressed disease, and death.
- Efficacy for amivantamab-chemotherapy was informed by the intervention arm of the Phase 3 PAPILLON trial (Section B.2.6). The efficacy of carboplatin plus pemetrexed ('chemotherapy') was informed by the control arm of the PAPILLON trial. The efficacy of pembrolizumab and carboplatin plus pemetrexed ('pembrolizumab-chemotherapy') was informed by the pooled RWE data from the NECTAR study.³
- In the absence of an established SoC for patients with EGFR Exon20 insertion mutation-positive advanced NSCLC, amivantamab-chemotherapy is anticipated to displace both chemotherapy and pembrolizumab-chemotherapy collectively in UK clinical practice, if recommended, in the absence of a single dominant comparator.
- As such, a weighted comparison was conducted, where the ICERs for each relevant comparator were weighted based on their expected use in UK clinical practice, informed by clinical expert opinion obtained across multiple advisory boards.^{5, 22, 23} This approach provides an overall ICER evaluating the cost-effectiveness for amivantamab-chemotherapy versus chemotherapy and pembrolizumab-chemotherapy.
- Health state utility values (HSUVs) for each health state were derived from EQ-5D-5L data from the PAPILLON trial, cross-walked to EQ-5D-3L using the method reported by Hernández Alava et al. (2017).^{103, 104}
- Costs included in the model comprised drug acquisition and administration costs, follow-up and monitoring costs, AE management costs and end-of-life costs.
- The cost-effectiveness analysis was conducted from the perspective of the NHS and PSSRU over a lifetime horizon.

Model results indicate that amivantamab-chemotherapy is a cost-effective treatment option versus relevant comparators and qualifies for the 1.2x severity modifier given the severe unmet need faced by patients with EGFR Exon20 insertion mutation-positive advanced NSCLC

- Results of the QALY shortfall analysis indicate that amivantamab-chemotherapy is eligible for a 1.2x severity modifier. The criteria are met when considering the total discounted QALYs calculated for patients in the NCRAS dataset (England-specific RWE).
- Once this severity modifier was applied, the probabilistic ICER for amivantamab-chemotherapy at the confidential PAS discount of █% for amivantamab, versus the weighted comparator was £24,049 per QALY gained.
- As such, amivantamab-chemotherapy represents a cost-effective treatment option versus chemotherapy and pembrolizumab-chemotherapy for patients with untreated EGFR Exon20 insertion mutation-positive advanced NSCLC.

- All scenario analyses, which explored key modelling assumptions and approaches, resulted in amivantamab-chemotherapy remaining a cost-effective use of NHS resources, demonstrating the robustness of the economic model results.

Amivantamab-chemotherapy represents an efficacious and cost-effective treatment for patients with EGFR Exon20 insertion mutation-positive advanced NSCLC, which is anticipated to displace ineffective, non-targeted treatments in the first-line setting

- In the absence of NICE guidance or any recommended treatments for patients with EGFR Exon20 insertion mutation-positive advanced NSCLC, a limited array of sub-optimal therapies are prescribed.
- Therefore, patients with EGFR Exon20 insertion mutation-positive advanced NSCLC face an extremely poor prognosis and there is an urgent unmet need for an efficacious, targeted therapy that can delay progression and improve survival.
- The introduction of amivantamab-chemotherapy into UK clinical practice is anticipated to fulfil this substantial unmet need given its ability to delay progression and improve survival rates, as demonstrated by the results from the Phase 3 PAPILLON registrational clinical trial in this patient population (Section B.2.6), and supportive results from the ITC (Section B.2.9).^{3, 10}
- The economic analysis demonstrates that amivantamab-chemotherapy is a cost-effective treatment option, thereby offering value for money for the NHS, while displacing treatments not specifically developed or used for patients with EGFR Exon20 insertion mutation-positive advanced NSCLC. If recommended, amivantamab would represent the first treatment available on the NHS for these patients in any line of therapy.

B.3.1 Published cost-effectiveness studies

A *de novo* economic SLR was conducted in May 2022 and subsequently updated in July 2022, September 2023, March 2024 and July 2024. The objective of this SLR was to identify the cost-effectiveness (economic evaluations), HSUVs, and cost and resource use (CRU) evidence associated with treatment options for patients with metastatic or surgically unresectable common NSCLC with either common EGFR mutations (Exon19 deletions or Exon21 L858R substitution mutations) or EGFR Exon20 insertion mutations. The databases and hand searches were conducted simultaneously for these three data streams, with each record identified assessed for eligibility across all three data streams.

A total of 7,634 records were retrieved from the July 2024 electronic database searches, of which 7,274 were duplicates, including duplicates against the previous SLR searches. Overall, 360 novel records were screened at the title/abstract review stage. Subsequently, 73 full publications were sought for retrieval and screened against the cost-effectiveness eligibility criteria at full-text review, resulting in all 73 records being excluded. This resulted in no records from electronic database searches. Supplementary searches retrieved two records (one from HTA body websites and one from reference list searches).

Full details of the cost-effectiveness SLR methods and results, including search terms and eligibility criteria, can be found in Appendix G.

In total, across the original and SLR updates, 56 economic evaluations, reporting on 52 unique studies, were included. However, only two economic evaluations were identified in the EGFR Exon20 insertion mutated advanced NSCLC patient population: a NICE evaluation for Company evidence submission template for amivantamab with carboplatin and pemetrexed for untreated EGFR Exon 20 insertion mutation-positive advanced non-small cell lung cancer [ID5110]

amivantamab conducted from a UK perspective in the second-line setting, and a CADTH evaluation for amivantamab conducted from a healthcare payer perspective in the second-line setting.^{19, 105}

B.3.2 Economic analysis

As outlined in Section B.3.1, no relevant CEMs investigating amivantamab-chemotherapy for the first-line treatment of EGFR Exon20 insertion mutated advanced NSCLC were identified in the economic SLR and therefore a *de novo* CEM was developed for the purpose of this submission.

The objective of the CEM was to determine the cost-effectiveness of amivantamab-chemotherapy compared with relevant therapies used in the UK to treat adult patients with untreated advanced NSCLC with EGFR Exon20 insertion mutations. As noted in Section B.1.3.2, there is a lack of guidance and recommended treatments specifically for this patient population in UK clinical practice, and as such, the relevant comparators in this submission were informed by clinical expert opinion obtained via three advisory boards conducted by Johnson & Johnson in June 2023, May 2024 and August 2024, in addition to UK RWE from the NECTAR study and NCRAS database.^{5, 11, 23} Using these insights, chemotherapy (informed by data from the PAPILLON trial) and pembrolizumab-chemotherapy (informed by data from the NECTAR study) are considered as the key comparators in UK clinical practice, and are modelled as weighted comparators in this evaluation (Section B.3.2.3). In the base case, the assigned weightings of each comparator were informed by clinical expert opinion.⁵ In addition, a scenario analysis is provided in Section B.3.11.3 whereby the distribution and efficacy of comparators in UK clinical practice is informed solely by the NCRAS dataset.

The analysis of costs was conducted from the perspective of the NHS and PSS in the UK and included direct medical costs over a lifetime horizon. Specifically, a lifetime horizon of 30 years was assumed to be a sufficient length of time to capture all important differences in costs or outcomes between the technologies being compared, given the mean age of patients within the PAPILLON trial was 59.6 years from the initiation of treatment, and since this disease is generally associated with a poor prognosis.¹² Sections B.3.2.1, B.3.2.2 and B.3.2.3 present details on the patient population, the model structure, and the included interventions and comparators, respectively.

B.3.2.1 Patient population

The patient population considered in this CEM was adult patients with advanced NSCLC with activating EGFR Exon20 insertion mutations in the first-line setting. As set out in the decision problem in Table 1, Section B.1.1, the population considered in this model is in line with the marketing authorisation for amivantamab and population within the PAPILLON trial.

B.3.2.2 Model structure

A *de novo* CEM was built in Microsoft Excel® to conduct a cost-utility analysis of amivantamab-chemotherapy versus the relevant comparators for the target patient population. The model was developed in accordance with 'Modeling Good Research Practices' disseminated by the International Society of Pharmacoeconomics and Outcomes Research and the Society for Medical Decision Making (ISPOR-SMDM).¹⁰⁶

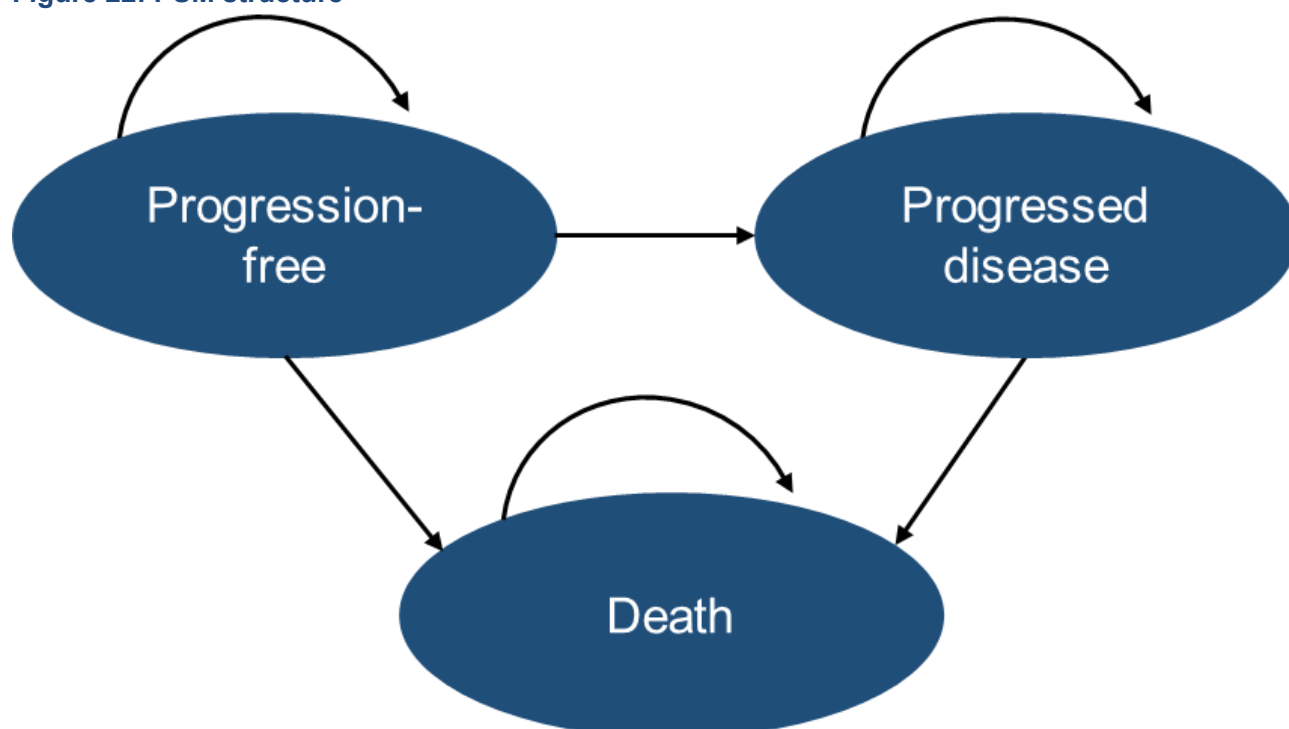
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Partitioned survival model

The CEM used a PSM approach to track the modelled cohort's costs and health outcomes from initiation of first-line treatment until the end of the time horizon. The PSM approach was selected as it is representative of the natural history and clinical pathway for NSCLC, as validated by a global advisory board conducted by Johnson & Johnson on 8th November 2023.¹⁰⁷ Furthermore, an economic SLR updated in August 2022, which identified economic evaluations associated with treatment options for patients with advanced common EGFR mutation positive NSCLC, found that out of a total of 50 economic evaluations, the most widely used model structures were PSMs (21/50) and Markov models (17/50), providing precedent for this modelling approach.¹⁰⁸

The PSM enables patients to move forwards through a set of health states, with a patient's treatment course and outcomes largely dependent on whether their disease has progressed or remained progression-free. The model includes three health states: progression-free, progressed disease and death. All patients start in the progression-free health state, and in each cycle, the cohort is distributed into the three health states; patients can transition to the other health states or remain in their current health state at each model cycle. Once progressed, patients cannot return to the progression-free state; they are assumed to continue living with progressed disease or transition to the 'dead' state, an absorbing health state. At any time point in the model, a patient can be alive with non-progressed disease (progression-free), alive with progressed disease (post-progression), or dead as shown in Figure 22.

Figure 22: PSM structure



Abbreviations: PFS: progression-free survival; PSM: partitioned survival model; TTNT: time to next treatment.

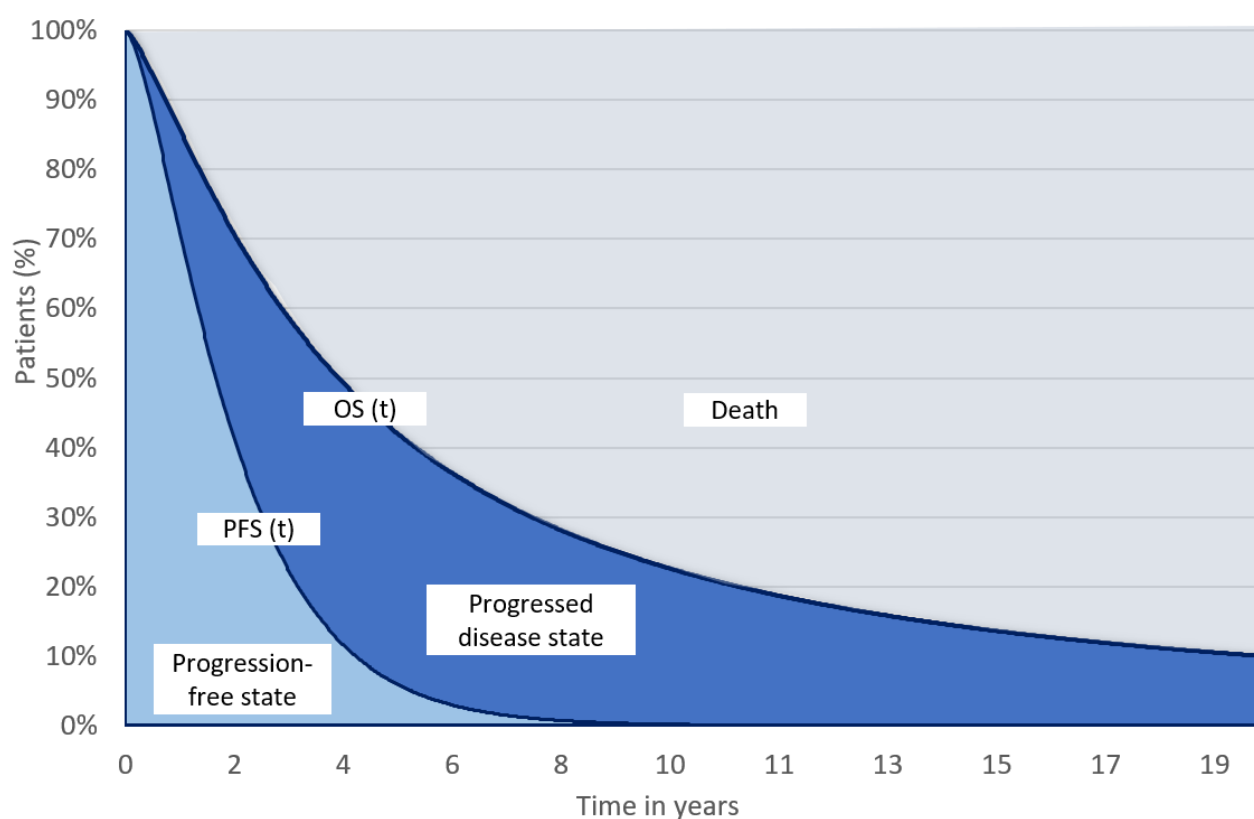
In the PSM, PFS and OS were modelled independently and the percentage of patients in each health state at any given time was estimated using an AUC approach. This method directly utilised treatment specific projections for PFS and OS to allocate patients into their respective health states, as shown in Figure 23. It should be noted that PFS data were not available in the Company evidence submission template for amivantamab with carboplatin and pemetrexed for untreated EGFR Exon 20 insertion mutation-positive advanced non-small cell lung cancer [ID5110]

RWE for pembrolizumab-chemotherapy, therefore a realistic estimation of PFS was derived by applying the per cycle HR of amivantamab-chemotherapy TTNT vs BICR-assessed PFS in the PAPILLON trial to the selected TTNT extrapolation for pembrolizumab-chemotherapy, informed by the RWE. Further information on the derivation of PFS for pembrolizumab-chemotherapy is presented in Section B.3.3.2.

The proportion of patients in the progression-free state was estimated by the difference between the BICR-assessed PFS survival function and zero (on the x axis). The proportion of patients in the post-progression state was estimated by taking the difference between the OS and estimated PFS survival functions. The proportion of patients who were dead in each model cycle was estimated by one minus estimated survival.

Time to treatment discontinuation or death (TTDD) data were used to accurately model the associated costs for amivantamab-chemotherapy and chemotherapy over the lifetime time horizon (the base-case assumes a 30-year time horizon). TTDD data for amivantamab-chemotherapy and chemotherapy were derived by adding death events prior to treatment discontinuation to TTD data from the PAPILLON trial. For the amivantamab-chemotherapy arm, TTDD for amivantamab and chemotherapy were modelled separately to reflect the expected use of amivantamab-chemotherapy in line with the different treatment durations observed in the PAPILLON trial and expected to be seen in clinical practice, as confirmed by clinical experts in the May 2024 advisory board.⁵ TTDD was not available in the RWE for pembrolizumab-chemotherapy. Therefore, the per cycle HR of TTDD for the amivantamab component of amivantamab-chemotherapy versus the PFS of amivantamab-chemotherapy was applied to the PFS curve derived for pembrolizumab-chemotherapy (the derivation of the PFS curve is described in the above paragraph).

Figure 23: Partitioned survival AUC approach



Abbreviations: AUC: area under the curve; OS: overall survival; PFS: progression-free survival; TTNT: time to next treatment.

Features of the *de novo* CEM

The CEM was conducted from the perspective of the NHS and PSS, with only direct costs and benefits considered in the base case. The time horizon for the base case was 30 years, which was considered to sufficiently capture the lifetime of the targeted population given the mean starting age of patients in the model (65 years), as per the population in the PAPILLON trial, and their poor prognosis. A one-week cycle length was selected for the model in order to capture the varied dosing schedules of the comparators, with a half-cycle correction applied. An annual discount rate of 3.5% was applied in the model base case to the costs and health benefits, in accordance with NICE guidelines.¹⁰⁹ Costs and health-related utilities were allocated to each health state and multiplied by state occupancy to calculate the weighted costs and QALYs.

A summary of the key features of the economic analysis can be found in Table 40, as compared to relevant previous NICE evaluations in EGFR Exon20 insertion mutated advanced NSCLC: TA850 and TA855.^{19, 110} TA850 and TA855 appraised amivantamab and mobocertinib, respectively, for treating EGFR Exon20 insertion mutated locally advanced or metastatic NSCLC after platinum-based chemotherapy. As detailed in Section B.1.3.2, the recommendation for mobocertinib (TA855) was withdrawn by NICE following the withdrawal of mobocertinib by the manufacturer; model features from this evaluation have therefore been accessed through the UK government web archive.¹¹⁰ Of note, no previous evaluations have been conducted in the first-line treatment setting for patients with EGFR Exon20 insertion mutated advanced NSCLC.

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Table 40: Features of the economic analysis

	Previous evaluations		Current evaluation	
Factor	TA850 ¹⁹	TA855 ¹¹⁰	Chosen values	Justification
Model structure	PSM; three health states: PFS, post-progression survival and death	PSM: three health states: progression-free, progressed disease, death	PSM; three health states: progression-free, progressed disease, death	Representative of the natural history and clinical pathway for NSCLC and is aligned with previous similar submissions
Time horizon	15 years	30 years	30 years	Based on the starting cohort age and their prognosis, 30 years is assumed to be sufficient length to capture the lifetime of the patient population
Cycle length	4 weeks	1 week	1 week	Allows for the varied dosing schedules of the comparators to be captured in the model
Discount	3.5%	3.5%	3.5%	As per NICE reference case ¹⁰³
Health effects measure	QALYs	QALYs	QALYs	As per NICE reference case ¹⁰³
Perspective	NHS/PSS	NHS/PSS	NHS/PSS	As per NICE reference case ¹⁰³
Source of health state utilities	TA484 ¹¹¹ /TA713 ¹¹²	Analysis of EQ-5D data collected in Part 3 (EXCLAIM) trial	EQ-5D-5L results collected in the PAPILLON trial, cross-walked to EQ-5D-3L ^{103, 104}	EQ-5D data from the PAPILLON trial provide the most appropriate source of HRQoL data, aligning with NICE's preference. ¹⁰⁹ These are the most applicable utilities as they are derived directly from the patient population of interest (i.e., patients with EGFR Exon20 insertion mutated locally advanced or metastatic NSCLC)
Source of costs	- NHS National Reference costs - PSSRU - Electronic market information tool (eMIT) - BNF	- NHS National Reference costs - PSSRU - eMIT - BNF	- National Schedule of NHS Costs 2021/2022 - PSSRU - eMIT - BNF	As per NICE reference case ¹⁰³

Abbreviations: BNF: British National Formulary; eMIT: electronic market information tool; EGFR: epidermal growth factor receptor; HRQoL: health-related quality of life; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; NSCLC: non-small-cell lung cancer; PFS: progression-free survival; PSM: partitioned survival model; PSS: personal social services; PSSRU: Personal Social Services Research Unit; QALYs: quality-adjusted life years; TA: technology appraisal.

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B.3.2.3 Intervention technology and comparators

Intervention

The intervention considered in the CEM was amivantamab in combination with carboplatin and pemetrexed (amivantamab-chemotherapy). The dosing for amivantamab included in the model is in line with the regimen included in the Phase 3 PAPILLON trial and the SmPC for amivantamab.^{21, 73} Carboplatin and pemetrexed are also modelled in line with the recommended dosing regimens included in the SmPC for these two treatments.^{113, 114}

Comparators

Validation of comparators in UK clinical practice

As discussed in Section B.1.3.2, there is an absence of UK-specific guidance for the management of patients with EGFR Exon20 insertion mutation-positive advanced NSCLC, and there is no NICE treatment pathway within the NG122 guideline that specifically covers this patient population.⁴

As such, insight was gained through three advisory boards (held in June 2023, May 2024 and August 2024 with UK oncologists) and RWE collected from the NCRAS dataset and the larger NECTAR study.^{3, 5, 22, 23} Insight from these evidence sources indicates that the most relevant first-line therapies prescribed to patients in clinical practice are platinum-based chemotherapy (carboplatin with pemetrexed) with or without IO (pembrolizumab).¹¹ The first-line treatments prescribed to adult patients with EGFR Exon20 insertion mutation-positive advanced NSCLC has also been reported in prior RWE studies.¹²

Further justification regarding the relevant comparators covered by this submission is presented in Table 1 and Section B.1.3.2. In summary, consistent feedback gained across the three advisory board meetings conducted by Johnson & Johnson indicates that IO monotherapy and EGFR TKIs should not be prescribed in patients with EGFR Exon20 insertion mutations, as they are considered against best practice by clinicians with leading experience in treating this mutation, due to a lack of efficacy in this population.^{3, 5, 22, 23}

As such, chemotherapy (informed by the PAPILLON trial) and pembrolizumab-chemotherapy (informed by pooled RWE accessed as part of the NECTAR study), have been included as the relevant comparators in the model. To maximise sample size, the NECTAR study pooled data for patients receiving platinum chemotherapy + IO regimens, assuming that outcomes for these patients would be representative of patients receiving pembrolizumab in combination with carboplatin and pemetrexed. This was considered a defensible assumption given █% of this treatment class in the NECTAR study received pembrolizumab in combination with carboplatin plus pemetrexed, further details in Section B.2.9.4.

The choice of comparators in this submission has been comprehensively validated and supported by clinical experts during the advisory boards, who confirmed that chemotherapy and pembrolizumab-chemotherapy represent the predominant treatments observed in UK clinical practice for the treatment of EGFR Exon20 insertion mutation-positive advanced NSCLC.^{5, 22, 23}

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Weighted comparator approach

Due to the lack of an established treatment pathway and no relevant NICE guidelines specifically for patients with untreated EGFR Exon20 insertion mutation-positive advanced NSCLC, there is no single dominant comparator in this population. As such, it is considered that both chemotherapy and pembrolizumab-chemotherapy represent relevant comparators that will both be displaced by amivantamab-chemotherapy, if recommended for use in UK clinical practice. Therefore, a weighted comparator arm within the economic model was used in this submission, in which the aggregated total costs and QALYs for chemotherapy and pembrolizumab-chemotherapy were weighted according to their proportions in UK clinical practice. The resulting overall ICER, which compares amivantamab-chemotherapy versus chemotherapy and pembrolizumab-chemotherapy, is considered to be the most appropriate reflection of the value of amivantamab-chemotherapy in current UK clinical practice.

The distribution used for the two comparators in the model is presented in Table 41. This distribution was informed by clinical expert opinion obtained during the May 2024 advisory board.^{5, 23} The ratio between chemotherapy and pembrolizumab-chemotherapy used in the base-case is similar to the ratio between these treatments in the NCRAS dataset (excluding TKIs and IO monotherapy), confirming that this split is reflective of UK clinical practice. The model includes the functionality to change the distributions of chemotherapy and pembrolizumab-chemotherapy in the weighted comparison to explore the impact of comparator distributions on the cost-effectiveness results, given that some clinical experts estimated higher usage of pembrolizumab-chemotherapy in clinical practice (80–90% of patients).^{5, 23}

Further details on these scenarios are presented in Section B.3.11.3. As such, the model captures all data and evidence available for the distribution of treatments prescribed to patients with EGFR Exon20 insertion mutation-positive advanced NSCLC in the first-line setting in UK clinical practice.

Table 41: Distribution of relevant comparators in the base case

Treatment	Proportion of patients receiving treatment (%)
Carboplatin plus pemetrexed (platinum chemotherapy)	70%
Pembrolizumab in combination with carboplatin and pemetrexed	30%

Source: Johnson & Johnson Data on File. Advisory Board Report (May 2024).⁵

B.3.3 Clinical parameters and variables

B.3.3.1 Baseline characteristics

The baseline characteristics for the modelled population in terms of age, gender and weight were derived from the Full Analysis Set population of the PAPILLON trial and are presented in Table 42.

Table 42: Baseline characteristics of modelled cohort

Characteristic	Base case value
Mean age, years (SD)	██████████

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Characteristic	Base case value
Female, %	57.8
Mean weight, kg (SD)	
Mean BSA, m ² (SD)	
Patients <80 kg, %	84.4

Abbreviations: BSA: body surface area; SD: standard deviation.

B.3.3.2 Survival inputs and assumptions

The key efficacy inputs in the model were PFS, OS and TTDD. TTDD data were used to inform time on treatment and hence inform acquisition costs of treatment; TTDD data do not impact the efficacy of each treatment in the model as pre-progression QALYs are derived from the PFS data.

Efficacy data for amivantamab-chemotherapy and chemotherapy were informed by the Phase 3 PAPILLON trial; specifically, PFS and TTDD (derived from TTD trial data) for the two treatment arms were informed by the 03rd May 2023 DCO. OS data for the two treatment arms were informed by the 31st October 2023 DCO. The TTDD for each component of amivantamab-chemotherapy (amivantamab and chemotherapy) was modelled separately to reflect the different treatment durations observed in the PAPILLON trial and expected to be seen in clinical practice.

Efficacy data for pembrolizumab-chemotherapy were informed by the pooled RWE databases from the NECTAR study. The pooled RWE used to inform the efficacy of pembrolizumab-chemotherapy did not provide complete details on the exact date of disease progression and as a result, an alternative approach to estimating PFS was required. PFS was estimated for pembrolizumab-chemotherapy by applying the per cycle HR of amivantamab-chemotherapy TTNT vs BICR-assessed PFS in the PAPILLON trial to the selected TTNT extrapolation for pembrolizumab-chemotherapy from the NECTAR study. This approach was taken following receipt of expert opinion from the August 2024 advisory board that TTNT is not a suitable proxy for PFS in this patient population.²² For completeness, a scenario is also explored where TTNT is used as a proxy for PFS in the economic model. Given that TTDD was not available in the RWE for pembrolizumab-chemotherapy, the per cycle HR of TTDD for the amivantamab component of amivantamab-chemotherapy versus the PFS of amivantamab-chemotherapy was applied to the PFS curve derived for pembrolizumab-chemotherapy (as described above).

The parametric distributions for amivantamab-chemotherapy, chemotherapy and pembrolizumab-chemotherapy for PFS, OS and TTDD were selected based on a rigorous process, as per the NICE DSU TSDs 14 and 21.^{115, 116} Specifically, the following steps were taken for each outcome and comparator:

1. **Assessment of the proportional hazards (PH) assumption:** The PH assumption between treatment arms in PAPILLON was assessed through use of log-log plots. The results of the PH assessment were used to inform the approach of applying joint parametric models across treatment arms or fitting independent models to each treatment arm. For the pembrolizumab-chemotherapy arm, the parametric survival curves for TTNT and OS were fitted directly to the KM data from the NECTAR study.
2. **Assessment of hazard functions:** The hazards observed in the available data for each treatment were assessed through smoothed hazard plots to determine whether standard

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parametric survival models or accelerated failure time (AFT) models would most appropriately capture the hazards observed.

3. **Visual assessment of fit:** A visual assessment was conducted to assess how well each extrapolation captured the shape of the observed KM curve from the underlying data set
4. **Goodness-of-fit statistics:** Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) statistics were assessed to measure the statistical fit of the extrapolations to the underlying data set
5. **Clinical plausibility of long-term projections:** The long-term plausibility of the extrapolations was clinically validated through obtaining survival estimates for patients with EGFR Exon20 insertion mutation-positive advanced NSCLC for each outcome included in the model from expert clinicians practising in the UK^{22, 23}

B.3.3.2.1 Adjusting for treatment switching

As detailed in Section B.2.6.2.3, at the 31st October 2023 DCO of the PAPILLON trial, 78/█ (█% of patients who experienced progression) patients in the chemotherapy arm had undergone treatment switching to receive amivantamab monotherapy following BICR-confirmed disease progression on an every three-week regimen, at the dose specified in the PAPILLON trial protocol.⁷⁹

Given that treatment with amivantamab monotherapy is not currently recommended by NICE (i.e., not available on the NHS) for adult patients with advanced NSCLC with activating EGFR Exon20 insertion mutations, after failure of platinum-based therapy, the chemotherapy OS data were adjusted to account for this treatment switching (i.e., to reflect the survival of patients receiving chemotherapy, had they followed UK clinical practice after progression). Treatment switch adjustment is used to mitigate potential confounding from subsequent therapies that would not typically be received by patients in the UK, ensuring that efficacy data are as reflective of clinical practice as possible. Several approaches for treatment switch adjustment were explored, in line with guidance provided by NICE TSD 24.⁸¹

Approaches explored for treatment switching adjustment

The treatment switching methods explored were the TSE, RPSFT and IPCW, as recommended by NICE DSU TSDs 16 and 24.^{81, 117} The key characteristics and assumptions of these methods are briefly summarised in Table 43.

Table 43: Overview of treatment switching adjustment methods

Method	Description	Core assumptions
TSE	The two-stage estimation method assumes disease progression as the secondary baseline, estimating the effect of receiving a subsequent therapy on the post-progression survival. This estimated effect is then used to derive counterfactual survival times for patients who received subsequent therapies	• No unmeasured confounders at secondary baseline • No time-dependent confounding between disease progression and treatment switch
RPSFT	The RPSFT method adjusts the survival times for patients receiving subsequent therapies using an acceleration factor (calculated through g-estimation) such that they represent the predicted survival time	A common treatment effect exists between patients who receive the intervention of

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	had the patient not received the treatment being adjusted for as subsequent therapy	interest at randomisation or at the time of treatment switch
IPCW	The IPCW method artificially censors patients at the time of receipt of subsequent therapy and then weights remaining non-censored patients using information on baseline and time-dependent covariates	No unmeasured confounders relating to the baseline and time-varying patient characteristics

Abbreviations: IPCW: inverse probability of censoring weight; RPSFT: rank preserving structural failure time; TSE: two stage estimation.

The three approaches outlined in Table 43 were firstly assessed based on the appropriateness of the core assumptions adopted by each method, guided by feedback received from health economist experts as part of the August 2024 advisory board. Subsequently, the clinical plausibility of the resulting survival estimates was considered by UK clinical experts at the same advisory board.²²

As explained by the health economist experts at the August 2024 advisory board, the RPSFT method uses a core assumption of a common treatment effect between patients who receive the intervention at randomisation or at the time of the treatment switch (Table 43). In the context of the PAPILLON trial, this approach assumes that the survival benefit of amivantamab monotherapy received in the second-line setting, following disease progression, is equal to the survival benefit received by patients randomised to amivantamab-chemotherapy in the first-line setting.

UK clinical and health economic experts agreed that such an assumption lacked clinical plausibility in the August 2024 advisory board, furthermore, no published evidence has been identified supporting this assumption.²² Specifically, while a direct comparison of amivantamab-chemotherapy in the first-line setting and amivantamab monotherapy in the second-line setting in the population of interest to this submission is not currently available. A naïve comparison between patients in the PAPILLON trial (untreated EGFR Exon20 insertion mutation-positive advanced NSCLC) and patients in the CHRYSALIS trial (EGFR Exon 20 insertion mutation-positive advanced NSCLC after prior platinum-based chemotherapy) showed a difference in the efficacy benefit of amivantamab-chemotherapy in the front-line setting versus amivantamab monotherapy in the second-line setting. The CHRYSALIS trial included a different patient population than the population investigated in the PAPILLON trial, and is only investigating amivantamab monotherapy, a full comparison cannot be made. However, when investigating some differences in the endpoints between the trials, the ORR in CHRYSALIS was 40% (95% CI: 29-51) versus 73.0% (95% CI: 62.5-79.9) in the amivantamab-chemotherapy arm of the PAPILLON trial; median PFS in the CHRYSALIS trial was 8.3 months (95% CI: 6.5-10.9) versus 11.37 months (95% CI: 9.79-13.70) for the amivantamab-chemotherapy arm in the PAPILLON trial. As such, the RPSFT approach was considered inappropriate and lacking face validity, as supported by the expert health economists and clinicians.²² As such, the two-stage estimation approach and IPCW were further considered as approaches for treatment switch adjustment.

Prognostic variables considered for treatment switch adjustment

Both IPCW and TSE analyses require the identification of factors that are prognostic of both treatment switching and OS. An iterative process was followed to identify key prognostic factors to be accounted for in the treatment switch adjustment. First, an extensive list of factors was obtained using a SLR and a Delphi panel including clinical experts, conducted in 2020–2021,

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with further details on this evidence source provided in the reference pack provided alongside this submission.⁹² Subsequently, the final list of prognostic factors was obtained after an extensive medical review and determination of data availability. An advisory board was conducted to validate the prognostic factors identified, and a final list was obtained:

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

Treatment switch adjustment: IPCW method

Methodology

The IPCW method is undertaken through three key steps: the creation of panel data, the estimation of stabilised, time dependent weights (for patients in the chemotherapy treatment arm) and a subsequent estimation of the adjusted treatment effect on OS. The IPCW method considered all covariates listed above, with the exception of time to progression and BOR as they could not be included as baseline or time-varying covariates. Further details on the IPCW methodology are provided in Appendix N.1, which outlines each key step associated with the generation of the IPCW-adjusted OS data for the chemotherapy treatment arm.

All treatment switch adjustment methodologies were applied to OS data for chemotherapy from the 31st October 2023 DCO of the PAPILLON trial.

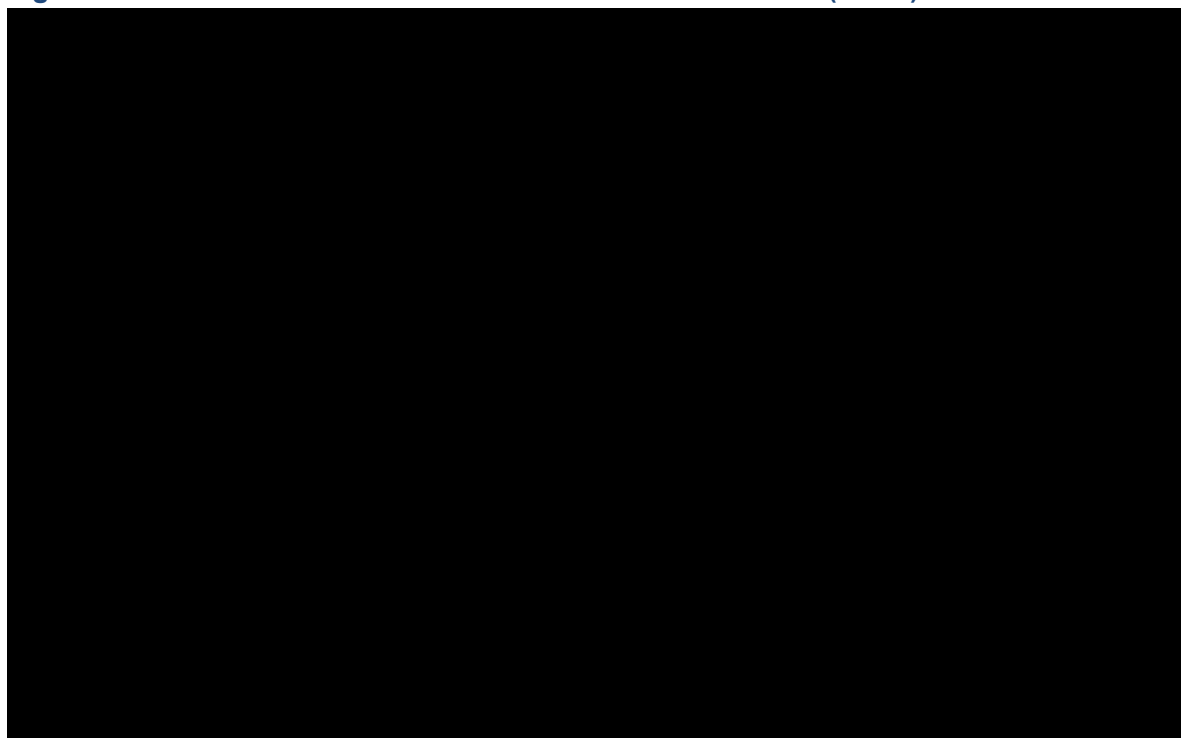
Results

Observed and counterfactual (adjusted using the IPCW method) KM curves for chemotherapy OS are presented in Figure 24.

Based on the Cox proportional hazards model with stabilised weights, the adjusted HR for amivantamab-chemotherapy versus chemotherapy was [REDACTED] (95% CI: [REDACTED]-[REDACTED]; p=[REDACTED]) when accounting for treatment switching.

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Figure 24: Observed versus counterfactual KM curves for OS (IPCW)



Abbreviations: IPCW: inverse probability of censoring weighting; KM: Kaplan Meier; OS: overall survival

The IPCW-adjusted OS KM curve for the chemotherapy arm was generated using the formula provided by Howe et al. 2011, with the estimated time-varying stabilised weights as inputs.¹¹⁸ To fit parametric distributions (detailed in Section B.3.3.2.4), the patient-level data needed to be simulated using the algorithm developed by Guyot et al. in 2012.¹¹⁹ The obtained simulated patient-level data of the IPCW was then used for fitting the parametric distribution.

Treatment switch adjustment: TSE

Methodology

The TSE method firstly estimates a treatment effect specific to switching patients in the chemotherapy treatment arm. Following this, the survival times of these patients are adjusted, which allows the treatment effect on OS without switching for these patients to be estimated. From the complete list provided above, the prognostic factor treatment-emergent febrile neutropenia could not be included in the analysis as no events were observed at the time of progression, and due to limited data, the prognostic factors ECOG performance status and BOR were redefined as binary variables.

Ultimately, the counterfactual OS for the treatment switchers in the chemotherapy treatment arm was estimated using a Weibull regression model. The approach was conducted both with and without re-censoring. Further details on the TSE method are provided in Appendix N.2.

Results

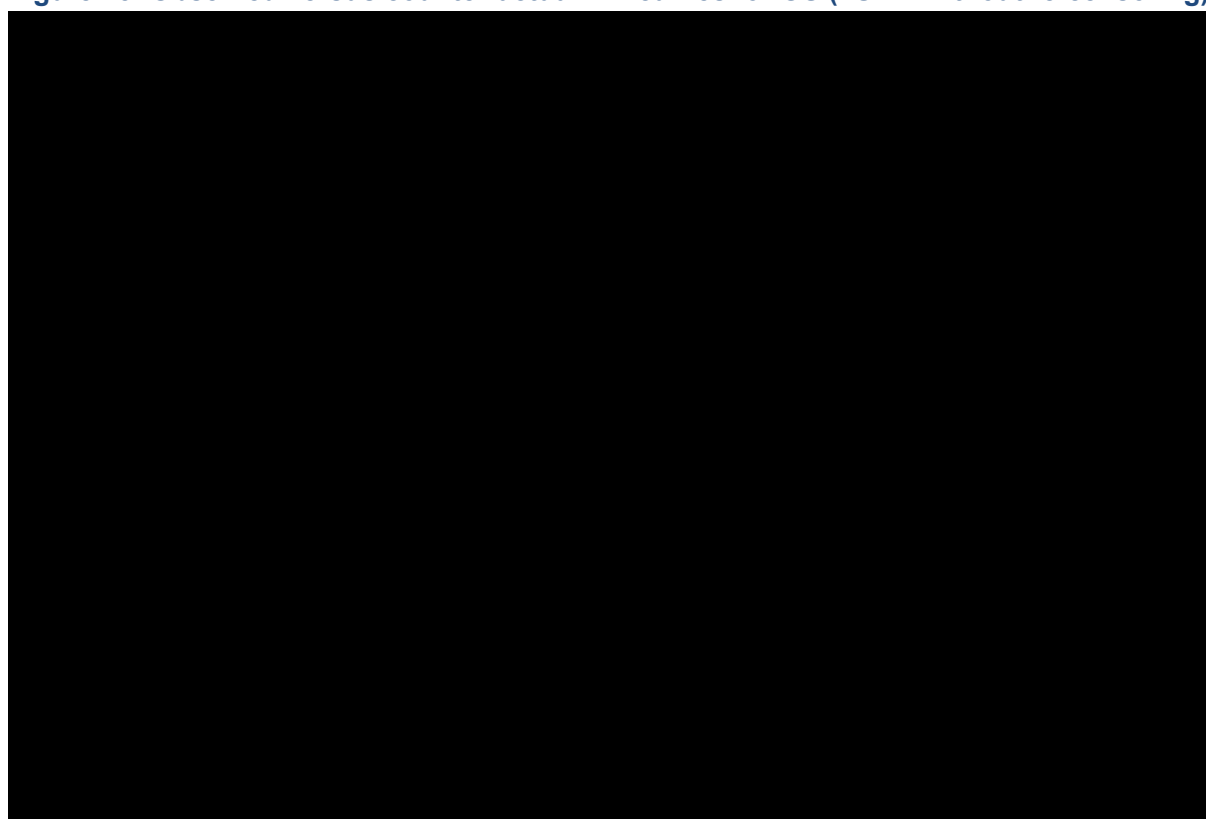
Observed and counterfactual (adjusted using the TSE method, without re-censoring) KM curves for OS are presented in Figure 25.

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Using the TSE method, the OS benefit observed for amivantamab-chemotherapy was greater once OS for the chemotherapy treatment arm had been adjusted for treatment switching, with an adjusted HR (without re-censoring) of ■■■ (95% CI: ■■■-■■■).

The TSE method with re-censoring was also explored. The resulting OS HR for amivantamab-chemotherapy versus chemotherapy was further reduced versus the analysis without re-censoring (OS HR: ■■■ [95% CI: ■■■-■■■]). However, re-censoring led to a substantially shorter follow-up for patients in the chemotherapy arm, and a higher loss of information due to additional censoring of patient death events leading to substantially increased uncertainty. Specifically, re-censoring led to a maximum survival time of approximately ■■ months for this method, compared with a maximum survival time of approximately ■■ months observed in the OS from CP arm of PAPILLON. Both NICE DSU TSD 24 and Latimer et al. 2019 caution that the loss of information due to re-censoring in these analyses can be detrimental if the ultimate goal is for long-term extrapolation in cost-effectiveness analyses. As such, the TSE method without re-censoring can be considered the more robust, and more conservative approach for the TSE method.^{81, 120}

Figure 25: Observed versus counterfactual KM curves for OS (TSE – without re-censoring)



Summary

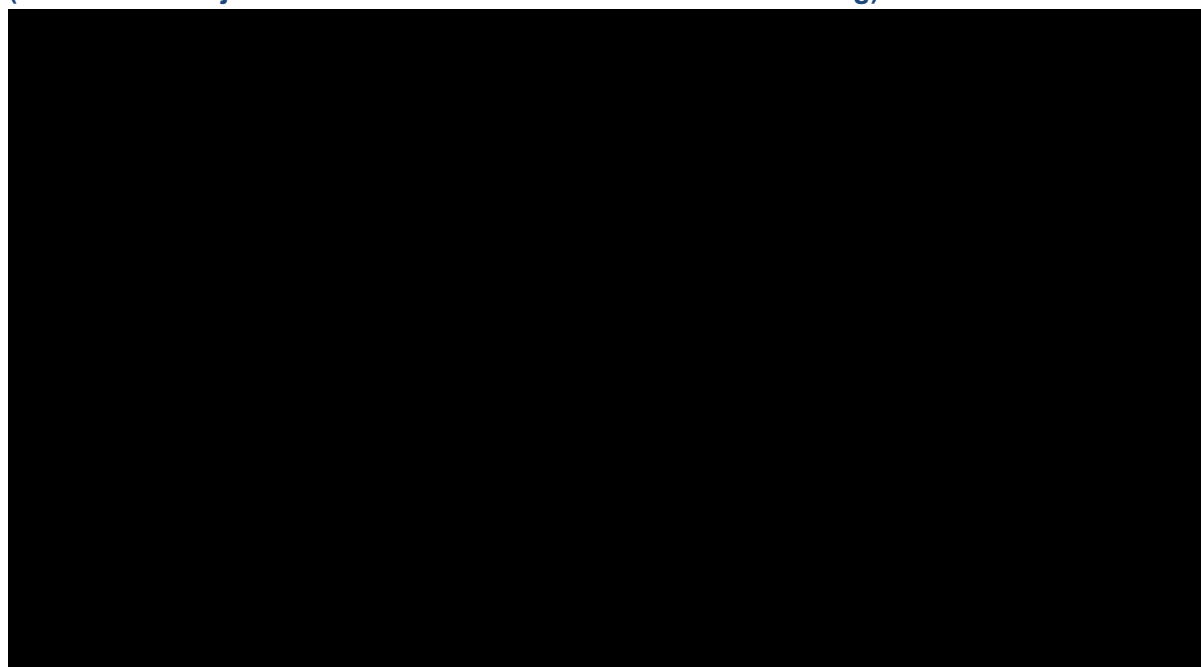
Both the IPCW and TSE (without re-censoring) methods were considered reasonable approaches for the treatment switch adjustment in the chemotherapy arm. For each approach, the face validity of the results has been considered, the limitations of each approach assessed and the method and results validated with health economists and clinical experts in the August 2024 advisory board.²²

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It should be noted that a core assumption of the TSE method is the absence of time-dependent confounding between the time of disease progression and the start of the next treatment. For patients in the chemotherapy treatment arm who switched to receive amivantamab monotherapy in the PAPILLON trial, the time from progression to treatment switch ranged from [REDACTED], indicating considerable variability. This was validated by the health economist experts in the August 2024 advisory board, highlighting a key limitation with one of the core assumptions of the TSE approach.

The OS data for the chemotherapy treatment arm, after applying either the IPCW or the TSE (without re-censoring) adjustment methodologies to the survival data from the 31st October DCO, are aligned with OS for chemotherapy from the NECTAR study. In the NECTAR study and the NCRAS database, OS results did not include patients who received subsequent amivantamab, as illustrated in Figure 26 below. This shows the face validity of each adjustment method.

Figure 26: Comparison of OS data for chemotherapy from the PAPILLON trial (with/without adjustment via IPCW and TSE without re-censoring) versus RWE sources



Abbreviations: ATT; average effect of the treated CP: carboplatin + pemetrexed; IPCW: inverse probability of censoring weighting; NCRAS: National Cancer Registration and Analysis Service; TSE: two-stage estimation

The NECTAR study (Section B.2.9) provided evidence for patients receiving chemotherapy using a real-world cohort of patients treated in the first-line setting, where amivantamab monotherapy is not available as a second-line option. These data were used in an ITC to estimate the efficacy of amivantamab-chemotherapy versus chemotherapy (Appendix O.1). Based on the ITC, the HR of amivantamab-chemotherapy versus chemotherapy, using ATT adjustment, was [REDACTED] [REDACTED]; $p=[REDACTED]$. This HR is comparable with the results from the IPCW-adjusted OS for chemotherapy (95% CI: HR: [REDACTED] [REDACTED]-[REDACTED], $p=[REDACTED]$).

These results demonstrate the clinical validity of the IPCW method due to the similarity of the HRs between the amivantamab-chemotherapy and chemotherapy arms in the PAPILLON trial

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(after IPCW adjustment) and the amivantamab-chemotherapy and chemotherapy arms in the ITC, based on RWE (where there is no use of subsequent amivantamab monotherapy).

Compared with the TSE approach with and without recensoring (which yielded OS HRs of [REDACTED] and [REDACTED], respectively), the OS HR for IPCW-adjusted chemotherapy data ([REDACTED]) is best aligned to the OS HR ([REDACTED]) for ATT-adjusted indirect comparison of chemotherapy data from the NECTAR study with amivantamab-chemotherapy data from PAPILLON, as detailed in Table 44. Chemotherapy data from NECTAR did not include subsequent amivantamab monotherapy. This indicates the improved clinical validity of the IPCW adjustment method compared to both TSE (with or without re-censoring) approaches.

Table 44: Comparative efficacy of amivantamab-chemotherapy versus chemotherapy for OS

Method	Median OS (months)	OS HR (95% CI)	P-value	Setting
PAPILLON trial (ITT)	28.86	0.76 (0.50-1.14)	0.1825	No adjustment for switching
PAPILLON trial (IPCW)	[REDACTED]	[REDACTED]	[REDACTED]	Censor at time of switch and reweight; stabilized weight
PAPILLON trial (TSE)	[REDACTED]	[REDACTED]	[REDACTED]	Weibull regression model; without re-censoring
	[REDACTED]	[REDACTED]	[REDACTED]	Weibull regression model; with re-censoring
RWE (NECTAR study) ^b	[REDACTED]	[REDACTED]	[REDACTED]	ATT-Adjusted Analysis Oct 23 data cut; n=230

^a Based on bootstrapping

^b Source: n=70 subjects. Data leveraged from four RW datasets – ENG-NCRAS, FR-ESME, US-ConcertAI, and US-COTA – between 2012 and 2023

Abbreviations: ATT: average treatment effect in the treated; ITT: inverse probability of censoring weight; OS: overall survival; TSE: two-stage estimation;

Due to the above reasons, the IPCW method for treatment switching adjustment was chosen to inform the base case. The IPCW was chosen considering the clinical plausibility of the IPCW results compared to the RWE and the health economist and clinical expert advice validating the IPCW methodology as appropriate during the August 2024 advisory board.²² However, for completeness, a scenario analysis (Section B.3.11.3) has been provided whereby the chemotherapy OS data is treatment switch adjusted using the TSE approach (with and without re-censoring).

B.3.3.2.2 Modelling PFS, OS and TTDD

A series of proportional hazards and AFT models were fitted to the relevant KM data to estimate long-term projections of PFS, OS and TTDD for amivantamab-chemotherapy and relevant comparators:

- Amivantamab with carboplatin and pemetrexed (amivantamab-chemotherapy) was informed by the PAPILLON trial
- Carboplatin and pemetrexed (chemotherapy) was informed by the PAPILLON trial

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- Pembrolizumab in combination with carboplatin plus pemetrexed (pembrolizumab-chemotherapy) was informed by RWE from the NECTAR study

For pembrolizumab-chemotherapy, the RWE data were weighted to have similar baseline characteristics to the amivantamab-chemotherapy treatment arm in the PAPILLON trial using an average treatment effect on the treated (ATT)-weighted approach (see Section B.2.9 for further details).

B.3.3.2.3 Progression free survival

For amivantamab-chemotherapy, chemotherapy and pembrolizumab-chemotherapy, seven standard parametric distributions (exponential, Weibull, log-logistic, log-normal, Gompertz, gamma, and generalised gamma) were fitted to PFS efficacy data.

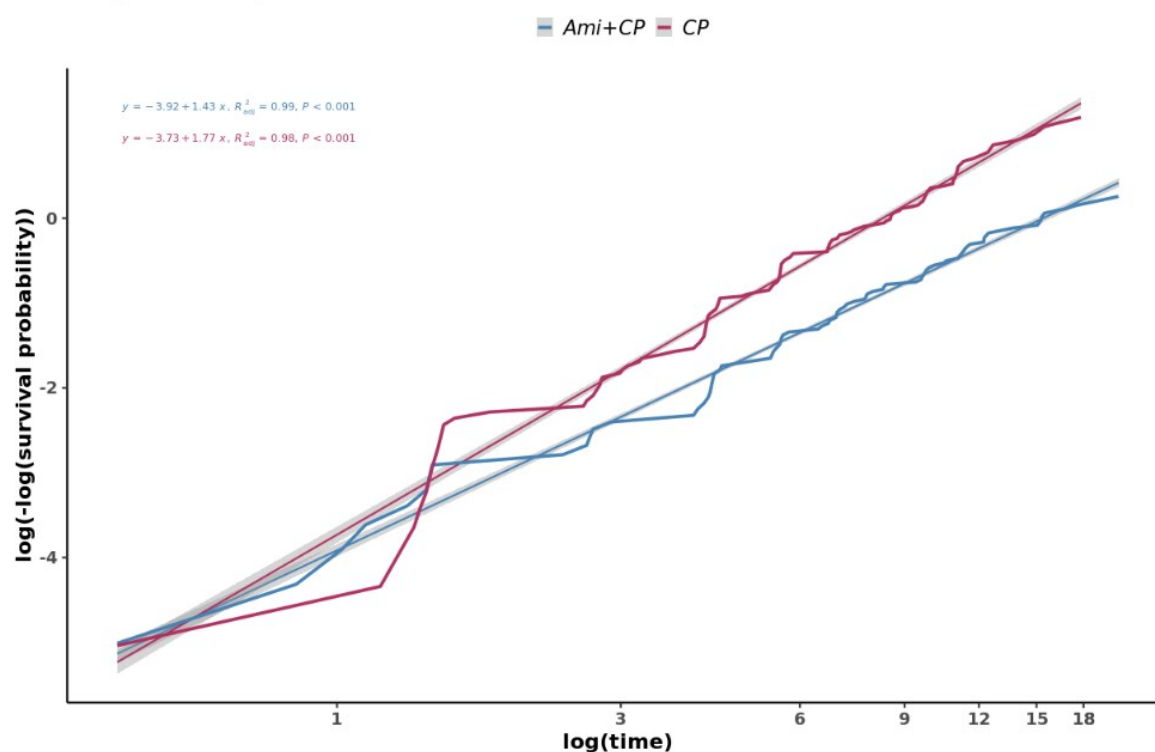
The selection of the most appropriate extrapolation for PFS for each treatment, as per the steps outlined in B.3.3.2, is described in the following sub-sections.

Amivantamab-chemotherapy

The PFS KM curve for amivantamab-chemotherapy and chemotherapy was generated based on data from the PAPILLON trial at the 3rd May 2023 DCO.

An assessment of proportional hazards and an assessment of the amivantamab-chemotherapy hazard function vs. the seven parametric distributions was conducted. Based on these analyses, there is evidence of non-proportionality between the amivantamab-chemotherapy and chemotherapy arms, as informed by the log-log plot for PFS (BICR) (Figure 27), suggesting independent fitting of treatment arms from PAPILLON would be optimal.

Figure 27. Log-logistic plot for amivantamab-chemotherapy and chemotherapy PFS (BICR)

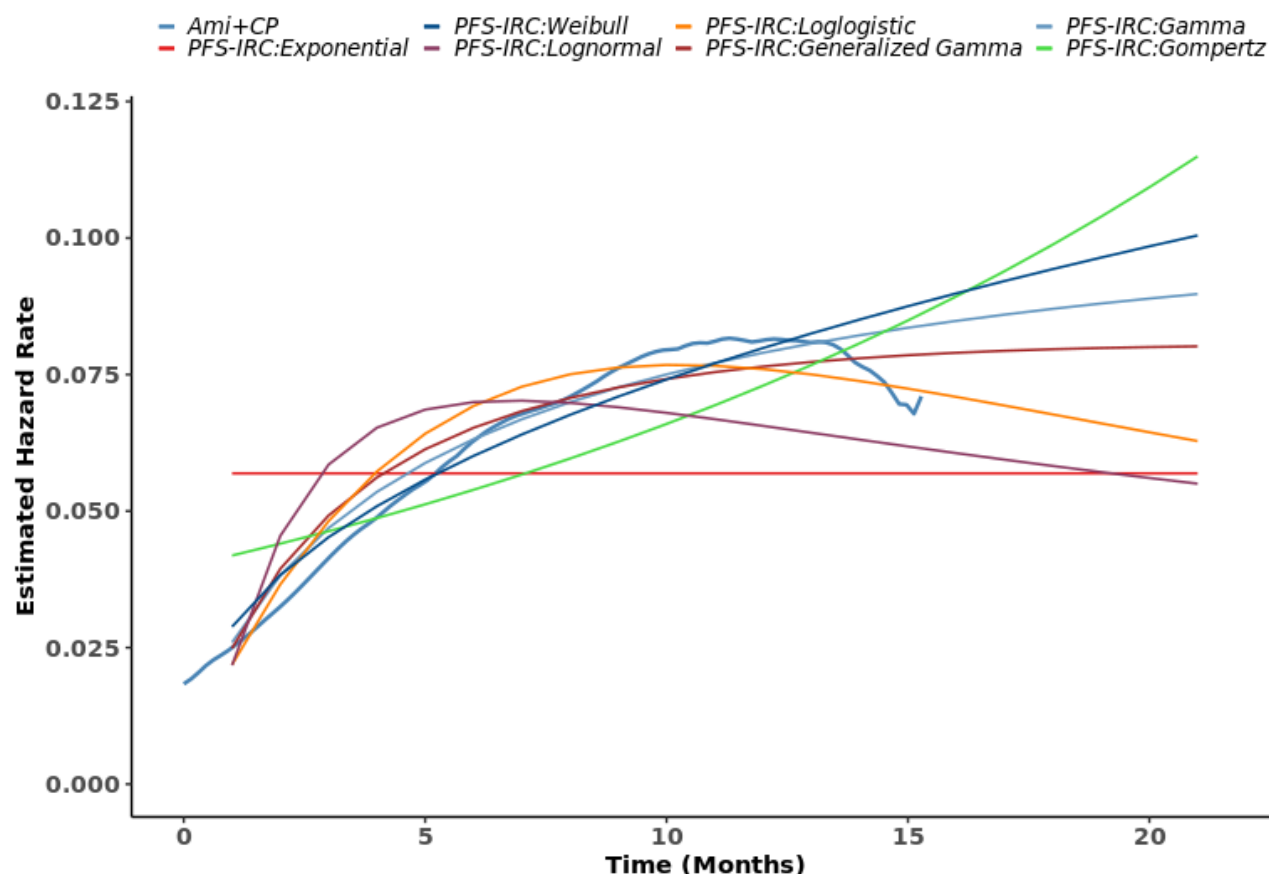


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Abbreviations: ACP: amivantamab + carboplatin + pemetrexed; BICR: blinded independent central review; CP: carboplatin + pemetrexed; PFS: progression-free survival

Alignment of the hazard function for amivantamab-chemotherapy KM data with the log-logistic and lognormal models was observed in the smoothed hazard plot (Figure 28).

Figure 28. Smoothed hazard plot with parametric extrapolations for amivantamab-chemotherapy for PFS (BICR)

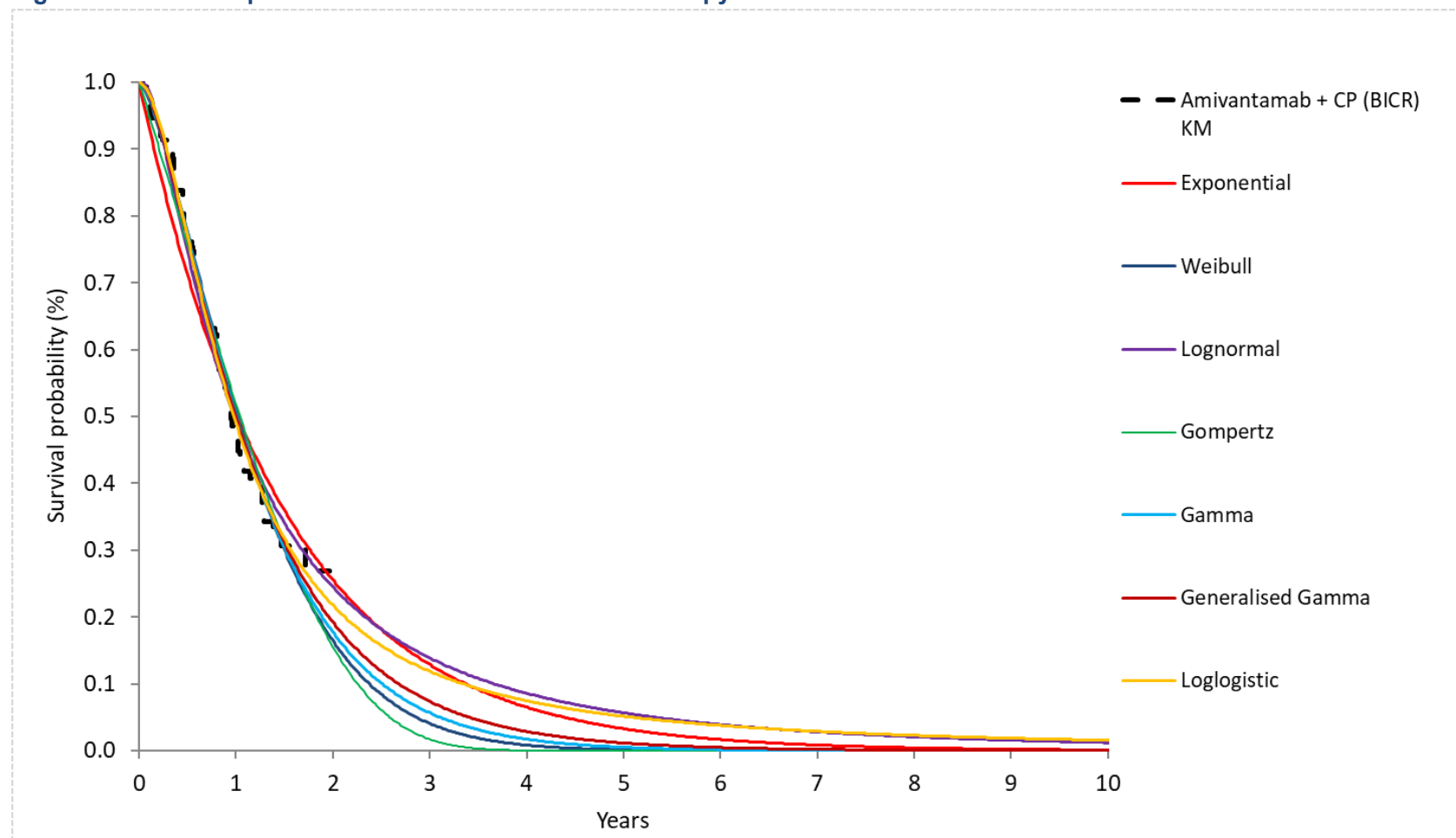


Abbreviations: ACP: amivantamab + carboplatin + pemetrexed; BICR: blinded independent central review; PFS: progression-free survival

All seven parametric distributions introduced above were independently fitted to the PFS KM data from the PAPILLON trial for amivantamab-chemotherapy, and these curves are presented in Figure 29. A summary of all the AIC and BIC values for the extrapolations is further presented in Table 45. Among the seven models, the log-logistic had the best statistical fit to the data.

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Figure 29: PFS extrapolations for amivantamab-chemotherapy



Abbreviations: BICR: Blinded independent central review; CP: carboplatin and pemetrexed; KM: Kaplan-Meier; PFS: progression-free survival.

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Table 45: AIC and BIC values for amivantamab-chemotherapy PFS extrapolations

Distributions	AIC	BIC	Sum of AIC / BIC
Exponential	651.52	654.55	1,306.07
Weibull	641.45	647.52	1,288.97
Lognormal	643.31	649.38	1,292.69
Log-logistic	639.32	645.38	1,284.71
Gompertz	647.68	653.74	1,301.43
Gamma	████	████	████
Generalised gamma	642.15	651.24	1,293.38

Lowest (i.e. best fitting) AIC and BIC scores for each distribution are in **bold** text.

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

Additionally, the median PFS for each distribution and the PFS estimates for each distribution at 1, 3 and 5-years for amivantamab-chemotherapy are presented in Table 46. The log-logistic extrapolation produced the most accurate estimation of median PFS (11.50 months) when compared to median PFS for amivantamab-chemotherapy observed in the PAPILLON trial (11.37 months).

Table 46: Summary of median PFS and 1, 3 and 5-year PFS estimates for amivantamab-chemotherapy extrapolations

Parametric curve	Median PFS (months)	1-year survival (%)	3-year survival (%)	5-year survival (%)
Median and landmark survival for each extrapolation				
Exponential	11.96	50.63%	12.98%	3.33%
Weibull	11.96	50.85%	4.14%	0.14%
Lognormal	11.73	49.49%	13.94%	5.70%
Log-logistic	11.50	49.04%	11.94%	5.17%
Gompertz	12.42	52.01%	1.77%	0.00%
Gamma	████	████	████	████
Generalised gamma	11.73	49.88%	7.43%	1.16%

Abbreviations: PFS: progression-free survival.

The PFS data in the model are relatively mature, given that median PFS had been reached in the PAPILLON trial for the amivantamab-chemotherapy treatment arm. All extrapolations featured similar statistical fits and similar long-term survival outcomes. Clinical expert estimates for PFS were not elicited as part of the advisory boards conducted by Johnson & Johnson, given that the initial modelling approach planned was to use TTNT as a proxy for PFS for amivantamab-chemotherapy and comparators. However, clinical experts consulted as part of the August 2024 advisory board advised that this approach would not be appropriate given that large majority of patients in the first-line setting would be expected to transition to receive palliative BSC in the second-line setting, and therefore, modelling PFS based on time to next (active treatment) would not reflect clinical practice. Additionally, there is anticipated to be a gap between progression and initiation of subsequent treatment.²²

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Therefore, PFS curve selection for amivantamab-chemotherapy was driven by considerations of statistical fit, based on the sum of the AIC and BIC scores, and aligning hazard functions. Although the log-logistic extrapolation had the best statistical fit and the log-logistic hazard plot aligned well with the hazard function, the extrapolation included a tail whereby over 5% of patients remained progression-free after five years. This was seen as clinically implausible by clinical experts consulted in the August 2024 advisory board.²² Therefore, a more clinically plausible extrapolation was selected and the next best statistically fitting extrapolation, the gamma extrapolation, was selected in the base-case for amivantamab-chemotherapy PFS.

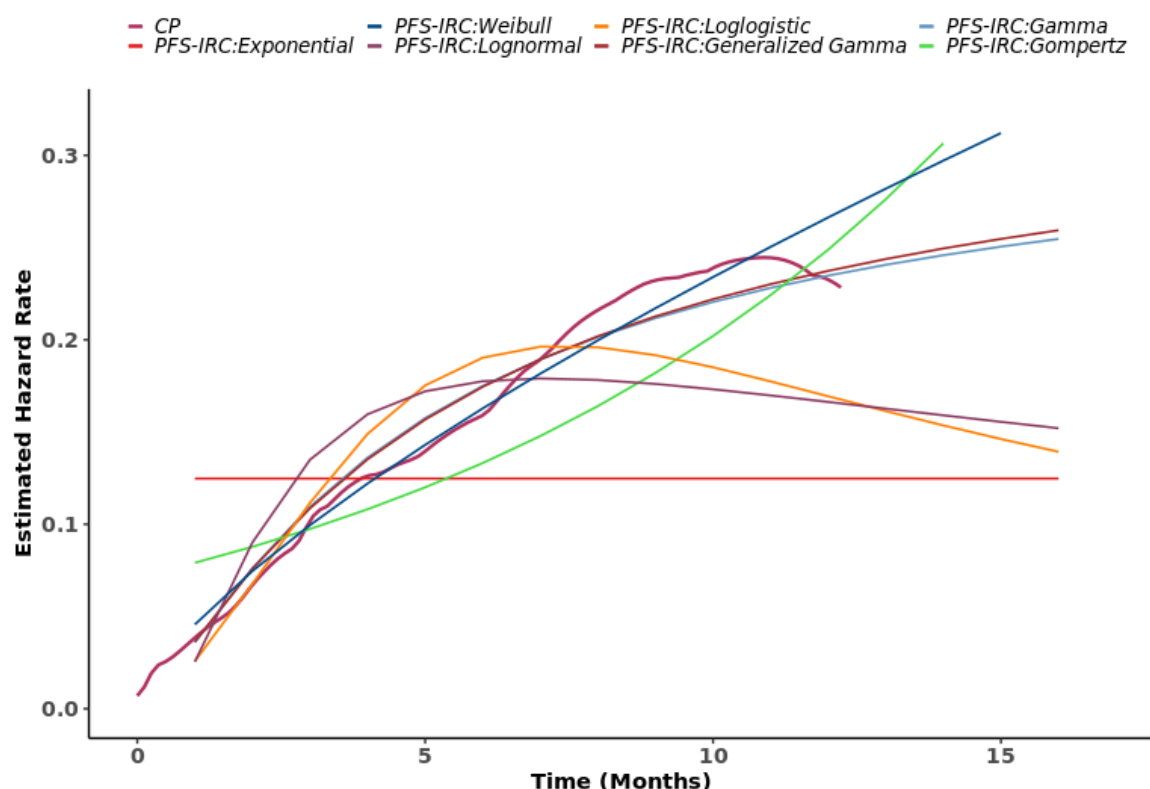
Chemotherapy

The PFS KM curve for chemotherapy was generated based on data from the chemotherapy arm of the PAPILLON trial at the 3rd May 2023 DCO.

As per amivantamab-chemotherapy, the seven parametric distributions listed above were independently fitted to the PFS data. The log-logistic plot for PFS (assessed by BICR) from PAPILLON is presented in Figure 27.

The smoothed hazard plot for the chemotherapy arm from PAPILLON versus the seven extrapolations explored is presented in Figure 30 below, showing that the hazard function for chemotherapy aligns well with the extrapolations for the gamma and generalised gamma extrapolations.

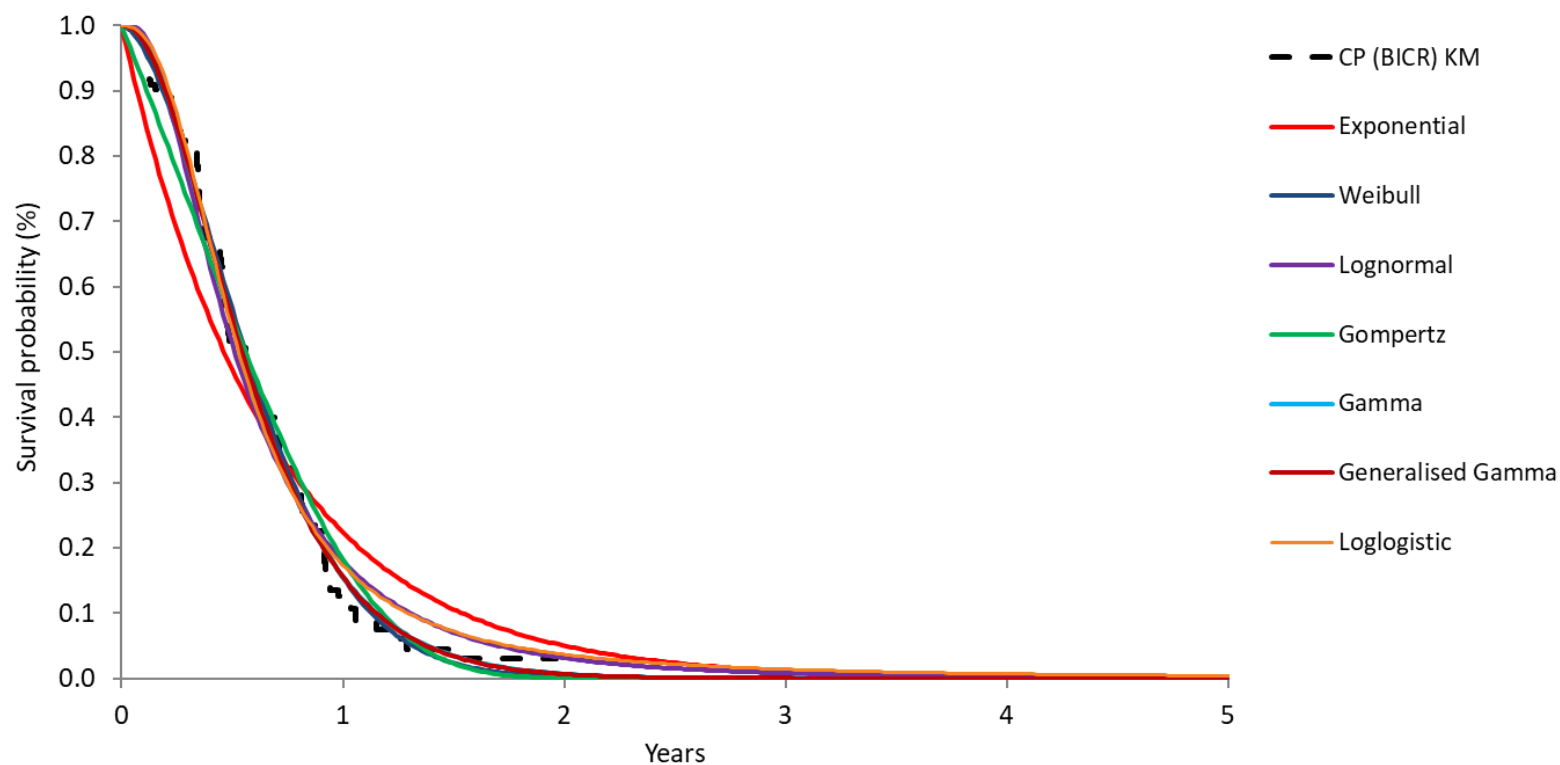
Figure 30. Smoothed hazard plot with parametric extrapolations for CP PFS (BICR)



Abbreviations: CP: carboplatin + pemetrexed; BICR: blinded independent central review; PFS: progression-free survival

The extrapolations applied to PFS data for the chemotherapy arm are presented in Figure 31. Company evidence submission template for amivantamab with carboplatin and pemetrexed for untreated EGFR Exon 20 insertion mutation-positive advanced non-small cell lung cancer [ID5110]

Figure 31: PFS extrapolations for chemotherapy



Abbreviations: CP: carboplatin and pemetrexed; KM: Kaplan-Meier; PFS: progression-free survival.

A summary of all the AIC and BIC values for the extrapolations is further presented Table 47.

Table 47: AIC and BIC values for chemotherapy PFS extrapolations

Distributions	AIC	BIC	Sum AIC / BIC
Exponential	815.42	818.46	1633.87
Weibull	769.78	775.87	1545.65
Lognormal	776.07	782.16	1558.23
Log-logistic	771.73	777.82	1549.54
Gompertz	789.60	795.69	1585.28
Gamma	████	████	████
Generalised gamma	769.47	778.60	1548.07

Lowest (i.e. best fitting) AIC and BIC scores for each distribution are in **bold** text.

Abbreviations: AIC: Akaike's Information Criterion; BIC: Bayesian Information Criterion; DCO: data cut-off; PFS: progression-free survival.

The median PFS for each distribution and the PFS estimates for each distribution at 1, 3 and 5-years for chemotherapy are presented in Table 48.

Table 48: Summary of median PFS and 1, 3 and 5-year PFS estimates for chemotherapy extrapolations

Parametric curve	Median PFS (months)	1-year survival (%)	3-year survival (%)	5-year survival (%)
Median and landmark survival for each extrapolation				
Exponential	5.52	22.48%	1.14%	0.06%
Weibull	6.67	15.59%	0.00%	0.00%
Lognormal	5.98	18.05%	0.79%	0.09%
Log-logistic	6.21	17.46%	1.40%	0.40%
Gompertz	6.67	18.37%	0.00%	0.00%
Gamma	████	████	████	████
Generalised gamma	6.44	15.67%	0.02%	0.00%

Abbreviations: DCO: data cut-off; TTNT: time to next treatment.

The PFS data in the model are relatively mature, given that median PFS had been reached in the PAPILLON trial. Most extrapolations had similar statistical fits plus long-term survival outcomes, with the exception of the exponential curve which predicted relatively high rates of PFS for chemotherapy. As noted above, clinical expert estimates for PFS were not elicited during the previous advisory boards. Therefore, curve selection was driven by statistical fit and, based on the sum of AIC and BIC, the gamma extrapolation had the best statistical fit, whilst also aligning closely with the observed hazard rate for chemotherapy in PAPILLON. Therefore, the base-case assumes a gamma distribution for chemotherapy PFS.

Pembrolizumab-chemotherapy

The pooled RWE data from the NECTAR study informing the clinical efficacy of pembrolizumab-chemotherapy did not provide sufficient information on PFS, given that details on the exact date

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of disease progression were not available from several of the relevant databases. Therefore, data were obtained for TTNT and OS for pembrolizumab-chemotherapy from the NECTAR study.

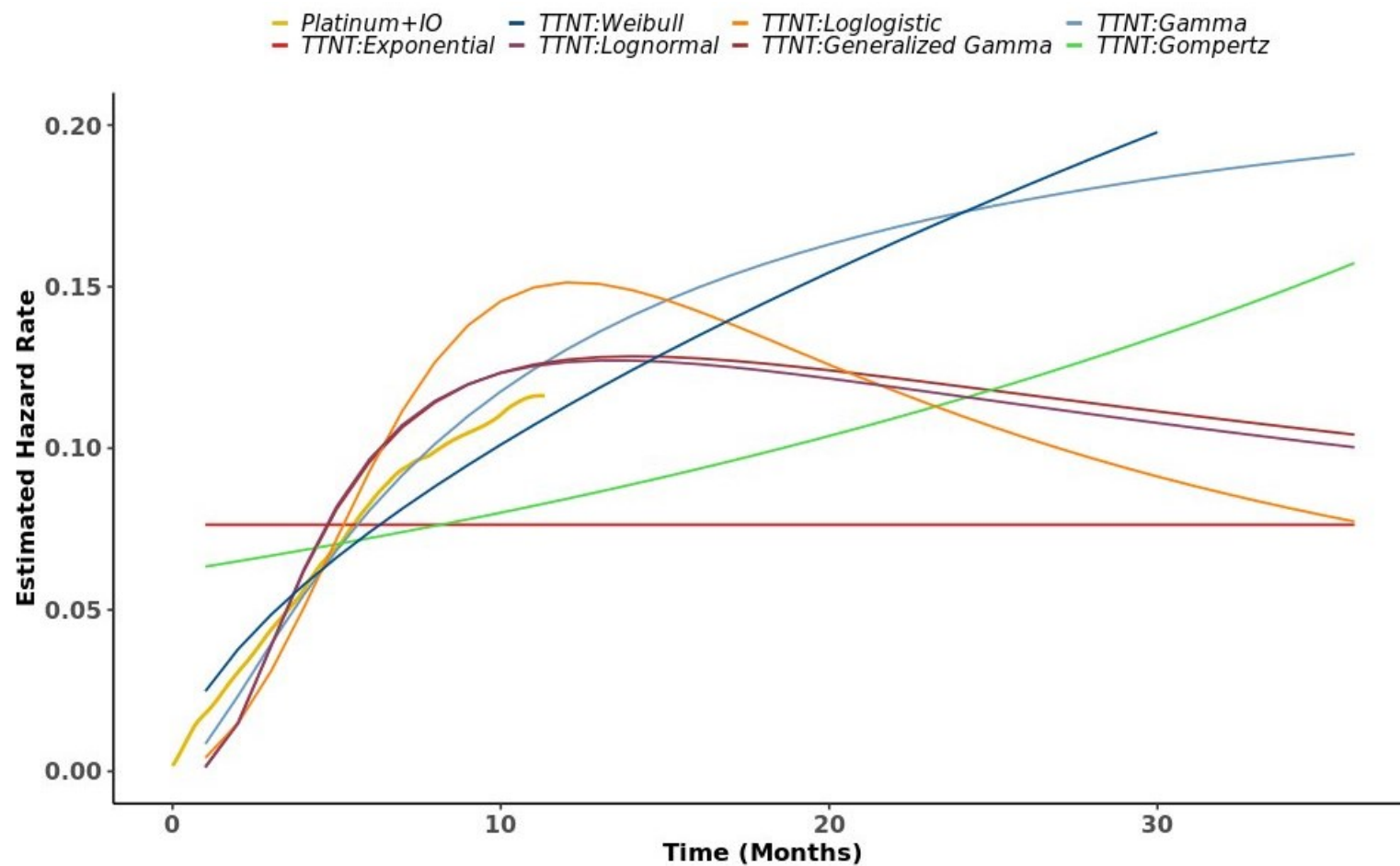
Accordingly, in order to model PFS for pembrolizumab-chemotherapy, firstly the appropriate extrapolation for the TTNT KM data for pembrolizumab-chemotherapy was selected (see below).

TTNT data for pembrolizumab-chemotherapy were ATT-weighted to have similar baseline characteristics to the amivantamab-chemotherapy treatment arm in the PAPILLON trial, as described in Section B.2.9. Subsequently, PFS for pembrolizumab-chemotherapy was estimated by applying the per cycle HR of amivantamab-chemotherapy TTNT vs BICR-assessed PFS in the PAPILLON trial to the selected extrapolation for pembrolizumab-chemotherapy TTNT.

The smoothed hazards plot for TTNT data for pembrolizumab-chemotherapy is presented in Figure 32, with the hazard function for the pembrolizumab-chemotherapy KM data aligning well with the log-logistic and gamma extrapolations.

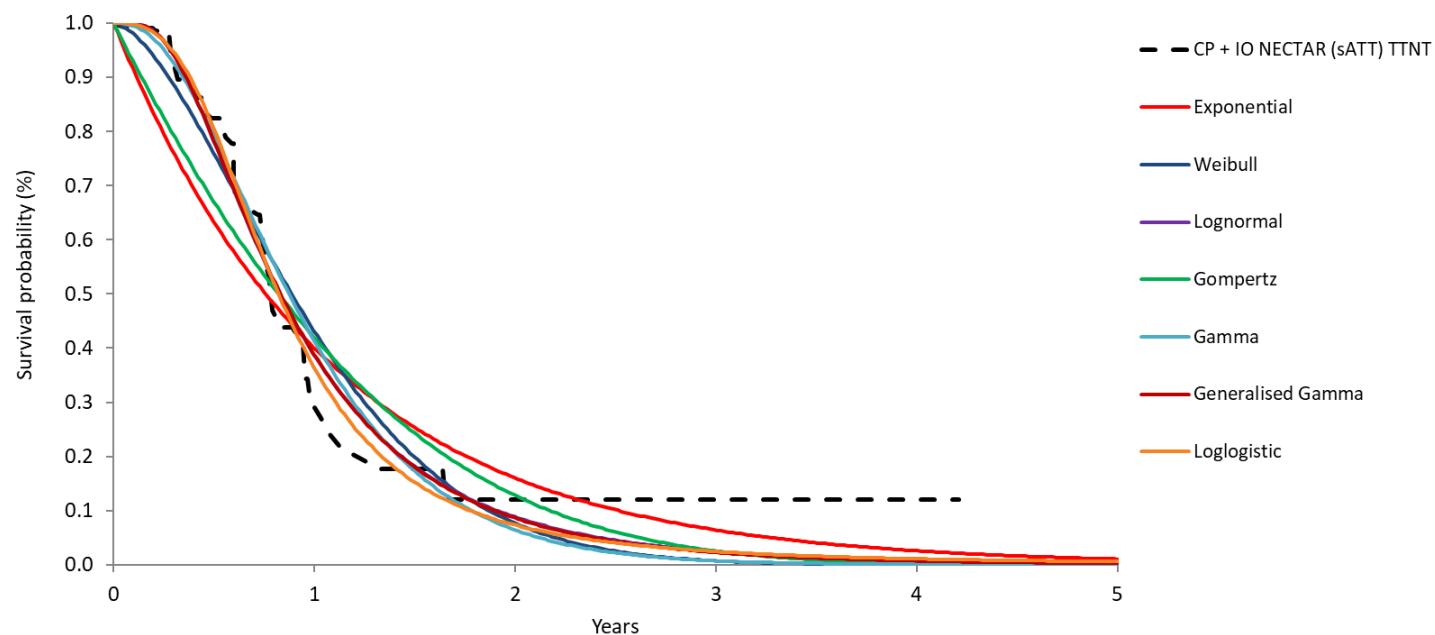
The fitted parametric models for pembrolizumab-chemotherapy TTNT data after ATT-weighting are presented in Figure 33. The AIC and BIC of each TTNT extrapolation, as well as the median PFS and landmark rates of PFS estimates at 1, 3 and 5 years are presented in Table 49 and Table 50, respectively.

Figure 32: Smoothed hazard plot with parametric extrapolations for pembrolizumab-chemotherapy TTNT



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Figure 33: TTNT extrapolations for pembrolizumab-chemotherapy (ATT-weighted)



Note: Due to small patient numbers, the ITC pooled data from individual chemotherapy-IO regimens to conduct a comparison to 'platinum chemotherapy-IO treatment class'. This is assumed to be representative of pembrolizumab-chemotherapy.

Abbreviations: ATT: average treatment effect on the treated; CP: platinum-based chemotherapy; IO: immuno-oncology; KM: Kaplan Meier; TTNT: time to next treatment

Table 49: AIC and BIC values for pembrolizumab with chemotherapy TTNT (ATT-weighted) extrapolations

Distributions	AIC	BIC	Sum of AIC and BIC
Exponential	329.89	331.88	661.77
Weibull	317.2	321.18	638.38
Lognormal	307.28	311.26	618.54
Log-logistic	■	■	■
Gompertz	329.63	333.61	663.24
Gamma	311.03	315.01	626.04
Generalised gamma	309.26	315.23	624.49

Lowest (i.e. best fitting) AIC and BIC scores for each distribution are in **bold** text.

Abbreviations: AIC: Akaike's Information Criterion; ATT: average treatment effect on the treated; BIC: Bayesian Information Criterion; TTNT: time to next treatment.

Table 50: Summary of median TTNT and 1, 3 and 5-year TTNT estimates for pembrolizumab-chemotherapy extrapolations (after ATT-weighting)

Parametric curve	Median TTNT (months)	1-year survival (%)	3-year survival (%)	5-year survival (%)
Median and landmark survival for each extrapolation				
Exponential	8.97	40.14%	6.47%	1.04%
Weibull	10.58	43.29%	0.73%	0.00%
Lognormal	9.89	38.89%	2.44%	0.29%
Log-logistic	■	■	■	■
Gompertz	9.66	42.07%	2.58%	0.01%
Gamma	10.35	41.50%	0.73%	0.01%
Generalised gamma	9.89	38.98%	2.29%	0.25%

Abbreviations: ATT: average treatment effect on the treated; PFS: progression-free survival

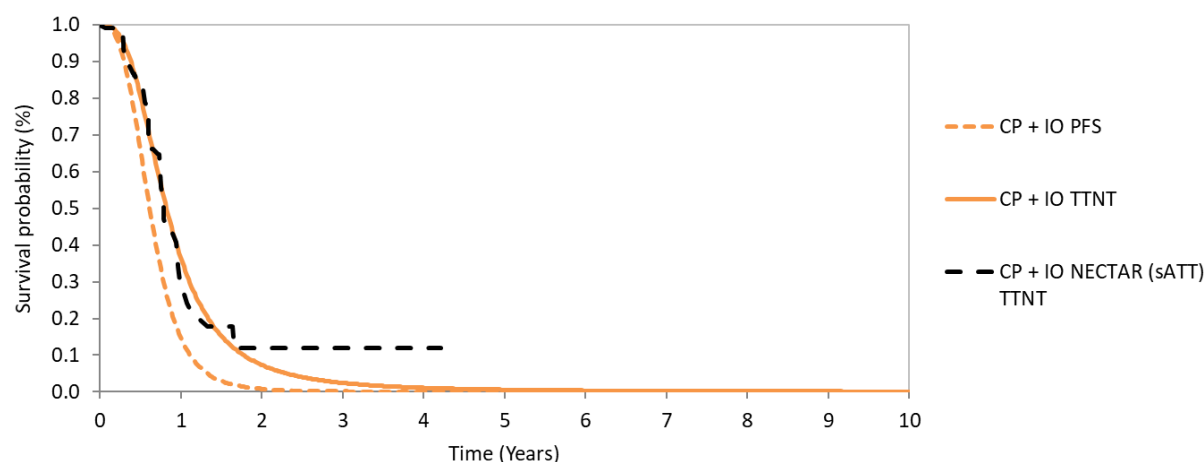
The TTNT data from the NECTAR study are relatively mature, given that median TTNT had been reached in this dataset. Furthermore, most extrapolations had similar statistical fits and long-term survival outcomes. Therefore, curve selection was driven by statistical fit and assessment of hazard functions. Based on the sum of the AIC and BIC values, the log-logistic extrapolation had the best statistical fit. Therefore, the log-logistic distribution was selected for pembrolizumab-chemotherapy TTNT in the base-case.

As previously noted, UK clinical experts confirmed at the 1st August 2024 advisory board that TTNT is not a valid proxy for PFS.²² As such, application of the per cycle HR for amivantamab-chemotherapy TTNT versus BICR-assessed PFS from the PAPILLON trial to the TTNT log-logistic extrapolation provided a more accurate estimation of PFS for pembrolizumab-chemotherapy.

The resulting PFS curve for pembrolizumab-chemotherapy is provided in Figure 34. This illustrates the down-adjustment between the derived PFS extrapolation curve and the KM curve for TTNT, derived from pooled RWE from the NECTAR study. An alternative approach whereby TTNT is assumed to equal PFS for all comparators has been explored in a scenario analysis.

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Figure 34: Base case pembrolizumab- chemotherapy PFS extrapolation (after applying per cycle HR of TTNT vs PFS of amivantamab-chemotherapy to log-logistic TTNT extrapolation)



Note: The PFS curve has been derived by applying the per cycle HR of amivantamab-chemotherapy TTNT versus BICR-assessed PFS from the PAPILLON trial to the log-logistic TTNT extrapolation

Abbreviations: ATT: average effect of the treated; CP: carboplatin with pemetrexed; IO: immune-oncology; KM: Kaplan-Meier; TTNT: time to next treatment.

B.3.3.2.4 Overall survival

OS is defined as the time from the date of randomisation until the date of death due to any cause. For amivantamab-chemotherapy and chemotherapy, the long-term OS extrapolations in the base case were informed by OS data at the 31st October 2023 DCO of the PAPILLON trial.

For pembrolizumab-chemotherapy, long-term OS extrapolations in the base case were informed by the NECTAR RWE study. OS efficacy data for pembrolizumab-chemotherapy were ATT-weighted to have similar baseline characteristics to patients in the amivantamab-chemotherapy treatment arm of the PAPILLON trial, as described in Section B.2.9.

Seven standard parametric distributions (exponential, Weibull, log-logistic, log-normal, Gompertz, gamma, and generalised gamma) were explored for modelling OS for all treatment arms.

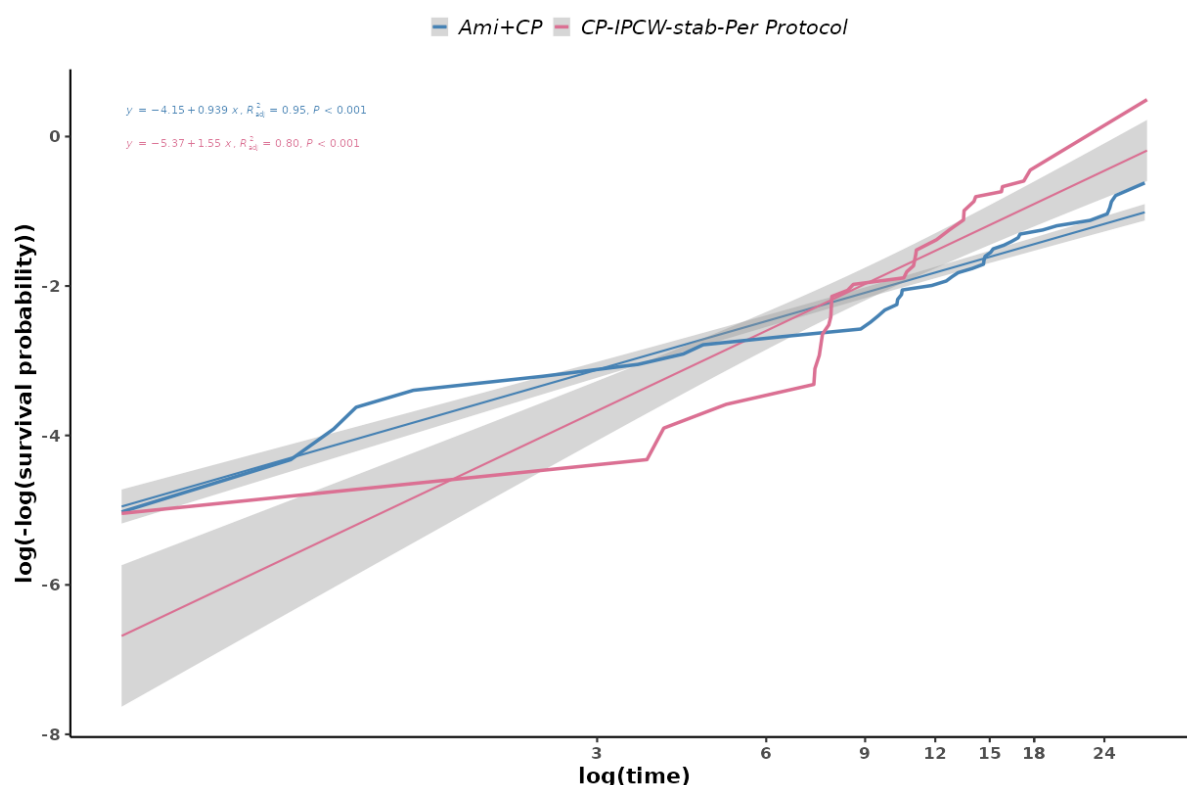
Amivantamab-chemotherapy

The OS KM curve for amivantamab-chemotherapy was generated based on data from the PAPILLON trial at the 31st October 2023 DCO.

An assessment of proportional hazards and an assessment of the amivantamab-chemotherapy hazard function versus the seven parametric distributions was conducted. Based on these analyses, there is evidence of non-proportionality between the amivantamab-chemotherapy and chemotherapy arms (with the chemotherapy arm having undergone IPCW adjustment), as informed by the log-log plot (Figure 35), and as such independent fitting of treatment arms from PAPILLON was deemed the optimal approach.

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Figure 35. Log-log plot for amivantamab-chemotherapy and chemotherapy (following IPCW adjustment)

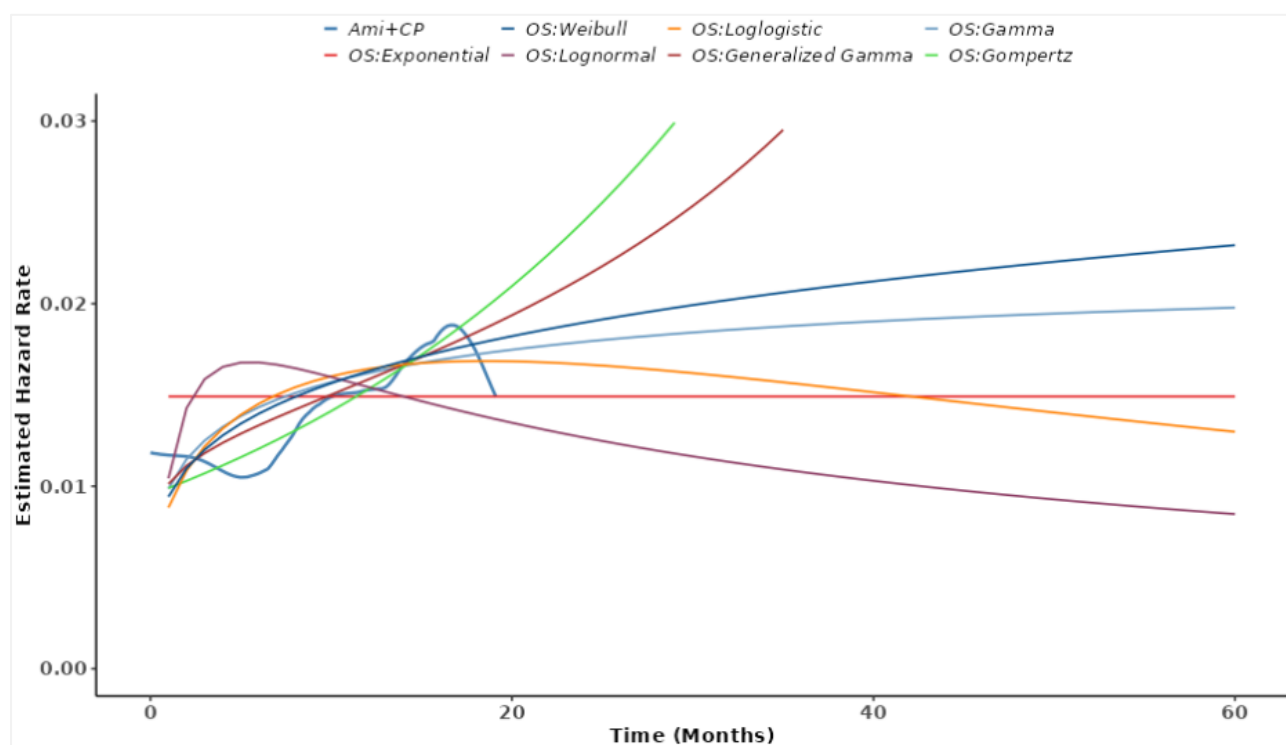


Note: The CP arm informing this plot had undergone IPCW adjustment

Abbreviations: ACP: amivantamab + carboplatin + pemetrexed; CP: carboplatin + pemetrexed; OS: overall survival.

When considering the hazard plots for all distributions explored, the Gompertz extrapolation shows a rapidly increasing hazard function over time, and the hazard plot for the exponential extrapolation also shows a constant hazard function over time, neither of which reflect the KM data, which indicates a slightly increasing hazard over time, as illustrated in Figure 36. As such, both functions may be expected to underestimate (Gompertz) or overestimate (exponential) the true value for OS for amivantamab-chemotherapy over time.

Figure 36: Comparison of the KM OS data for amivantamab-chemotherapy with the hazard functions for each extrapolation curve

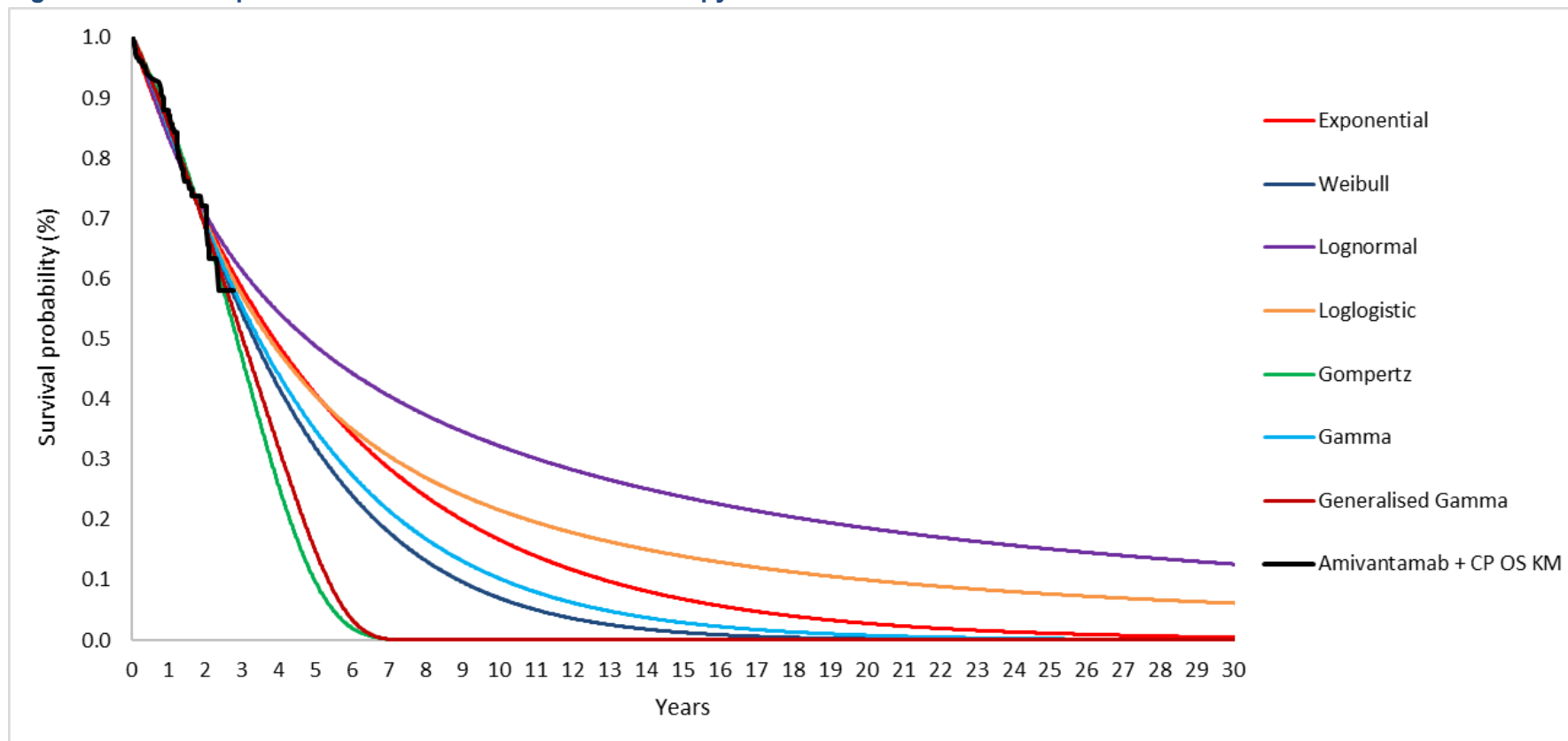


The KM data for amivantamab-chemotherapy have been cut-off when the number of patients at risk of death dropped below 10.

Abbreviations: OS: overall survival.

The OS KM curve and independently fitted extrapolations for amivantamab-chemotherapy are presented in Figure 37. A summary of all the AIC and BIC values for the extrapolations is further presented in Table 51.

Figure 37: OS extrapolations for amivantamab-chemotherapy



Abbreviations: CP: carboplatin and pemetrexed (chemotherapy); DCO; data cut-off; OS: overall survival.

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Table 51: AIC and BIC values for amivantamab-chemotherapy OS extrapolations

Distributions	AIC	BIC	Sum of AIC and BIC
Exponential	418.43	421.46	839.89
Weibull	████	████	████
Lognormal	424.07	430.13	854.20
Log-logistic	419.92	425.98	845.90
Gompertz	417.11	423.17	840.28
Gamma	419.05	425.11	844.16
Generalised gamma	419.77	428.86	848.63

Lowest (i.e. best fitting) AIC and BIC scores for each distribution are in **bold** text.

Abbreviations: AIC: Akaike's Information Criterion; BIC: Bayesian Information Criterion; DCO: data cut-off; OS: overall survival.

The median OS for each distribution and the OS estimates for each distribution at 3, 5 and 10-years for amivantamab-chemotherapy are presented in Table 52.

Table 52: Summary of median OS and 3, 5 and 10-year OS estimates for amivantamab-chemotherapy extrapolations

Parametric curve	Median OS (months)	3-year survival (%)	5-year survival (%)	10-year survival (%)
Median and landmark survival for each extrapolation				
Exponential	46.46	58.56%	40.99%	16.74%
Weibull	████	████	████	████
Lognormal	57.26	61.46%	48.93%	32.29%
Log-logistic	44.85	57.36%	40.76%	21.65%
Gompertz	34.27	47.11%	9.87%	0.00%
Gamma	41.40	55.54%	34.97%	10.30%
Generalised gamma	36.11	50.59%	15.07%	0.00%

^a No range given as both advisors gave the same value.

Abbreviations: NR: not reported; OS: overall survival.

When fitting the seven parametric distributions to the observed KM OS data for amivantamab-chemotherapy, the exponential and Gompertz extrapolations had the best statistical fit according to AIC and BIC values. However, visual inspection of the curves show that these distributions do not fit the KM OS data for amivantamab-chemotherapy well as they represent a highly optimistic estimate (exponential) and the most pessimistic (Gompertz) predictions of OS.

After discounting the exponential and Gompertz extrapolations due to poor alignment of the hazard functions with the amivantamab-chemotherapy OS data, the Weibull and gamma extrapolations had the next best statistical fits. Clinical expert opinion from the August 2024 advisory board validated that the Weibull, as well as the gamma, extrapolations were the most clinically plausible for amivantamab-chemotherapy OS. During the August 2024 advisory board, UK clinical experts aligned on a consensus that around 27.5% of patients receiving amivantamab-chemotherapy were expected to be alive after 5-years and 7.5% were expected to be alive after 10-years, which is closely aligned with the proportions of patients alive at those

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landmarks in the Weibull extrapolation (32% and 7% respectively).²² Additionally, the Weibull and gamma extrapolations both include a tail, representing a small proportion of patients remaining alive beyond 10 years. UK clinical experts have highlighted that this is plausible for amivantamab considering the immune-modulating mechanism of action and strong level of response that has been demonstrated by patients receiving amivantamab monotherapy in the second-line setting and beyond.^{5, 22} The tail associated with the survival extrapolation of amivantamab-chemotherapy reflects the long-term survival benefit observed for amivantamab monotherapy in the CHRYSALIS trial where, after a median follow-up of 19.2 months, the median OS of patients receiving amivantamab monotherapy in the second line setting after progressing on chemotherapy was 23 months (95% CI, 18.5–29.5).⁴³

Therefore, the base case assumed a Weibull distribution for amivantamab-chemotherapy OS. The more optimistic gamma distribution was considered as a scenario.

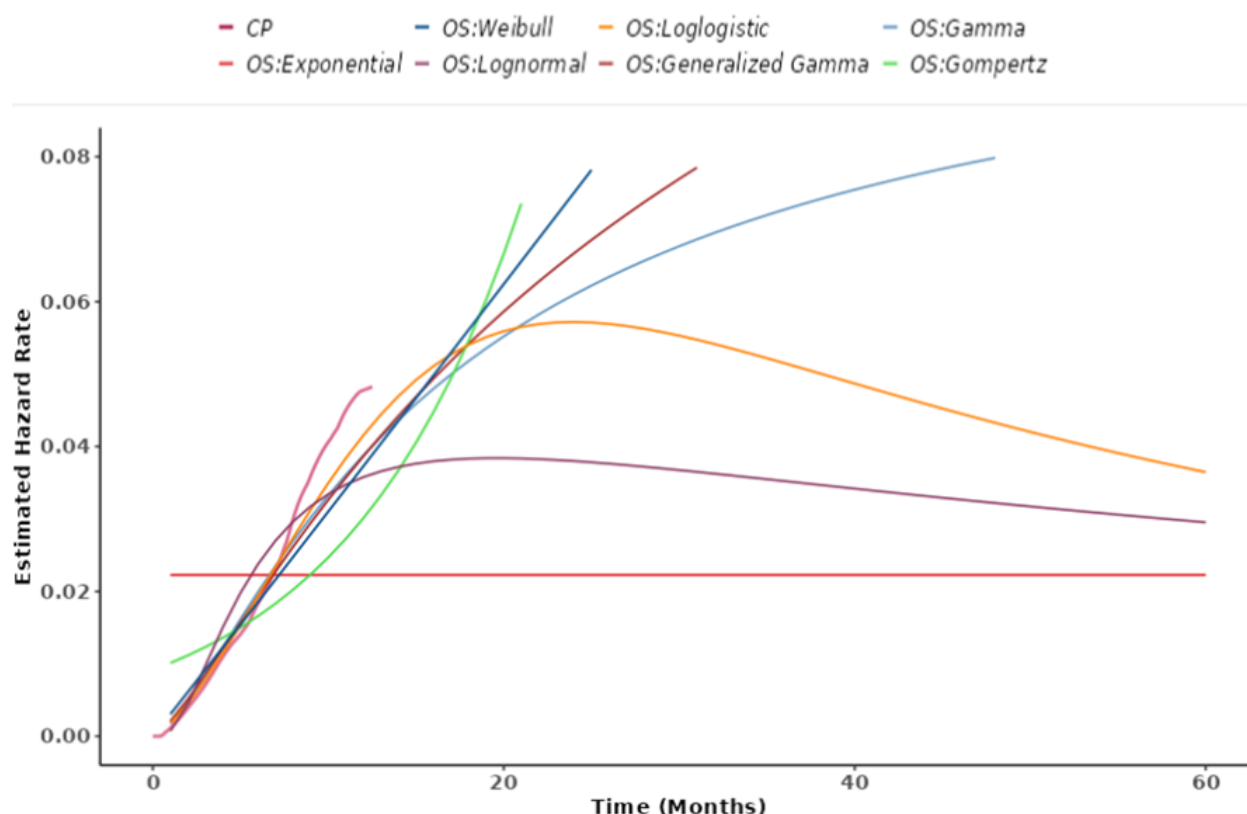
Chemotherapy

The OS KM curve for chemotherapy was generated based on data from the chemotherapy arm of the PAPILLON trial at the 31st October 2023 DCO. As detailed in Section B.3.3.2.1, at this DCO, 78 (50.3%) patients in the chemotherapy arm had undergone treatment switching to receive amivantamab monotherapy at the dose specified in the PAPILLON trial following BICR-confirmed disease progression. As such, the OS KM data for chemotherapy was adjusted for treatment switching using the IPCW method in the base-case (Section B.3.3.2.1). As described above, extrapolations were fitted independently to the treatment arms from PAPILLON for OS.

To fit parametric distributions, the patient-level data needed to be simulated using the algorithm developed by Guyot et al. in 2012.¹¹⁹ The obtained simulated patient-level data of the IPCW was then used for fitting the parametric distributions.

The hazard plot for chemotherapy OS data (adjusted for treatment switching using IPCW) and all explored extrapolations is presented in Figure 38. The log-logistic extrapolation showed a decreasing hazard function after ~20 months which did not reflect the KM OS data for chemotherapy. The KM OS data shows a continuing upward trend in hazard, which is anticipated to increase over time due to the poor prognosis associated with this patient population. Therefore, the lognormal (decreasing hazard function) and exponential (approximately constant) extrapolations may also be discounted due to poor alignment of hazard function with the chemotherapy OS KM data.

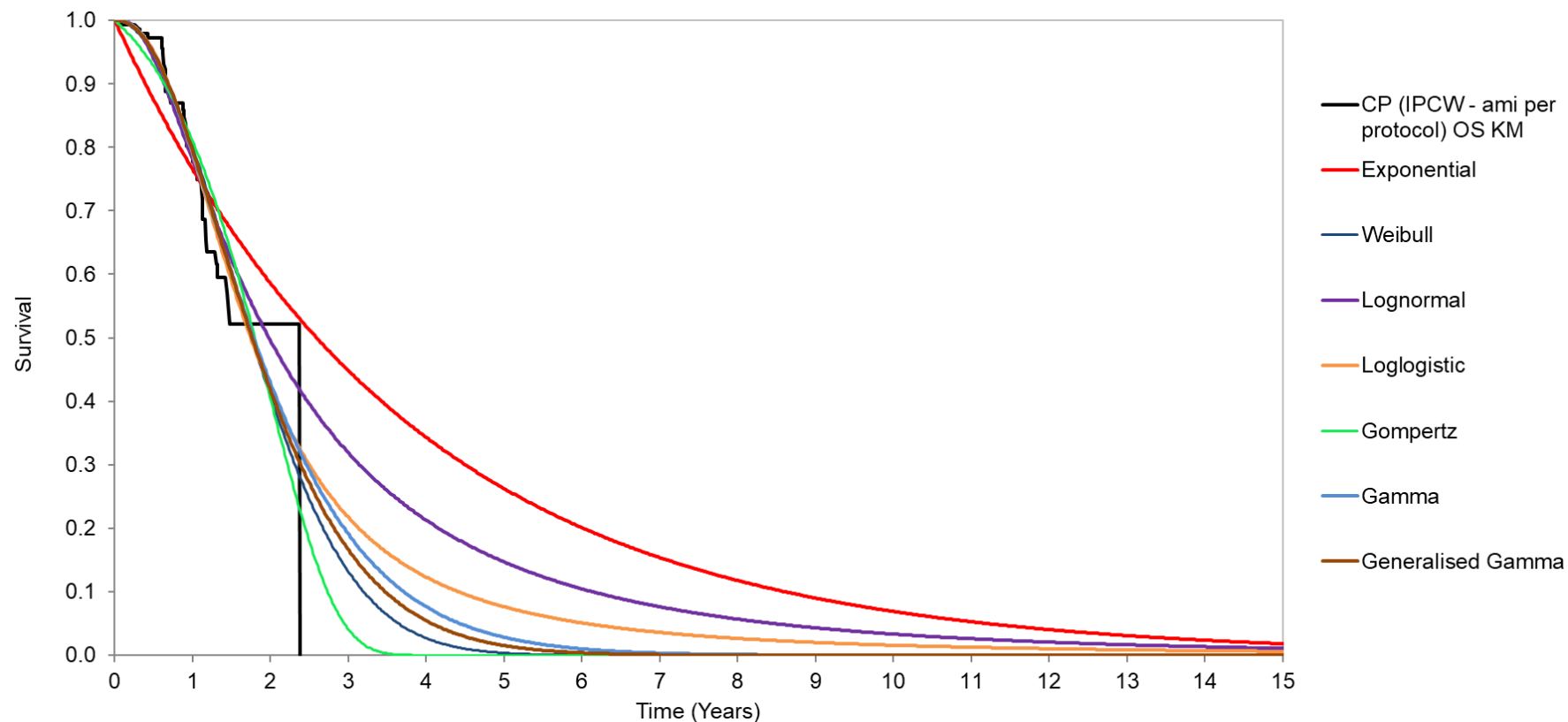
Figure 38: Comparison of the KM OS data for chemotherapy (IPCW adjusted) with the hazard functions for each extrapolation curve



The KM data for chemotherapy have been cut-off when the number of patients at risk of death dropped below 10
Abbreviations: CP: chemotherapy; KM: Kaplan-Meier; OS: overall survival.

The OS KM curve and extrapolations for chemotherapy OS (adjusted for treatment switching using IPCW) are presented in Figure 39. A summary of all the AIC and BIC values for the extrapolations is further presented in Table 53.

Figure 39: OS extrapolations for chemotherapy (IPCW-adjusted)



Abbreviations: CP: carboplatin with pemetrexed; IPCW: inverse probability of censoring weighting; KM; Kaplan-Meier; OS: overall survival.

Table 53: AIC and BIC values for chemotherapy OS extrapolations (adjusted via the IPCW method)

Distributions	AIC	BIC	Sum AIC / BIC
Exponential	376.72	379.76	756.48
Weibull	356.00	362.09	718.09
Lognormal	361.6	367.69	729.29
Log-logistic	354.3	360.39	714.69
Gompertz	362.68	368.77	731.45
Gamma	████	████	████
Generalised gamma	357.53	366.66	724.19

Lowest (i.e. best fitting) AIC and BIC scores for each distribution are in **bold** text.

Abbreviations: AIC: Akaike's Information Criterion; BIC: Bayesian Information Criterion; DCO: data cut-off; OS: overall survival.

The median OS for each distribution and the OS estimates for each distribution at 3, 5 and 10-years for chemotherapy are presented in Table 54.

Table 54: Summary of median OS and 3, 5 and 10-year OS estimates for chemotherapy extrapolations (after adjustment via the IPCW method)

Parametric curve	Median OS (months)	3-year survival (%)	5-year survival (%)	10-year survival (%)
Median and landmark survival for each extrapolation				
Exponential	31.05	44.96%	26.39%	6.93%
Weibull	20.93	13.39%	0.37%	0.00%
Lognormal	23.69	32.03%	14.80%	3.35%
Log-logistic	20.93	21.87%	7.70%	1.58%
Gompertz	21.39	4.28%	0.00%	0.00%
Gamma	████	████	████	████
Generalised gamma	21.16	16.82%	1.57%	0.00%

Abbreviations: IPCW: inverse probability of censoring weighting; NR: not reported; OS: overall survival.

Based on the sum of the AIC and BIC values, the best statistical fit for chemotherapy OS was the log-logistic extrapolation, followed by the gamma and Weibull extrapolations which have comparable fits.

Clinical expert opinion from the August 2024 advisory board, informed through a discussion-based consensus, confirmed that the Weibull extrapolation was the most clinically plausible for the OS of patients receiving chemotherapy. Advisors also agreed that an extremely low proportion of patients receiving chemotherapy would be alive after five years, highlighting that the exponential, lognormal and log-logistic curves were unrealistic and overly optimistic.

The consensus that the Weibull extrapolation was most clinically plausible was based on CP OS data that had been adjusted via the TSE approach, given this was the defensible adjustment methodology at the time of the advisory board.

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The Weibull extrapolation for two-stage-adjusted CP OS data predicted survival rates of 22%, 2%, and 0% at 3-, 5-, and 10-years respectively, which were most aligned to the survival estimates for the gamma extrapolation of IPCW-adjusted CP OS data.

Therefore, based on the statistical fit, validation with clinical experts and assessment of the hazard plots, the base case assumed a gamma distribution for chemotherapy OS. This approach is conservative, given that the Weibull distribution predicts poorer outcomes for patients receiving chemotherapy. The more pessimistic Weibull distribution was considered as a scenario.

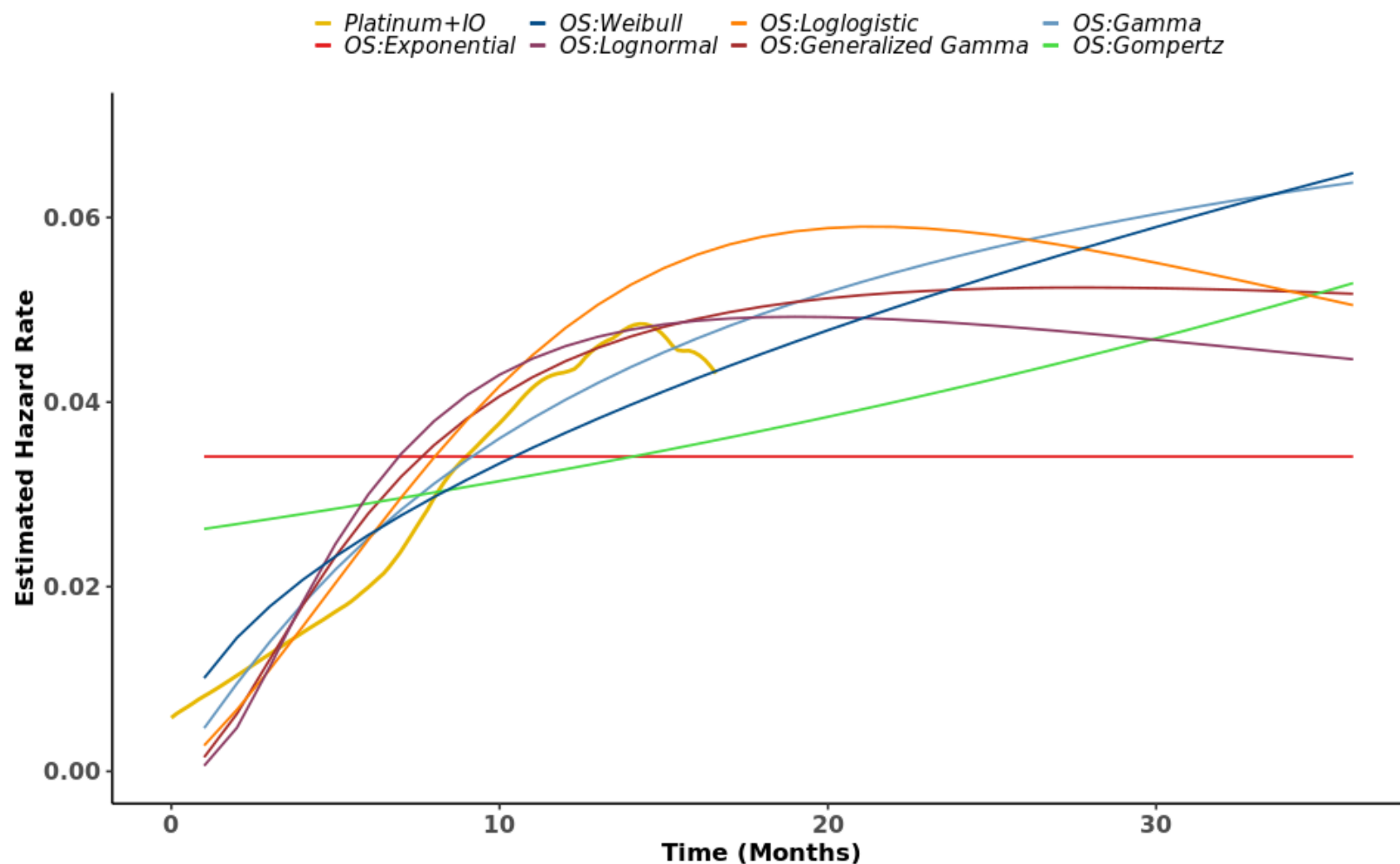
Pembrolizumab-chemotherapy

The OS KM curve for pembrolizumab-chemotherapy was generated based on pooled efficacy data from the RWE NECTAR study. Seven parametric distributions were fitted to the OS data from the NECTAR RWE study for pembrolizumab-chemotherapy. The data were ATT-weighted to have similar baseline characteristics to the amivantamab-chemotherapy treatment arm in the PAPILLON trial.

A comparison of the pembrolizumab-chemotherapy KM OS data and the hazard functions for each parametric distribution is provided in Figure 40. The pembrolizumab-chemotherapy KM OS data features a decreasing hazard rate following ~15 months, aligning well with the hazard functions of the log-logistic and lognormal distributions.

The ATT-weighted OS KM curve extrapolations for pembrolizumab-chemotherapy are presented in Figure 41, with a summary of AIC and BIC values for all extrapolations further presented in Table 55.

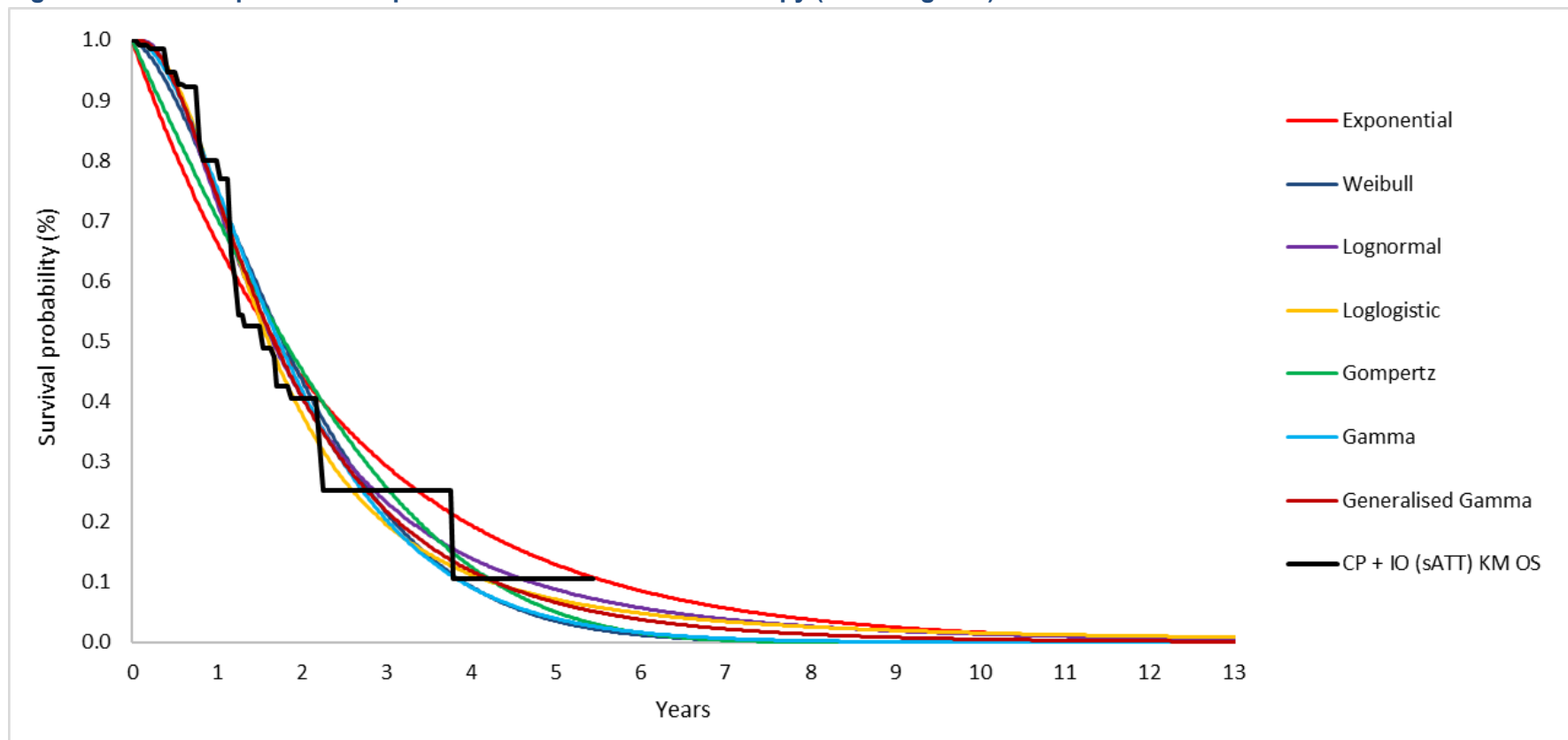
Figure 40: Comparison of the KM OS data for pembrolizumab-chemotherapy with the hazard functions for each extrapolation curve



Abbreviations: IO: immune-oncology; KM: Kaplan-Meier; OS: overall survival.

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Figure 41: OS extrapolations for pembrolizumab with chemotherapy (ATT-weighted)



Abbreviations: ATT: average treatment effect on the treated; IO: immuno-oncology; OS: overall survival.

Table 55: AIC and BIC values for pembrolizumab-chemotherapy OS extrapolations

Distributions	AIC	BIC	Sum AIC / BIC
Exponential	304.15	306.15	610.30
Weibull	297.83	301.85	599.68
Lognormal	294.70	298.71	593.41
Log-logistic	■	■	■
Gamma	295.54	299.56	595.10
Gompertz	303.91	307.93	611.84
Generalised gamma	296.19	302.31	598.50

Lowest (i.e. best fitting) AIC and BIC scores for each distribution are in **bold** text.

Abbreviations: AIC: Akaike's Information Criterion; BIC: Bayesian Information Criterion; OS: overall survival.

The median OS for each distribution and the OS estimates for each distribution at 3, 5 and 10 years for pembrolizumab-chemotherapy are presented in Table 56.

Table 56: Summary of median OS and 3, 5 and 10-year OS estimates for pembrolizumab-chemotherapy extrapolations (after ATT-weighting)

Parametric curve	Median OS (months)	3-year survival (%)	5-year survival (%)	10-year survival (%)
Median and landmark survival for each extrapolation				
Exponential	20.24	29.42%	13.01%	1.68%
Weibull	21.16	21.69%	3.61%	0.01%
Lognormal	19.78	23.43%	8.85%	1.39%
Log-logistic	■	■	■	■
Gamma	20.70	20.51%	4.01%	0.04%
Gompertz	21.39	21.95%	5.13%	0.00%
Generalised gamma	20.01	25.91%	6.69%	0.52%

Abbreviations: ATT: average treatment effect of the treated; NR: not reported; OS: overall survival.

OS data for pembrolizumab-chemotherapy are relatively mature. All extrapolations explored had similar statistical fits and long-term estimated survival outcomes. Therefore, curve selection was driven by statistical fit and, based on the sum of the AIC and BIC values, the log-logistic extrapolation was selected in the base-case. The log-logistic extrapolation represents one of the more optimistic distributions when considering long-term survival at 5 and 10 years.²² As such, the log-logistic extrapolation provides a conservative estimate of the comparative OS efficacy of pembrolizumab-chemotherapy versus amivantamab-chemotherapy.

B.3.3.2.5 Time to treatment discontinuation or death

TTDD is defined as the time from randomisation to discontinuation of all study treatments for any reason, including death. Importantly, Section B.2.6.2.6 of the submission presents TTD efficacy data for patients in the PAPILLON trial, which considers discontinuation events in the trial. TTDD, which is utilised in the economic model, considers TTD events in addition to death events occurring prior to treatment discontinuation.

Amivantamab-chemotherapy

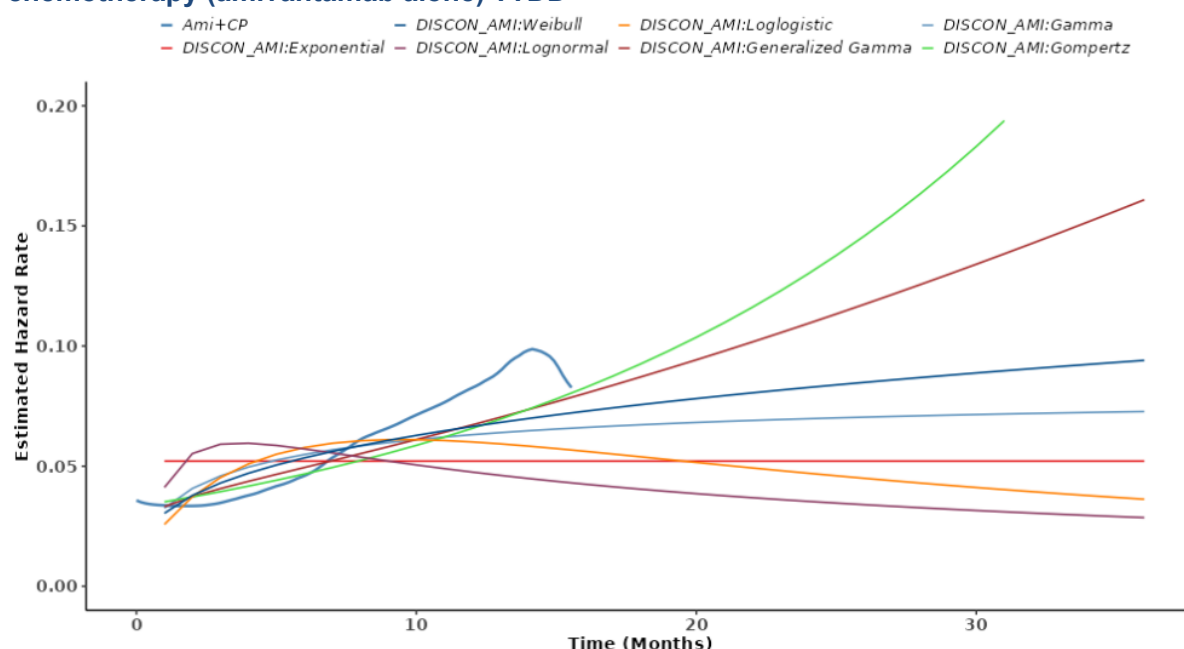
Company evidence submission template for amivantamab with carboplatin and pemetrexed for untreated EGFR Exon 20 insertion mutation-positive advanced non-small cell lung cancer [ID5110]

The TTDD KM curve for amivantamab-chemotherapy was generated by incorporating death events prior to discontinuation into TTD data from the PAPILLON trial (3rd May 2023 DCO). In the base case, separate TTDD curves were derived for both amivantamab and chemotherapy within the amivantamab-chemotherapy arm. This enabled a specific modelling approach to accurately capture the actual use of both amivantamab and chemotherapy within the combination treatment arm, aligning with observed outcomes in the trial. In the May 2024 advisory board, clinical experts validated this approach as appropriate, given amivantamab and chemotherapy would be expected to have different treatment durations in clinical practice.⁵

The smoothed hazard plots for amivantamab and chemotherapy within the amivantamab-chemotherapy treatment arm are presented in Figure 42 and Figure 43. Based on visual inspection, none of the hazard functions for the extrapolations align well with the individual amivantamab and chemotherapy KM data, which show decreasing hazard rates after ~15 months. As such, curve selection was driven by statistical fit and considerations of clinical plausibility.

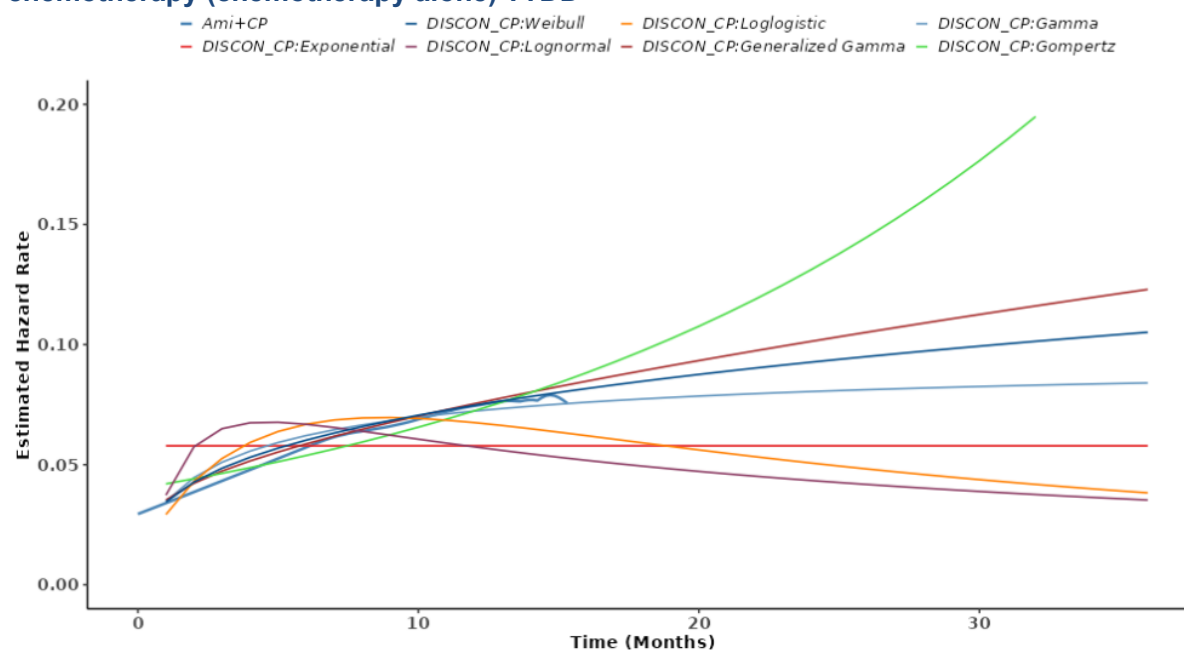
Seven parametric distributions were fitted to the trial data. The TTDD extrapolations for amivantamab and chemotherapy within the amivantamab-chemotherapy treatment arm are presented in Figure 44 and Figure 45, respectively. with a summary of corresponding AIC and BIC values for the TTDD extrapolations presented in Table 57 and Table 58, respectively.

Figure 42. Smoothed hazard plot with parametric extrapolations for amivantamab-chemotherapy (amivantamab alone) TTDD



Abbreviations: ACP: amivantamab-chemotherapy; TTDD: time to treatment discontinuation or death.

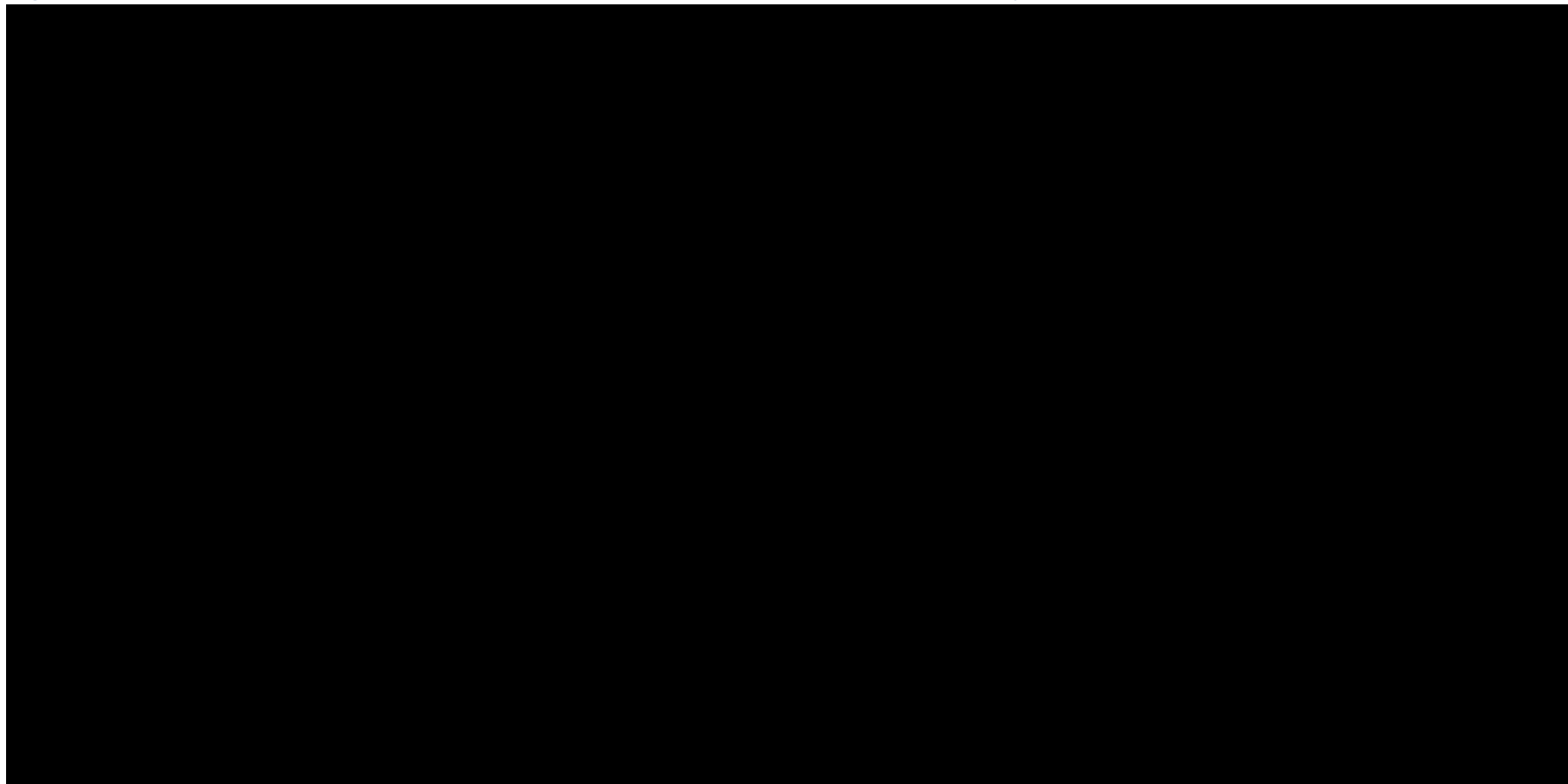
Figure 43. Smoothed hazard plot with parametric extrapolations for amivantamab-chemotherapy (chemotherapy alone) TTDD



Abbreviations: ACP: amivantamab-chemotherapy; TTDD: time to treatment discontinuation or death

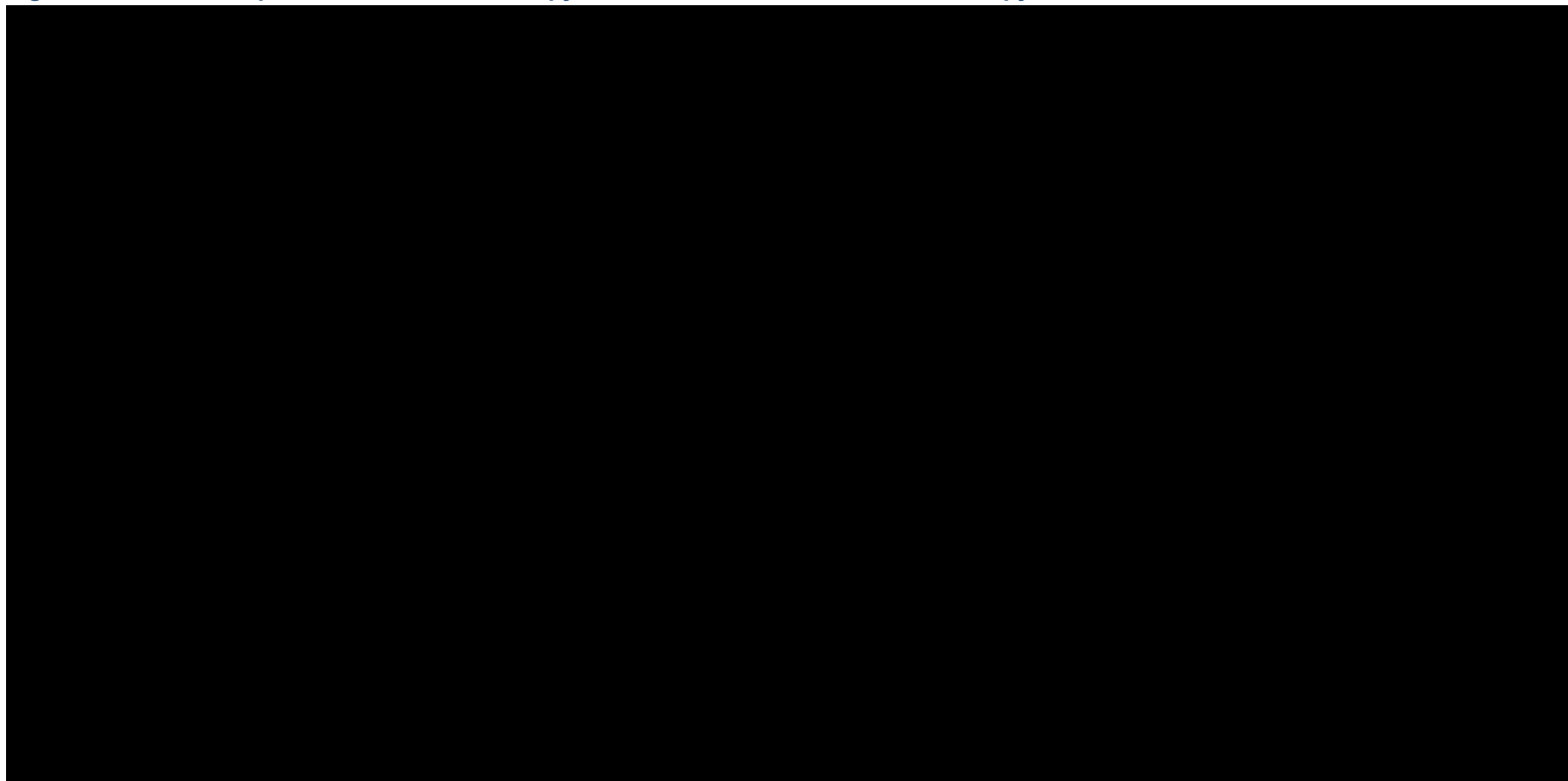
Company evidence submission template for amivantamab with carboplatin and pemetrexed for untreated EGFR Exon 20 insertion mutation-positive advanced non-small cell lung cancer [ID5110]

Figure 44: TTDD extrapolations for amivantamab within the amivantamab-chemotherapy treatment arm



Abbreviations: DCO: data cut-off; KM: Kaplan-Meier; TTDD: time to treatment discontinuation or death.

Figure 45: TTDD extrapolations for chemotherapy within the amivantamab-chemotherapy treatment arm



Abbreviations: DCO: data cut-off; KM: Kaplan-Meier; TTDD: time to treatment discontinuation or death.

Table 57: AIC and BIC values for TTDD extrapolations for amivantamab within the amivantamab-chemotherapy treatment arm

Distributions	AIC	BIC	Sum AIC / BIC
Exponential	682.10	685.13	1367.23
Weibull	████	████	████
Lognormal	698.74	704.80	1403.54
Log-logistic	683.04	689.10	1372.14
Gompertz	674.90	680.97	1355.87
Gamma	678.14	684.20	1362.34
Generalised gamma	676.67	685.76	1362.43

Lowest (i.e. best fitting) AIC and BIC scores for each distribution are in **bold** text.

Abbreviations: AIC: Akaike's Information Criterion; BIC: Bayesian Information Criterion; DCO: data cut-off; TTDD: time to treatment discontinuation or death.

Table 58: AIC and BIC values for TTDD extrapolations for chemotherapy within the amivantamab-chemotherapy treatment arm

Distributions	AIC	BIC	Sum AIC / BIC
Exponential	694.90	697.93	1392.83
Weibull	████	████	████
Lognormal	700.00	706.06	1406.06
Log-logistic	692.52	698.58	1391.10
Gompertz	690.21	696.28	1386.49
Gamma	689.38	695.44	1384.82
Generalised gamma	690.69	699.78	1390.47

Lowest (i.e. best fitting) AIC and BIC scores for each distribution are in **bold** text.

Abbreviations: AIC: Akaike's Information Criterion; BIC: Bayesian Information Criterion; DCO: data cut-off; TTDD: time to treatment discontinuation or death.

The median TTDD of each distribution and the TTDD estimates for each distribution at 1, 3 and 5-years for amivantamab alone and chemotherapy alone for amivantamab-chemotherapy are presented in Table 59 and Table 60, respectively. Clinician expert estimates for TTDD in the August 2024 advisory board, considering the patient population enrolled in the PAPILLON trial, are also presented for these parameters.²²

Table 59: Summary of median TTDD and 1, 3 and 5-year TTDD estimates for amivantamab (component of amivantamab-chemotherapy) extrapolations

Parametric curve	Median TTDD (months)	1-year TTDD (%)	3-year TTDD (%)	5-year TTDD (%)
Median and landmark survival for each extrapolation				
Exponential	████	████	████	████
Weibull	████	████	████	████
Lognormal	████	████	████	████
Log-logistic	████	████	████	████
Gompertz	████	████	████	████
Gamma	████	████	████	████

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Parametric curve	Median TTDD (months)	1-year TTDD (%)	3-year TTDD (%)	5-year TTDD (%)
Generalised gamma	■	■	■	■

Abbreviations: DCO: data cut-off; TTDD: time to treatment discontinuation or death.

Table 60: Summary of median TTDD and 1, 3 and 5-year TTDD estimates for chemotherapy (component of amivantamab-chemotherapy) extrapolations

Parametric curve	Median TTDD (months)	1-year TTDD (%)	3-year TTDD (%)	5-year TTDD (%)
Median and landmark survival for each extrapolation				
Exponential	■	■	■	■
Weibull	■	■	■	■
Lognormal	■	■	■	■
Log-logistic	■	■	■	■
Gompertz	■	■	■	■
Gamma	■	■	■	■
Generalised gamma	■	■	■	■

Abbreviations: DCO: data cut-off; TTDD: time to treatment discontinuation or death.

Based on the sum of the AIC and BIC values, the best statistical fit for the TTDD of amivantamab within the amivantamab-chemotherapy arm was the Gompertz extrapolation, closely followed by the Weibull extrapolation. Upon visual inspection, the Weibull extrapolation had a better fit to the observed KM TTDD data. Results from a pre-survey conducted for the August 2024 advisory board showed that clinical expert estimates for TTDD at 3 and 5 years varied quite broadly due to difficulties in advisors interpreting the data and therefore held limited relevance and value. Because of the broad ranges elicited in the pre-survey, these ranges were discussed during the advisory board and the clinical experts agreed that the Weibull or gamma extrapolations were the most clinically plausible extrapolations, based on the low proportions of patients remaining on treatment at the 5-year timepoint. The UK clinical experts agreed that the Gompertz and generalised gamma extrapolations were overly pessimistic.²² Therefore, the base-case assumed a Weibull distribution for the TTDD of amivantamab within the amivantamab-chemotherapy arm. This is a conservative choice, since selection of the Weibull will accumulate greater acquisitions costs over the model time horizon compared to the best fitting Gompertz extrapolation.

Based on the sum of the AIC and BIC values, the best statistical fit for the TTDD of chemotherapy within the amivantamab-chemotherapy arm was the Weibull extrapolation. Additionally, UK clinical expert opinion from the August 2024 advisory board validated that the Weibull or gamma extrapolations were the most clinically plausible. Therefore, the base case assumed a Weibull distribution for the TTDD of chemotherapy within the amivantamab-chemotherapy arm.

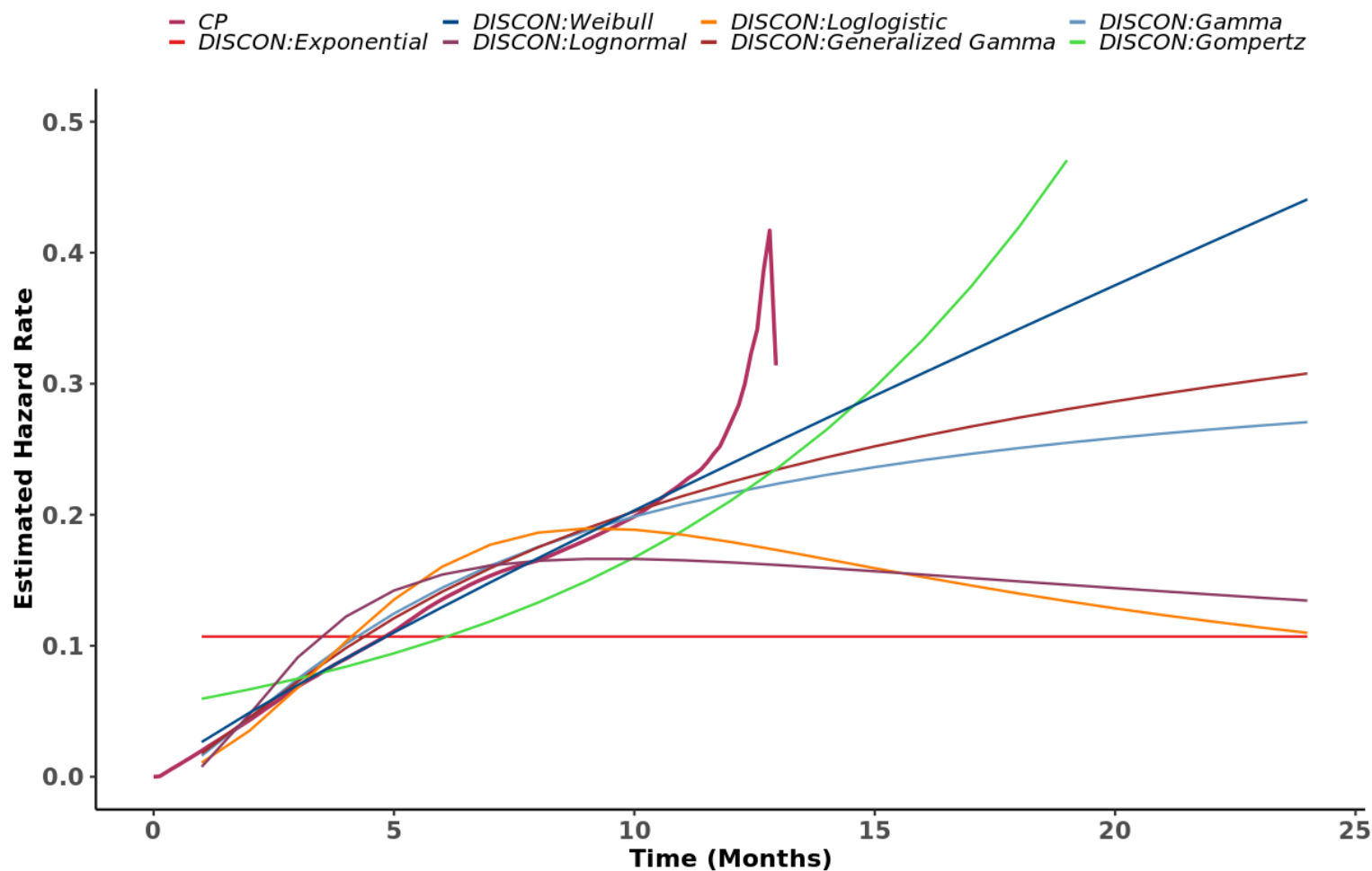
Chemotherapy

The TTDD KM curve for the chemotherapy treatment arm was generated based on data from the control arm of the PAPILLON trial at the 3rd May 2023 DCO. Seven parametric distributions were fitted to the TTDD data.

The smoothed hazard plot for chemotherapy TTDD and all the parametric distributions is provided in Figure 46. The smoothed hazard plots for chemotherapy TTDD align well with the gamma, Weibull, and Generalised gamma hazard functions up to around the 12-month landmark.

All extrapolations applied to the chemotherapy TTDD data are presented in Figure 47. A summary of all the AIC and BIC values for the extrapolations is further presented in Table 61.

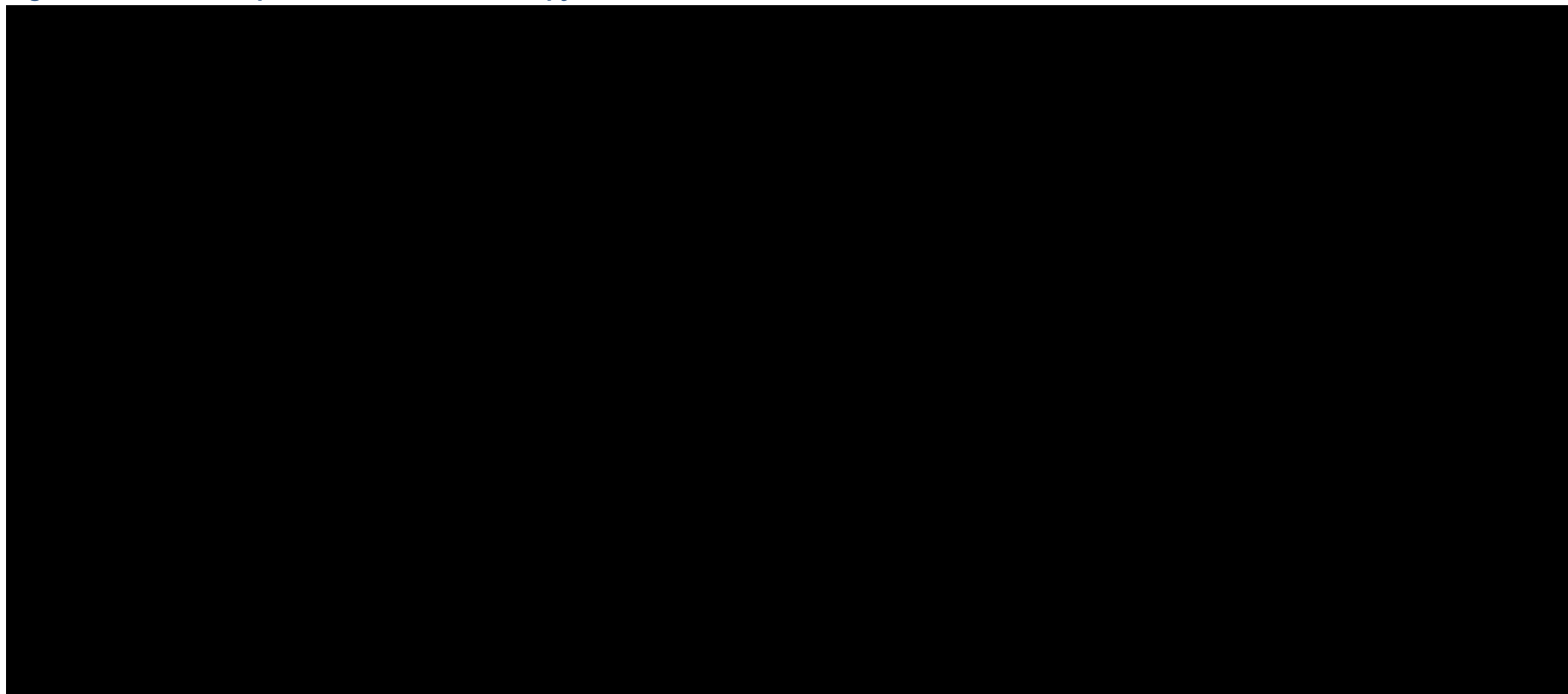
Figure 46. Smoothed hazard plot with parametric extrapolations for chemotherapy TTDD



Abbreviations: CP: carboplatin + pemetrexed; TTDD: time to treatment discontinuation or death

Company evidence submission template for amivantamab with carboplatin and pemetrexed for untreated EGFR Exon 20 insertion mutation-positive advanced non-small cell lung cancer [ID5110]

Figure 47: TTDD extrapolations for chemotherapy



Abbreviations: DCO: data cut-off; KM: Kaplan-Meier; TTDD: time to treatment discontinuation or death.

Table 61: AIC and BIC values for chemotherapy TTDD extrapolations estimations

Distributions	AIC	BIC	Sum AIC / BIC
Exponential	849.48	852.52	1702.00
Weibull	787.61	793.70	1581.32
Lognormal	797.69	803.78	1601.48
Log-logistic	787.98	794.07	1582.05
Gompertz	811.07	817.16	1628.23
Gamma			
Generalised gamma	787.23	796.36	1583.59

Lowest (i.e. best fitting) AIC and BIC scores for each distribution are in **bold** text.

Abbreviations: AIC: Akaike's Information Criterion; BIC: Bayesian Information Criterion; DCO: data cut-off; TTDD: time to treatment discontinuation or death

The median TTDD for each distribution and the TTDD estimates for each distribution at 1, 3 and 5 years for chemotherapy are presented in Table 62. The clinician expert estimates sought in the August 2024 advisory board, considering the patient population receiving chemotherapy in the PAPILLON trial, are also presented for these parameters.

Table 62: Summary of median TTDD and 1, 3 and 5-year TTDD estimates for chemotherapy extrapolations

Parametric curve	Median TTDD (months)	1-year TTDD (%)	3-year TTDD (%)	5-year TTDD (%)
Median and landmark survival for each extrapolation				
Exponential				
Weibull				
Lognormal				
Log-logistic				
Gompertz				
Gamma				
Generalised gamma				

Abbreviations: DCO: data cut-off; TTDD: time to treatment discontinuation or death.

Based on the sum of the AIC and BIC values, the best statistical fit for chemotherapy TTDD was the gamma extrapolation. Results from a pre-survey conducted for the August 2024 advisory board showed that clinical expert estimates for TTDD at 3 and 5 years varied quite broadly due to difficulties in advisors interpreting the data and therefore contained limited relevance and value. Because of the broad ranges, the estimates were discussed during the August 2024 advisory board and a consensus was reached whereby clinical experts considered that all extrapolations for modelling TTDD for chemotherapy were acceptable given the low rates of TTDD predicted at 5 years. Therefore, the base-case assumed a gamma distribution for chemotherapy TTDD.

Pembrolizumab- chemotherapy

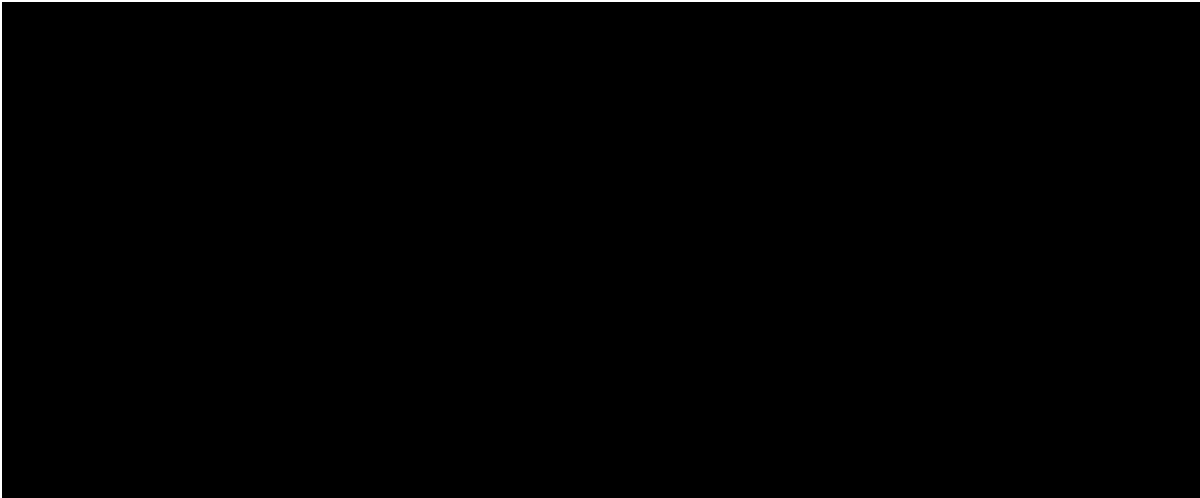
In a similar approach to the estimation of PFS for pembrolizumab-chemotherapy in the model base case, TTDD for pembrolizumab-chemotherapy was calculated using the ratio between the

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per cycle hazard of TTDD for the amivantamab component of amivantamab-chemotherapy and TTNT for the amivantamab-chemotherapy treatment arm in the PAPILLON trial, which was multiplied by the per cycle hazard of the selected TTNT extrapolation of pembrolizumab-chemotherapy to generate a TTDD curve.

The resulting TTDD curve for pembrolizumab-chemotherapy is provided in Figure 48 and landmark estimates for this extrapolation are presented in Table 63.

Figure 48: Derived TTDD extrapolation curve for pembrolizumab-chemotherapy



Abbreviations: CP: carboplatin + pemetrexed; IO: immuno-oncology; TTDD: time to treatment discontinuation or death

Table 63: Summary of median TTDD and 1, 3 and 5-year TTDD estimates for the selected base-case pembrolizumab-chemotherapy extrapolation (log-logistic)

Parametric curve	Median TTDD (months)	1-year TTDD (%)	3-year TTDD (%)	5-year TTDD (%)
Median and landmark survival for each extrapolation				
Log-logistic	■	■	■	■

Abbreviations: DCO: data cut-off; TTDD: time to treatment discontinuation or death

Summary

The distributions selected to model PFS, OS and TTDD for amivantamab-chemotherapy, chemotherapy and pembrolizumab-chemotherapy were selected in line with guidance available from NICE DSU TSD 14 and 21, considering statistical fit, visual fit, alignment with clinical expert opinion (based on a discussion-based consensus) for long-term survival outcomes and assessment of the hazard functions for each extrapolation. In multiple instances, the more conservative extrapolation was selected from a group of plausible distributions. As such, the most appropriate extrapolation applied to each outcome was comprehensively assessed using a robust and systematic methodology.^{22, 115, 116}

It should be acknowledged that, in NICE DSU TSD 14, it is only considered appropriate to fit different distributions for the same outcome (i.e., OS, PFS, TTDD) across all treatment arms considered when there is sufficient biological rationale. Both the clinical and health economist experts in attendance at the August 2024 advisory board confirmed that it would be appropriate

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for each treatment to be modelled with separate curves for each outcome due to the distinct mechanisms of actions associated with each technology. In line with this feedback, the most appropriate extrapolation for each treatment for each outcome was assessed on an individual basis using the steps outlined in the above section.^{22, 115}

B.3.3.3 Adverse reactions

AEs are included in the analysis for the first-line setting (i.e., amivantamab-chemotherapy, chemotherapy and pembrolizumab-chemotherapy). For these treatments, the impact of AEs on both costs and health-related quality of life (HRQoL) is included.

In lieu of a trial investigating pembrolizumab-chemotherapy in adult patients with EGFR Exon20 insertion mutated advanced NSCLC in the first-line setting, the KEYNOTE-189 trial, which assessed pembrolizumab-chemotherapy in adult patients with previously untreated advanced NSCLC with no sensitising EGFR mutations, was deemed a generalisable source of AE incidence data. AEs considered in the model were limited to treatment-emergent Grade 3 or 4 events that had occurred in at least 5% of patients in either treatment arm of the PAPILLON trial (for amivantamab-chemotherapy and chemotherapy) or Grade 3–5 that had occurred in at least 5% of patients in the KEYNOTE-189 trial.¹²¹

The frequency of AEs in the first-line setting for each intervention in the model is presented in Table 64.

Table 64. Incidence of TEAEs with a toxicity of grade 3 or higher which occurred in at least 5% of any treatment group in the first line setting

AE	Amivantamab-chemotherapy	Chemotherapy	Pembrolizumab-chemotherapy
Anaemia	10.6%	12.3%	19.0%
Paronychia	6.6%	0.0%	0.0%
Hypokalaemia	8.6%	1.3%	0.0%
Asthenia	5.3%	2.6%	6.7%
Neutropenia	33.1%	22.6%	16.8%
Leukopenia	11.3%	3.2%	0.0%
Rash	11.3%	0.0%	2.0%
Thrombocytopenia	9.9%	10.3%	8.6%
Fatigue	0.7%	1.3%	7.7%
Diarrhoea	3.3%	1.3%	5.2%
Source	PAPILLON	PAPILLON	KEYNOTE-189

Abbreviations: AE: adverse event.
Source: Zhou et al. (2023)¹⁰, Garassino et al. (2023).¹²¹

B.3.4 Measurement and valuation of health effects

Health effects in the model are expressed in QALYs. Utility values were applied to capture patient HRQoL associated with treatment and disease outcomes.

B.3.4.1 Health-related quality-of-life data from clinical trials

As described in Section B.2.6.3, in the PAPILLON trial, patients completed PRO questionnaires related to their HRQoL. These included the EQ-5D-5L, EORTC QLQ-C30 and PROMIS-PF. For the cost-effectiveness analysis base case, utility values for the progression-free and progressed disease health states were obtained from analysis of the EQ-5D-5L data, in line with NICE's preferred measure of HRQoL.¹⁰⁹ EQ-5D-5L data were collected at Cycle 1 Day 1, on the first day of every other following cycle (Cycle 3, 5, 7, etc.) $\pm$ 3 days, 30 days after last dose ($\pm$ 7 days) and every 12 weeks ($\pm$ 14 days) during study follow-up for 1 year.

B.3.4.2 Mapping

EQ-5D-5L utility scores were derived using UK-specific utility weights. In alignment with NICE guidelines,¹⁰⁹ these values were subsequently mapped onto the EQ-5D-3L value set using the mapping function developed by the DSU based on the "EEPRU" (Policy Research Unit in Economic Evaluation of Health and Care Interventions) dataset.¹⁰⁴

B.3.4.3 Health-related quality-of-life studies

As described in Section B.3.1, a *de novo* economic SLR and subsequent updates were conducted to identify cost-effectiveness, HSUVs and CRU data associated with the treatment options for patients with advanced common EGFR or EGFR Exon20 insertion mutation-positive NSCLC.

In the July 2024 economic SLR update, 60 articles reporting on 58 unique utility studies were identified. However, no utility studies were identified that reported outcomes in a patient population with EGFR Exon20 insertion mutation-positive NSCLC specifically, thus, utility data from the PAPILLON trial remained the most appropriate source of evidence for HRQoL for the population considered in this submission. Full details on the methods and results of this SLR are presented in Appendix H.

B.3.4.4 Adverse reactions

As discussed in Section B.3.3.3, AEs considered in the model were limited to treatment-emergent Grade 3 or 4 events that had occurred in at least 5% of patients in either treatment arm of PAPILLON or the pembrolizumab-chemotherapy arm of KEYNOTE-189 (Grade 3–5 AEs were reported in the Garassino et al. 2023 publication).¹²¹

Duration of AE episodes with missing end dates were imputed as the average of the duration of the AE records with known end dates. AE disutilities were considered for first-line treatments and were sourced from the published literature. For each AE, this disutility was multiplied by the corresponding AE incidence and mean duration (all derived from the PAPILLON trial) and then applied as a one-time utility decrement to each treatment arm upon entry to the progression-free health state. A summary of the AE disutilities applied in the cost-effectiveness model and their respective source, is presented in Table 65.

Table 65: Summary of AE disutilities applied in the cost-effectiveness model

AE	Disutility	Source (disutility)	Duration (mean, days) Source: PAPILLON ⁷³	AE QALY decrement
Anaemia	-0.07	TA850, ¹⁹ Nafees et al. 2008 ¹²²	■	■
Paronychia	-0.03	Tolley et al. 2013 ¹²³	■	■
Hypokalaemia	-0.05	TA653 ¹²⁴	■	■
Asthenia	-0.07	Assumption: equal to fatigue in Nafees et al. 2008 ¹²²	■	■
Neutropenia	-0.09	TA850, ¹⁹ Nafees et al. 2008 ¹²²	■	■
Leukopenia	-0.09	Assumption: same as neutropenia in Nafees et al. 2008 ¹²²	■	■
Rash	-0.03	TA850, ¹⁹ Nafees et al. 2008 ¹²²	■	■
Thrombocytopenia	-0.11	TA850, ¹⁹ Tolley et al. 2013 ¹²³	■	■
Fatigue	-0.07	TA850, Nafees et al 2008 ¹²²	■	■
Diarrhoea	-0.05	TA850, Nafees et al 2008 ¹²²	■	■

Abbreviations: AE: adverse event; QALY: quality-adjusted life year.

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

A single health-state specific utility value was assigned to all patients in the progression-free or progressed disease health states within the PSM. The CEM included the option for incorporating age-adjusted utility values as a baseline in the calculation of QALYs according to the methods of Ara and Brazier (2010).¹²⁵ In the model base case, age-adjusted utilities were included.

The mean utility per health state was estimated based on pooled utility data derived using EQ-5D-5L data from the PAPILLON trial which were cross walked to EQ-5D-3L using the method reported by Hernández Alava et al. (2017). A summary of the health state utility values included in the base case analysis is presented in Table 66. In the EORTC-QLQ-C30 more patients showed improved/stable GHS and physical functioning at 6 and 12 months in the amivantamab-

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chemotherapy arm compared to the chemotherapy arm. However, this does not translate to improved utility scores on generic instruments such as EQ-5D, and therefore using pooled utility values is considered a conservative approach.

Progression-free state utilities were estimated at each cycle in PAPILLON. The AUC of the time-specific progression-free state utilities was used to inform the progression-free state utility. Progressed disease state utilities were estimated from patients who progressed in the PAPILLON trial, using a mixed-model repeated measures (MMRM) model that accounted for correlations between PRO measurements from the same patients.

Table 66: Summary of utility values for the base case CEM

Health state	Utility value: mean (SE)
Progression-free	
Progressed disease	

Abbreviations: CEM: cost-effectiveness model; SE: standard error.

B.3.5 Cost and healthcare resource use identification, measurement and valuation

Published cost and resource use studies

As described in Section B.3.1, an SLR and subsequent updates were conducted to identify any relevant cost or resource use data associated with the first-line treatment of EGFR Exon20 insertion mutation-positive NSCLC that should be included in the model. Full details of the SLR search strategy, study selection process and results are presented in Appendix I.

As described in Section B.3.1, the economic SLR searched for evidence for patients with common EGFR and EGFR Exon20 insertion-mutation positive advanced NSCLC. In the July 2024 economic SLR updates, 147 articles reporting on 133 cost and HRU studies were identified and included. A total of 57 studies either exclusively focused on treatments indicated for patients with EGFR-mutated NSCLC or reported outcomes of interest separately for patients with EGFR mutations. Four studies reported on costs for patients with EGFR Exon20 insertion mutations; however, three out of the four studies investigated costs for patients with EGFR Exon20 insertion mutation-positive NSCLC in the second-line treatment setting, and all four studies were based in the US or Canada and are therefore have limited generalisability to UK clinical practice.^{68, 126, 127}

Costs incorporated into the cost-effectiveness analysis

The cost-effectiveness analysis was conducted from an NHS and PSS perspective and therefore only included costs that would be directly incurred by the healthcare system. Appropriate sources of unit costs, the drugs and pharmaceutical electronic market information tool (eMIT), British National Formulary (BNF) and the National Schedule of NHS Reference Costs (2021/2022) were used for cost inputs in the model. The 2021/2022 NHS Reference Costs were used in the economic model due to withdrawal of the 2022/2023 shortly ahead of submission.

The following cost types were included in the model:

- Drug acquisition costs

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- Drug administration costs
- Follow-up and monitoring costs
- Subsequent treatment costs
- AE management costs
- End-of-life costs

Indirect costs (i.e., caregiver and sick leave) are not included in the base case of the economic model from the healthcare payer perspective, in line with the NICE reference case in the guide to the methods of technology appraisal.¹⁰³

B.3.5.1 Intervention and comparators' costs and resource use

B.3.5.1.1 Drug acquisition costs

The drug acquisition costs for amivantamab-chemotherapy and the comparators applied in the model are presented in Table 67. The unit drug costs were sourced from the BNF 2024 for amivantamab and pembrolizumab, and from eMIT for carboplatin and pemetrexed.^{128, 129}

Pembrolizumab is associated with a PAS discount to the list price. However, given this is confidential, the analysis was run at the list price. Amivantamab is also associated with a PAS discount of █%; this discount has been incorporated into the model.

Costs associated with amivantamab-chemotherapy and chemotherapy vary by treatment cycle and patient weight. Therefore, dosing schedules in the model are based on the PAPILLON trial.^{73, 76} The base case did not consider vial sharing, therefore, drug wastage was assumed. RDI proportions were applied from the PAPILLON trial for amivantamab-chemotherapy and chemotherapy. The RDI values were applied to the required number of vials for each study treatment (amivantamab, carboplatin, and pemetrexed) based on the dose reductions observed in the PAPILLON trial.

Skipped doses are also accounted for in the economic model. For amivantamab-chemotherapy and chemotherapy, the percentage of dose administrations that are expected to be skipped and not made up were derived from the PAPILLON trial. The dose skipping percentages were estimated separately for amivantamab, and pemetrexed and carboplatin, and were calculated by dividing the number of doses that were observed to be given in the PAPILLON trial by the doses that were expected were to be given, based on the label dosing, using the time to treatment discontinuation.⁷³

Accounting for the RDI for these treatments and the occurrence of dose skipping was validated in the May 2024 advisory board, with clinical experts supporting that this reflects UK clinical practice. Adjusting the acquisition costs in this way ensured that costs and efficacy for amivantamab-chemotherapy and chemotherapy were derived from the same source: the PAPILLON trial.⁵

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For pembrolizumab-chemotherapy, the dose skipping percentages for pembrolizumab were derived from the assumption used in previous NICE evaluation TA683, and for chemotherapy the same percentages were used as for the doses skipped in the chemotherapy arm in the PAPILLON trial.^{73, 130} RDI was assumed to be 100% for pembrolizumab-chemotherapy.

Table 67: Drug acquisition costs for intervention

Treatment	Adminis- tration route	Unit strength (mg)	Units per pack	Price per pack (£)	PAS discount (%)	Cost per unit (£)	Source
Amivantamab	IV	350	1	1,079.00	■	■	BNF 2024 ¹²⁸
Carboplatin	IV	600	1	71.44	-	71.44	eMIT 2024 ¹²⁹
Pemetrexed	IV	500	1	24.52	-	24.52	eMIT 2024 ¹²⁹
Pembrolizumab	IV	100	1	2,630.00	NR ^a	2,630.00	BNF 2024 ¹²⁸

^a The PAS discount of pembrolizumab is confidential.
Abbreviations: BNF: British national formulary; eMIT: electronic market information tool; IV: intravenous.

The dosing regimen and respective cost per cycle of amivantamab-chemotherapy is presented in Table 68, with the drug acquisition costs by treatment phase of chemotherapy and pembrolizumab-chemotherapy presented in Table 69 and Table 70, respectively.

In NICE evaluation TA683, pembrolizumab with pemetrexed and platinum chemotherapy was recommended by NICE for untreated, metastatic, non-squamous NSCLC with the condition that this treatment must be stopped at two years of uninterrupted treatment, or earlier if the disease progresses. As such, this stopping rule was incorporated into the economic analysis with no drug acquisition costs modelled after two years of initiation of treatment, for those patients who had not yet progressed to the progressed disease health state.¹³⁰

Table 68: Weekly drug acquisition costs by cycle for amivantamab-chemotherapy

Component	Dose	Treatment duration	Dose reduction (amivantamab) /RDI	Units (vials/caps) per admin	Cost per average dose required (£)	Dose skipping (%)	Cost per week in cycle 1 (£)	Cost per week in cycle 2 (£)	Cost per week in cycle 3-4 (£)	Cost per week in subsequent cycles (£)
Amivantamab	1,400 mg	< 80 kg patients: 4 weeks (up to C2D1)	████	██	████	██	████	██	██	██
Amivantamab	1,750 mg	≥ 80 kg patients: 4 weeks (up to C2D1)	████	██	████	██	████	██	██	██
Amivantamab	1,750 mg	< 80 kg patients: C3D1 until progression	████	██	████	██	██	██	████	████
Amivantamab	2,100 mg	≥ 80 kg patients: C3D1 until progression	████	██	████	██	██	██	████	████
Pemetrexed	500 mg/m ²	Until progression	████	██	██	██	██	██	██	██
Carboplatin	AUC 5 ^a	4 cycles	████	██	██	██	██	██	██	██
Total amivantamab-chemotherapy							████	██	████	████
Total amivantamab							████	██	████	████
Total chemotherapy							██	██	██	██

No vial sharing (i.e. wastage is assumed); weekly costs are adjusted for dose skipping.

^aAn average dose per administration of 550 mg is assumed for carboplatin.

Abbreviations: AUC: area under the curve; C: cycle; D: day; RDI: relative dose intensity.

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Table 69: Weekly drug acquisition costs by treatment phase for chemotherapy

Component	Dose	Treatment duration	RDI	Units (vials/caps) per admin	Cost per average dose required (£)	Dose skipping (%)	Cost per week of induction (£)	Cost per week of maintenance (£)
Pemetrexed	500 mg/m ²	Until progression	████	████	████	████	████	████
Carboplatin	AUC 5 ^a	4 cycles	████	████	████	████	████	████
Total chemotherapy							████	████

No vial sharing (i.e. wastage is assumed); weekly costs are adjusted for dose skipping.

^aAn average does per administration of 550 mg is assumed for carboplatin.

Abbreviations: AUC: area under the curve; RDI: relative dose intensity.

Table 70: Weekly drug acquisition costs by treatment phase for pembrolizumab-chemotherapy

Component	Dose	Treatment duration	RDI	Units (vials/caps) per admin	Cost per average dose required (£)	Dose skipping (%)	Cost per week of induction (£)	Cost per week of maintenance (£)
Pembrolizumab	200 mg	2 years maximum	100.00%	2.00	5,260.00	4.40	1,676.19	1,676.19
Pemetrexed	500 mg/m ²	Until progression	████	████	████	████	████	████
Carboplatin	AUC 5 ^a	4 cycles	████	████	████	████	████	████
Total pembrolizumab-chemotherapy							████	████

No vial sharing (i.e. wastage is assumed); weekly costs are adjusted for dose skipping.

^aAn average does per administration of 550 mg is assumed for carboplatin.

Abbreviations: AUC: area under the curve; IO: immuno-oncology; RDI: relative dose intensity.

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B.3.5.1.2 Drug administration costs

The drug administration costs used in the model are presented in Table 71. The weekly drug administration costs split by treatment phase for amivantamab-chemotherapy, chemotherapy and pembrolizumab-chemotherapy are further presented in Table 72, Table 73, and Table 74, respectively. It should be noted that pembrolizumab is not associated with administration costs, however, administration costs are accrued through the addition of carboplatin and pemetrexed.

For all interventions, a combination (complex) IV cost of £440.71 is applied in each of the first four 21-day cycles, to account for the administration of all parts of the intervention; amivantamab, carboplatin and pemetrexed. An additional monotherapy (simple) IV administration cost of £207.59 is added twice in Cycle 1, accounting for the fact that amivantamab is administered weekly in the first cycle.

Starting from Cycle 5, monotherapy (simple) IV administration costs are applied to amivantamab-chemotherapy, chemotherapy and pembrolizumab-chemotherapy.

Table 71: Drug administration unit costs

Mode of administration	Cost (£)	Source ^a
Cost per IV administration, monotherapy	207.59	National Schedule of NHS Costs 2021/22, CHEM_SB12Z: Deliver Simple Parenteral Chemotherapy at First Attendance; Outpatient ¹³¹
Cost per IV administration, combination therapy	440.71	National Schedule of NHS Costs 2021/22, CHEM_SB14Z: Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance; Outpatient ¹³¹
Oral therapy one-off cost ^b	216.90	National Schedule of NHS Costs 2021/22, SB11Z: Deliver Exclusively Oral Chemotherapy

^a 2022/2023 NHS Reference Costs were withdrawn ahead of submission.

^b Relevant to subsequent treatments only.

Abbreviations: IV: intravenous; NHS: National Health Service.

Table 72: Weekly drug administration costs by cycle for amivantamab-chemotherapy

Component	Route of administration	Dose	Treatment duration	Cost per week in cycle 1 (£)	Cost per week in cycle 2 (£)	Cost per week in cycle 3-4 (£)	Cost per week in subsequent cycles (cycle 5+) (£)
Amivantamab	IV	1,400 mg	< 80 kg patients: 4 weeks (up to C2D1)	████	██	██	██
Amivantamab	IV	1,750 mg	≥ 80 kg patients: 4 weeks (up to C2D1)	████	██	██	██
Amivantamab	IV	1,750 mg	< 80 kg patients: C3D1 until progression	██	██	██	██
Amivantamab	IV	2,100 mg	≥ 80 kg patients: C3D1 until progression	██	██	██	██
Pemetrexed ^d	IV	500 mg/m ²	Until progression	██	██	██	████
Carboplatin	IV	AUC 5 ^c	4 cycles	████	████	████	██
Total administration cost per week amivantamab-chemotherapy				████	████	████	████
Total administration cost per week amivantamab				████	██	██	██
Total administration cost per week chemotherapy				████	████	████	████

^aAssumed one IV administration counted as part of carboplatin administration costs and two monotherapy IV administrations in the first cycle.

^bAssumed one IV administration counted as part of carboplatin combination administration cost.

^cAn average dose per administration of 550 mg is assumed for carboplatin.

^dThe administration cost for pemetrexed is included within the cost associated with carboplatin (cost per IV administration of combination therapy).

Abbreviations: AUC: area under the curve; C: Cycle; D: Day; IV: intravenous.

Table 73: Weekly drug administration costs by treatment phase for chemotherapy

Component	Route of administration	Dose	Treatment duration	Cost per week of induction (£)	Cost per week of maintenance (cycle 5+) (£)
Pemetrexed	IV	500 mg/m ²	Until progression	■	■
Carboplatin	IV	AUC 5 ^a	4 cycles	■	■
Total cost per week (chemotherapy)				■	■

^a An average dose per administration of 550 mg is assumed for carboplatin.

Abbreviations: AUC: area under the curve; IV: intravenous.

Table 74: Weekly drug administration costs by treatment phase for pembrolizumab-chemotherapy

Component	Route of administration	Dose	Treatment duration	Cost per week of induction (£)	Cost per week of maintenance (£)
Pembrolizumab	IV	200 mg	Until progression	0.00	0.00
Pemetrexed	IV	500 mg/m ²	Until progression	■	■
Carboplatin	IV	AUC 5 ^a	4 cycles	■	■
Total cost per week (pembrolizumab-chemotherapy)				■	■

^a An average dose per administration of 550 mg is assumed for carboplatin.

Abbreviations: AUC: area under the curve; IV: intravenous.

B.3.5.1.3 Subsequent treatments

Subsequent treatments were modelled for patients receiving amivantamab-chemotherapy, chemotherapy and pembrolizumab-chemotherapy following disease progression. Subsequent treatments were modelled for both the second-line and third-line settings; both settings are modelled using a one-off cost applied following disease progression, based on the distribution of subsequent treatments at each line and the duration of each treatment. Patients not receiving subsequent treatment following progression are assumed to receive BSC, which has a £0 cost assumed in the base case of the model.

A one-off cost for subsequent treatments was considered appropriate due to the relatively short duration of subsequent treatment expected in patients with EGFR Exon20 insertion mutation-positive advanced NSCLC, the indication of relevance to this submission; the same approach was also used in NICE evaluations TA683 and TA850.^{19, 130} The distribution of subsequent treatments in the second- and third-line settings are presented in Table 75 and Table 76, respectively. These distributions were informed by clinical expert opinion obtained in the May 2024 advisory board conducted by Johnson & Johnson.⁵

The duration assumed for each subsequent treatment was sourced from the published literature. For subsequent treatments in the second-line setting, durations were based on the Bazhenova et al. 2021 study introduced in Section B.1.3.1.1, and were based on median PFS.¹² For subsequent treatments in the third-line setting (excluding IO monotherapy), durations were based on the Park et al. 2019 study; for IO monotherapy, duration was based on the Migliorino et al. 2017 study, based on nivolumab.^{80, 132, 133}

Table 75: Distribution of subsequent treatments in the second-line setting

Subsequent treatment	First-line treatment		
Source	ACP	CP	Pembrolizumab-CP
Proportion receiving active subsequent treatment	40%	40%	40%
Platinum-based chemotherapy	10.0%	10.0%	25.0%
Docetaxel	21.0%	21.0%	22.5%
Docetaxel plus nintedanib	49.0%	49.0%	52.5%
IO monotherapy	20.0%	20.0%	0.0%

Abbreviations: ACP: amivantamab-chemotherapy; CP: chemotherapy; IO: immune-oncology.

Table 76: Distribution of subsequent treatments in the third-line setting

Subsequent treatment	First-line treatment		
Source	ACP	CP	Pembrolizumab-CP
Proportion receiving subsequent treatment	10%	10%	10%
IO monotherapy	50.0%	50.0%	0.0%
Gemcitabine	25.0%	25.0%	50.0%
Vinorelbine	25.0%	25.0%	50.0%

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Abbreviations: ACP: amivantamab-chemotherapy; CP: chemotherapy; IO: immune-oncology. Health-state unit costs and resource use

Drug monitoring costs

The drug monitoring unit costs included in the analysis are presented in Table 77. Additionally, the weekly drug monitoring costs for each treatment are presented in Table 78.

Table 77: Drug monitoring unit costs

Mode of administration	Cost (£)	Source ^a
Full blood count	2.96	National Schedule of NHS Costs 2021/22, DAPS05 - Haematology ¹³¹
Liver function	1.55	National Schedule of NHS Costs 2021/22, DAPS04 - Clinical Biochemistry ¹³¹
Renal function	1.55	National Schedule of NHS Costs 2021/22, DAPS04 - Clinical Biochemistry ¹³¹

^a 2022/2023 NHS Reference Costs were withdrawn ahead of submission.

Abbreviations: NHS: National Health Service.

Table 78: Weekly drug monitoring costs for all treatments

Regimen	Component requiring monitoring	Lab tests	Frequency per week	Cost per week (£)
All	Pemetrexed	Full blood count	0.30	0.89
	Pemetrexed	Liver function	0.30	0.46
	Pemetrexed	Renal function	0.30	0.46
	Total cost per week		1.81	

Source: Pemetrexed SmPC.¹¹⁴

Disease management costs

Health-state specific routine monitoring and follow-up care costs were included in the analysis, using a micro-costing approach. The types, costs and frequencies of medical resources by health state are presented in Table 79. The types and frequencies of resources were based on previous HTA submissions and unit costs were based on the 2021/22 National Schedule of NHS costs or the 2023 PSSRU report on unit costs of health care.¹³⁴

Disease management costs were assumed to be the same for patients receiving amivantamab-chemotherapy, chemotherapy and pembrolizumab chemotherapy.

Table 79: Resource use and costs for routine follow-up care by health state

Resource	Unit cost (£)	Annual resource usage		Source ^a
		Progression-free	Progressed disease	
Oncology outpatient visit	162.93	9.6	7.9	NHS reference costs 2021/22. WF01A. Consultant Led, Non-Admitted Face-to-Face Attendance, Follow-up, NICE TA531
Clinical nurse specialist (hours)	88.00	12.0	12.0	PSSRU 2023: Cost per hour Band 8B nurse P.61, NICE TA584
GP surgery visit	49.00	12.0	0.0	PSSRU 2023: Unit costs for a GP Per surgery consultation lasting 10 minutes incl. direct care staff costs & qualifications p.64, NICE TA584
Therapist visit	52.00	0.0	26.1	PSSRU 2023: Cost per hour for a community occupational therapist (local authority), incl. qualification p.77, NICE TA584
GP home visit	49.00	0.0	26.1	PSSRU 2023: Unit costs for a GP. Assumed the same costs as per surgery consultation lasting 10 minutes incl. direct care staff costs & qualifications p.64 (as per TA850), NICE TA584
Community nurse home visit	76.00	8.7	8.7	PSSRU 2023: Cost per hour Band 8A nurse P.61, NICE TA584
Chest radiography	26.71	6.8	6.5	National Schedule of NHS Costs 2021/22, IMAGDA_PF Plain Film, NICE TA531
CT scan (chest)	133.99	0.6	0.2	National Schedule of NHS Costs 2021/22,IMAGDA_RD24Z, Computerised Tomography Scan of Two Areas, with Contrast, NICE TA531
CT scan (other)	139.49	0.4	0.4	National Schedule of NHS Costs 2021/22, IMAGDA_RD26Z , Computerised Tomography Scan of Two Areas, with Contrast, NICE TA531
Electrocardiogram	74.91	1.0	0.9	National Schedule of NHS Costs 2021/22,DADS_EY51Z, Electrocardiogram Monitoring or Stress Testing, NICE TA531
Average annual cost by health state (£)		4,263.54	5,971.37	Calculation
Average weekly cost by health state (£)		81.71	114.44	Calculation

a. 2021/2022 NHS Reference Costs were used due to withdrawal of the 2022/2023 shortly ahead of submission

Abbreviations: CG: clinical guideline; CT: computed tomography; GP: general practitioner; HCHS: hospital and community health services; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; PSS: Personal Social Services; PSSRU: Personal Social Services Research Unit; TA: technology appraisal.

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B.3.5.2 Adverse reaction unit costs and resource use

Most Grade 3 or 4 AEs were costed using the standard approach of a weighted average of non-elective short stay admissions from the 2021/22 National Schedule of NHS Costs, with assumptions made for asthenia and fatigue; all AE unit costs are detailed in Table 80.¹³¹ The incidence of AEs for each intervention are reported in Section B.3.3.3.

Table 80: Adverse event unit costs

AE	Unit cost (£)	Source ^a
Anaemia	770.29	Weighted average of National Schedule of NHS Costs 2021/22, SA01G–SA01K (non-elective short stay) ¹³¹
Paronychia	516.57	Weighted average of National Schedule of NHS Costs 2021/22, JD07A–JD07K (non-elective short stay); assuming the same as 'Rash' ¹³¹
Hypokalaemia	574.69	Weighted average of National Schedule of NHS Costs 2021/22, KC05G–KC05N (non-elective short stay) ¹³¹
Asthenia	770.29	Assumed to be the same as anaemia (as per NICE TA653) ¹²⁴
Neutropenia	627.97	Weighted average of National Schedule of NHS Costs 2021/22, SA35A–SA35E (non-elective short stay) ¹³¹
Leukopenia	542.77	Weighted average of National Schedule of NHS Costs 2021/22, SA08G–SA08J (non-elective short stay) ¹³¹
Rash	516.57	Weighted average of National Schedule of NHS Costs 2021/22, JD07A–JD07K (non-elective short stay) ¹³¹
Thrombocytopenia	699.05	Weighted average of National Schedule of NHS Costs 2021/22, SA12G–SA12K (non-elective short stay) ¹³¹
Fatigue	770.29	Assumed to be the same as anaemia (as per NICE TA850 and TA653)
Diarrhoea	582.08	Weighted average of National Schedule of NHS Costs 2021/22, FD01–FD01J (non-elective short stay)

a. 2021/2022 NHS Reference Costs were used due to withdrawal of the 2022/2023 shortly ahead of submission
Abbreviations: AE = adverse event; NHS = National Health Service; NICE = National Institute of Health and Care Excellence; TA = technology appraisal.

B.3.5.3 Miscellaneous unit costs and resource use

B.3.5.3.1 End-of-life costs

A one-time cost of £4,152.64 for terminal care was incurred upon patient death, in accordance with assumptions used in the NICE submission for amivantamab for treating EGFR Exon20 insertion mutation-positive advanced NSCLC after platinum based chemotherapy (TA850) and atezolizumab for treating locally advanced or metastatic NSCLC after chemotherapy (TA520), based on NHS reference costs 2021/22 and PSSRU 2023.¹³⁵ The breakdown of the end-of-life costs is presented in Table 81.

Table 81: Cost components in end-of-life costs

Component	Frequency	Patients receiving care (%)	Unit cost (£)	Weighted costs (£)	Source
Hospitalisation admission and excess bed days	1	55.8	4,724.00	2,634.50	National Schedule of NHS Costs 2021/22, DZ17S (non-elective long stay) ¹³¹
Macmillan Nurse (home setting)	50	27.3	38.00	518.70	Assumed two thirds of the cost of a community nurse: £57 per working hour (assuming band 6 per TA520, PSSRU 2023 ¹³⁴)
Hospice care	1	16.9	5,905.00	997.40	Assumed 25% increase on hospitalisation setting
Total cost (£):				4,152.64	Calculation

Abbreviations: NHS: National Health Service; PSSRU: Personal Social Services Research Unit; TA: technology appraisal.

B.3.6 Severity

The severity modifier tool developed by the Sheffield Centre for Health and Related Research (SCHARR) and Lumanity was used to calculate the absolute and proportional severity modifiers.¹³⁶

The quality-adjusted life expectancy (QALE) used in the severity modifier calculation was based on the ONS life tables (2020-2022), and QALYs for the SoC were derived from the CEM, using the total discounted QALYs calculated for patients in the NCRAS dataset (n=24), which represents an England-specific, real-world population dataset. When calculating the QALY shortfall, the results of the analysis demonstrate that amivantamab-chemotherapy is eligible for a 1.2x severity modifier as the proportional shortfall is greater than 0.85, as demonstrated in Table 83.

Table 82: Summary of QALY shortfall analysis

	NCRAS
QALE after model starting age	12.58
QALYs for SoC	■
Absolute shortfall	■
Proportional shortfall	■
Severity modifier	1.20

Abbreviations: QALE: quality-adjusted life expectancy; QALY: quality-adjusted life year; SoC: standard of care.

It should be noted that the QALY shortfall analysis was also repeated considering the weighted comparator and the individual populations in the weighted comparator arm (chemotherapy informed by the PAPILLON trial and pembrolizumab-chemotherapy informed by the NECTAR study). Throughout these different analyses, a 1.2x severity modifier was always met and is therefore robust to the patient population considered in the calculation.

B.3.7 Uncertainty

The development of the economic model was guided by multiple global and UK advisory boards, consulting health economist experts and clinical experts in NSCLC to ensure the modelling approaches used were robust and appropriate for the indication being evaluated. Further details on the model validation process are provided in Section B.3.14.

There are several modelling limitations that should be acknowledged when taking into account the economic evidence for amivantamab-chemotherapy:

The comparative efficacy of OS for amivantamab-chemotherapy versus chemotherapy is associated with uncertainty, given the presence of treatment switching from the chemotherapy treatment arm to amivantamab monotherapy (permitted following BICR-confirmed disease progression). The presence of treatment switching confounds comparative OS results making the true survival benefit of amivantamab-chemotherapy less certain. However, treatment switching adjustment was performed using a robust and validated methodology (IPCW, as described in Section B.3.3.2.1) that was selected based on guidance from NICE DSU TSD 24 and health economist opinion obtained during the August 2024 advisory board.^{22, 81} Following treatment switch adjustment, the true survival benefit of amivantamab-chemotherapy was inferred, and the

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adjusted OS KM data for chemotherapy was utilised in the economic model following validation from clinical and health economist experts.²² Furthermore, alternative approaches for treatment switching were explored in scenario analysis to investigate the influence of treatment switch adjustment methods on the cost-effectiveness results.

A limitation in the comparison for amivantamab-chemotherapy versus pembrolizumab-chemotherapy is the comparison between data from the PAPILLON study (patients receiving amivantamab-chemotherapy) to pooled RWE from the NECTAR study (patients receiving pembrolizumab-chemotherapy regimens). While there are inherent limitations to RWE, as described in Section B.2.9.6, a comparison to RWE was necessary due to the absence of studies evaluating pembrolizumab-chemotherapy in the population of interest to this submission. To account for potential differences between populations, patients in the pooled RWE who received pembrolizumab-chemotherapy in the first-line setting were reweighted to provide a similar distribution of confounders (characteristics that may be considered as prognostic factors) compared to the amivantamab-chemotherapy arm of the PAPILLON trial. The prognostic factors were systematically identified (through an SLR and expert validation), and reweighting was carried out using the ATT approach given the availability of IPD from the data sources included in the NECTAR study.

Despite limitations associated with the use of RWE data within the ITC, the results from the ITC vs pembrolizumab-chemotherapy can be considered robust given the similarity between the OS HR of amivantamab-chemotherapy vs chemotherapy from the PAPILLON trial (direct comparison after IPCW-adjustment for subsequent amivantamab monotherapy) and the OS HR of amivantamab-chemotherapy vs chemotherapy from the NECTAR study (ITC after ATT-weighting of RWE data). This is further described in section B.3.3.2.1.

Pooled data from the NECTAR study, which assumed that outcomes for patients receiving pembrolizumab in combination with a range of platinum chemotherapy regimens were representative of patients receiving pembrolizumab in combination with carboplatin and pemetrexed, provided a sufficient sample size for comparison. The assumption that the 'platinum chemotherapy-IO' treatment class within the NECTAR study is reflective of patients receiving pembrolizumab with carboplatin and pemetrexed is considered defensible given [REDACTED] of patients within the 'platinum chemotherapy-IO' treatment class comprised patients receiving pembrolizumab with carboplatin and pemetrexed.

While the utilisation of HRs (TTNT versus PFS and TTNT versus TTDD) for amivantamab-chemotherapy to generate PFS and TTDD data, respectively, for pembrolizumab-chemotherapy may be associated uncertainty, this approach was taken from advice provided by UK clinical experts that TTNT cannot be considered a suitable proxy for PFS. Additionally, this is a more conservative approach when compared to using TTNT directly as a proxy for PFS. As such, the comparison for amivantamab-chemotherapy versus pembrolizumab-chemotherapy was derived using the most robust clinical evidence available, provided by the NECTAR study, and taking conservative approaches were possible.²²

There are additionally unavoidable uncertainties associated with the extrapolation of long-term survival data, in this instance, KM data from the PAPILLON trial (amivantamab-chemotherapy and chemotherapy) and the NECTAR study (pembrolizumab-chemotherapy). To mitigate some uncertainty inherent within the OS extrapolations, the economic model utilises OS data from the most recent (31st October 2023) DCO rather than the primary analysis (3rd May 2023)

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The extrapolations selected for PFS (HR applied to TTNT, in the instance of pembrolizumab-chemotherapy, as described above), OS and TTDD (HR applied to TTNT for pembrolizumab-chemotherapy) were selected based on a systematic and rigorous approach. A range of standard parametric functions were explored and evaluated based on agreement of the hazard functions with the associated KM data, statistical fit, visual fit, and clinical plausibility based on estimates and clinical opinion obtained during the August 2024 advisory board.²² Guidance outlined in NICE DSU TSD 14 was also considered throughout the curve selection process.¹¹⁵ By considering alternative extrapolations as part of the scenario analyses, the robustness of model results to different distributions was explored.

In conclusion, each modelling approach and assumption was guided by available guidance in addition to clinical and health economist opinion. Throughout this submission, conservative approaches have been taken where necessary, increasing confidence in the cost-effectiveness of amivantamab-chemotherapy versus relevant comparators.

B.3.8 Managed access proposal

Johnson & Johnson consider that the clinical and economic evidence is sufficiently robust to support routine NHS commissioning of amivantamab in combination with carboplatin and pemetrexed. For instance, at the 3rd May 2023 DCO, the primary endpoint of the PAPILLON trial, PFS, had reached its median value in both treatment arms as presented in Section B.2.6.1. Furthermore, median DOR and median TTST were reached as secondary objectives (Table 15 and Table 18, respectively, in Section B.2.6.2). After adjustment of OS data (via IPCW, see Section B.3.3.2.1) to account for treatment switching in the PAPILLON trial, a clear OS benefit is observed for amivantamab-chemotherapy versus chemotherapy (adjusted HR: [REDACTED] [95% CI: [REDACTED]-[REDACTED]; p=[REDACTED]]).³

As such, Johnson & Johnson believe that amivantamab-chemotherapy addresses a significant unmet need in patients with EGFR Exon20 insertion mutation-positive advanced NSCLC, who currently face an extremely poor prognosis, without the need for managed access. However, Johnson & Johnson are open to discuss the potential for managed access with the NICE committee if needed.

B.3.9 Summary of base-case analysis inputs and assumptions

B.3.9.1 Summary of base-case analysis inputs

A summary of the base case model inputs and settings are presented in Table 83.

Table 83: Summary of variables applied in the economic base case

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty (distribution)	Reference to section in submission
Model characteristics			
Time horizon	Lifetime (30 years)	NA	B.3.2.2
Cycle length	1 week	NA	

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Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty (distribution)	Reference to section in submission
Discount rate for effects	3.5%	NA	
Discount rate for costs	3.5%	NA	
Patient characteristics			
Mean starting age, years	■	Normal	B.3.3.1
Proportion female, %	57.8	NA	
Mean weight, kg	■	Normal	
Mean BSA, m²	■	Normal	
Proportion <80kg, %	84.4	Beta	
Efficacy data			
Amivantamab-chemotherapy PFS	Gamma extrapolation	NA	B.3.3.2
Amivantamab-chemotherapy OS	Weibull extrapolation	NA	
Amivantamab-chemotherapy TTDD	Weibull extrapolation for both amivantamab and chemotherapy within the amivantamab-chemotherapy arm	NA	
Chemotherapy PFS	Gamma extrapolation	NA	
Chemotherapy OS	Gamma extrapolation	NA	
Chemotherapy TTDD	Gamma extrapolation	NA	
Pembrolizumab-chemotherapy PFS	TTNT log-logistic extrapolation with per cycle HR of amivantamab-chemotherapy TTNT versus PFS applied	NA	
Pembrolizumab with chemotherapy OS	Log-logistic extrapolation	NA	
Pembrolizumab with chemotherapy TTDD	TTNT log-logistic extrapolation with per cycle hazard of amivantamab TTDD versus TTNT applied	NA	
Drug acquisition costs for intervention (per week)			
Amivantamab-chemotherapy: Cycle 1	■	Gamma	B.3.5.1.1

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Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty (distribution)	Reference to section in submission
Amivantamab-chemotherapy: Cycle 2	████	Gamma	
Amivantamab-chemotherapy: Cycle 3–4	████	Gamma	
Amivantamab-chemotherapy: Cycle 5 onwards	████	Gamma	
Drug acquisition costs for comparators (per week): induction			
Chemotherapy	████	Gamma	B.3.5.1.1
Pembrolizumab-chemotherapy	████	Gamma	
Drug costs for comparators (per week): maintenance			
Chemotherapy	████	Gamma	B.3.5.1.1
Pembrolizumab-chemotherapy	████	Gamma	
Administration costs (per week) for intervention			
Amivantamab-chemotherapy: Cycle 1	████	Gamma	B.3.5.1.2
Amivantamab-chemotherapy: Cycle 2	████	Gamma	
Amivantamab-chemotherapy: Cycle 3–4	████	Gamma	
Amivantamab-chemotherapy: Cycle 5+	████	Gamma	
Administration costs for comparators (per week): induction			
Chemotherapy	████	Gamma	B.3.5.1.2
Pembrolizumab-chemotherapy	████	Gamma	
Administration costs for comparators (per week): maintenance			
Chemotherapy	████	Gamma	B.3.5.1.2
Pembrolizumab-chemotherapy	████	Gamma	
AE management costs			
Amivantamab-chemotherapy	£627.14	Gamma	B.3.5.2

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Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty (distribution)	Reference to section in submission
Chemotherapy	£371.10	Gamma	
Pembrolizumab with chemotherapy	£463.49	Gamma	
Disease management costs (weekly), progression-free			
Amivantamab-chemotherapy	£81.71	Gamma	B.3.5.3
Chemotherapy			
Pembrolizumab with chemotherapy			
Disease management costs (weekly), progressed disease			
Amivantamab-chemotherapy	£114.44	Gamma	B.3.5.3
Chemotherapy			
Pembrolizumab with chemotherapy			
Disease management costs, one-off cost			
End-of-life	£4,152.64	Gamma	B.3.5.3
Subsequent treatment costs (one-off)			
Amivantamab-chemotherapy	████	Gamma	B.3.5.1.3
Chemotherapy	████	Gamma	
Pembrolizumab-chemotherapy	████	Gamma	
Health state utility values			
Progression-free	██	████████	B.3.4.5
Progressed disease	██	████████	
AE disutilities			
Amivantamab-chemotherapy	████	Beta	-
Chemotherapy	████	Beta	
Pembrolizumab with chemotherapy	████	Beta	

Abbreviations: AE: adverse event; BSA: body surface area; NA: not applicable; OS: overall survival; TTDD: time to treatment discontinuation or death; TTNT: time to next treatment.

B.3.9.2 Assumptions

A list of the key assumptions and inputs used in the base case analysis of the economic model is provided in Table 84.

Table 84: List of key assumptions and inputs for the base case analysis model

Model input and cross reference	Source/assumption	Justification
Clinical effectiveness		
Efficacy source	Efficacy data for amivantamab-chemotherapy and chemotherapy were sourced from the PAPILLON trial. Efficacy data for pembrolizumab-chemotherapy were sourced from RWE (NECTAR study) which includes NCRAS data.	PAPILLON is the only RCT available to provide data for amivantamab and carboplatin with pemetrexed in this population. Use of RWE for pembrolizumab-chemotherapy is in line with TA850, where the committee acknowledged RWE may have been the best source of evidence available given no trial information is available.¹⁹ Due to the rarity of EGFR Exon20 insertion mutations, only a small sample size (n=24) was included in the UK RWE NCRAS dataset. Therefore, pooled RWE from the larger NECTAR study was used to ensure a sufficiently robust sample size for the ITC analysis. The data sources included in the NECTAR study were systematically sourced and selected through a robust relevance assessment. The NECTAR RWE population used for pembrolizumab-chemotherapy includes adult patients aged 18+ with advanced NSCLC without prior systematic treatment, with confirmed EGFR Exon20 insertion mutations. This aligns with the PAPILLON trial and model populations. ATT weighting was applied to adjust for differences in patient characteristics across PAPILLON and NECTAR to produce balanced patient populations.
OS	OS data from the 31st October 2023 DCO were used to model survival for amivantamab-chemotherapy and carboplatin with pemetrexed-chemotherapy. The proportional hazards assumption did not hold between arms, and so OS for each arm was modelled independently. For amivantamab-chemotherapy, a Weibull extrapolation was selected in the base-case. Chemotherapy OS data were adjusted to account for patients switching onto amivantamab	The 31 October 2023 DCO provides the longest follow-up to inform the survival extrapolation. The selection of extrapolation curves for OS for amivantamab-chemotherapy, carboplatin with pemetrexed, and pembrolizumab-chemotherapy were based on statistical fit, assessment of the hazard plots, visual inspection, and clinical plausibility based on expert advice. For amivantamab-chemotherapy, the Weibull extrapolation was selected in the base-case and a gamma extrapolation was explored

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	monotherapy after BICR-confirmed progression in PAPILLON. Chemotherapy was modelled based on the adjusted OS data, and a gamma curve selected in the base-case. Pembrolizumab-chemotherapy OS was based on real-world OS data from NECTAR, and a loglogistic curve was selected in the base case.	as a scenario. The full rationale for curve selection is given in section B.3.3.2.4 Amivantamab in the second-line setting (after platinum-based chemotherapy) is not recommended by NICE and therefore does not reflect UK clinical practice. NICE TSD 24 highlights the appropriateness of adjusting for the impact of treatment switching that would not be expected to occur in UK clinical practice.⁸¹ Therefore, OS data for carboplatin with pemetrexed have been adjusted using the IPCW method in the base case. This is an advanced methodology recommended in TSD 24.⁸¹ The rationale for choosing the IPCW in the base-case is further detailed in section B.3.3.2.1. For the adjusted chemotherapy OS, the gamma extrapolation was selected in the base-case, with the Weibull extrapolation being explored as a scenario. The rationale for curve selection is detailed in B.3.3.2.4 For pembrolizumab-chemotherapy, all extrapolations had similar statistical fits, with the loglogistic extrapolation having the best statistical fit and, as such, was chosen in the base-case.
PFS	For amivantamab-chemotherapy and chemotherapy, PFS was modelled as independent extrapolations of the PFS data from the PAPILLON trial. Gamma extrapolations for both amivantamab-chemotherapy and chemotherapy were selected in the base case. For pembrolizumab-chemotherapy, PFS was estimated by applying the per cycle HR of amivantamab-chemotherapy TTNT vs BICR-assessed PFS to the real-world TTNT data for pembrolizumab-chemotherapy. Independent extrapolations were subsequently fitted to the estimated PFS data, and a loglogistic curve was selected in the base case.	Given PFS data were relatively mature, and the distributions were relatively similar, curve selection has been driven by statistical fit. For amivantamab-chemotherapy, the gamma extrapolation was selected in the base-case. The curve selection is further detailed in section B.3.3.2.3 The progression date is not available from RWE data and clinical experts have highlighted that TTNT is not a valid proxy for PFS. Therefore, a more conservative approach was taken to derive PFS for pembrolizumab-chemotherapy, applying the per cycle HR of TTNT vs BICR-assessed PFS for amivantamab-chemotherapy to the selected TTNT extrapolation of pembrolizumab-chemotherapy. Given PFS data were relatively mature, and the distributions were relatively similar, curve selection was driven by statistical fit. For pembrolizumab-chemotherapy, the log-logistic extrapolation had the best statistical fit for pembrolizumab-chemotherapy TTNT.

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TTDD	TTDD was modelled as independent extrapolations of the TTDD data from each arm of the PAPILLON trial. Within amivantamab-chemotherapy, the TTDD of each component (amivantamab and carboplatin with pemetrexed) was modelled separately. For both amivantamab and carboplatin with pemetrexed, Weibull extrapolations have been selected in the base-case. For chemotherapy, TTDD was modelled as independent extrapolations of the TTDD data from the PAPILLON trial. A gamma extrapolation has been selected in the base-case. For pembrolizumab-chemotherapy, the TTDD was estimated by applying the per cycle HR of amivantamab TTDD vs BICR-assessed PFS to the PFS data.	TTDD was used to estimate the acquisition costs for amivantamab-chemotherapy and carboplatin with pemetrexed to accurately reflect the duration of each treatment in the PAPILLON trial. There was variation in the TTDD of each component of amivantamab-chemotherapy and, as such, TTDDs for amivantamab and chemotherapy within the amivantamab-chemotherapy arm have been modelled separately. Clinical expert opinion has confirmed that this is valid and reflects what would be expected in clinical practice for amivantamab-chemotherapy. For both components of amivantamab-chemotherapy (amivantamab as well as chemotherapy), the Weibull extrapolation was selected in the base-case, and the gamma extrapolation was explored as a scenario. Further detail on curve selection is provided in section B.3.3.2.5 For the chemotherapy arm, the gamma extrapolation was selected in the base-case based on statistical fit and clinical plausibility, as detailed in section B.3.3.2.5 As TTDD was not available from NECTAR, the per cycle HR of TTDD for amivantamab vs PFS for amivantamab-chemotherapy was applied to the selected PFS extrapolation for pembrolizumab-chemotherapy to estimate the TTDD and generate an extrapolation curve.
Comparators and subsequent treatments		
Weighted comparator	A weighted comparator comprising chemotherapy (70%) and pembrolizumab in combination with carboplatin and pemetrexed (30%) was included in the base case.	There is no established SoC in patients with untreated EGFR Exon20 insertion mutation-positive advanced NSCLC in the UK and no single treatment option will be displaced with the introduction of amivantamab in this setting. The two relevant regimens which will be displaced by the introduction of amivantamab-chemotherapy are carboplatin with pemetrexed (chemotherapy) as well as pembrolizumab with

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		carboplatin and pemetrexed (pembrolizumab-chemotherapy). Therefore, a weighted comparator-arm was modelled whereby the individual ICERs of chemotherapy and pembrolizumab-chemotherapy were weighted according to their use in clinical practice. Weightings for each comparator in the base case are based on expert opinion elicited at the advisory board held in May 2024.⁵
Distribution and duration of subsequent treatments	The distribution of subsequent (2L and 3L) treatments have been sourced from the advisory board carried out with UK oncologists held in May 2024.⁵ The median duration of subsequent 2L treatments is based on the PFS seen in RWE (Bazhenova, et al., 2021).¹² The median duration of 3L treatments have been based on literature. Park et al., 2019 has been used as an appropriate reference for the duration of 3L platinum-based chemotherapy, docetaxel, docetaxel with nintedanib, gemcitabine, and vinorelbine.¹³³ Migliorino, et al., 2017 (Nivolumab) has been used as an appropriate reference for the duration of 3L IO + chemotherapy.¹³²	Subsequent therapies used in the model are reflective of UK clinical practice.
Health-related quality of life		
Health state utility values	Health state utility inputs are derived from the EQ-5D-5L QoL questionnaire administered in the PAPILLON trial.	PAPILLON is the only RCT for this indication and is therefore a suitable source for utility values. This aligns with the NICE reference case.
Disutilities	AE-specific utility decrements are applied to any grade 3+ AEs which occur in 5% or more of patients in either arm of the PAPILLON trial.	Disutility values for AEs are informed by prior TAs and modelled to accurately reflect the decrease in utility associated with the treatment.

	AE QALY decrements are applied as a one-off decrement at treatment initiation. Each AE has an associated utility decrement (based on the literature) and a duration (calculated from the PAPILLON trial [for amivantamab-chemotherapy and chemotherapy] or KEYNOTE 189 [for pembrolizumab-chemotherapy]). The AE incidence for each treatment arm is multiplied by the utility decrement and duration of each AE to calculate an overall QALY decrement for each treatment.	The approach to AE disutilities is appropriate given grade 3 and higher AEs are not captured within EQ-5D data. Additionally, the same as the approach taken and accepted in TA850. ¹⁹
Costs		
Dose skipping	Acquisition costs in the model account for dose skipping seen in the PAPILLON trial. Dose skipping percentages were estimated separately for amivantamab, pemetrexed, and carboplatin, calculated by dividing the number of observed doses in the PAPILLON trial by the number of doses expected based on the label, as per SmPC and the time to treatment discontinuation. Dose skipping percentages have also been estimated for pembrolizumab-chemotherapy, based on literature (TA683).	Dose skipping is seen in the PAPILLON trial and reflects what would be expected in clinical practice.
Dose reductions	Acquisition costs in the model account for dose reductions seen in the PAPILLON trial. A RDI value was applied to required number of vials for amivantamab, based on the dose reductions observed in the PAPILLON trial.	Dose reductions are seen in the PAPILLON trial and reflect what would be expected in clinical practice.
Subsequent therapy costs	Subsequent treatment costs are split into 2L and 3L+ costs and are based on a one-off cost applied upon disease progression, based on the distribution of subsequent treatments at each line and the duration of treatment.	The clinical impact of subsequent treatment is assumed to already be captured in the OS curves. Applying a one-off cost for subsequent treatment is appropriate given the short-term duration of subsequent treatments expected in this indication. Additionally, this reflects the approach was taken in TA683 and TA850.^{19, 130}

	Subsequent treatments costs include the cost associated with drug acquisition, administration, and monitoring	

Abbreviations: AE: adverse event; ATT: average effect of the treated; BICR: blinded independent central review; DCO: data cut-off; EG-5D-5L: EuroQol-5 Dimension 5-levels; HR: hazard ratio; HRQoL: health related quality of life; IPCW: inverse probability of censoring weighting; ITC: indirect treatment comparison; NCRAS: National Cancer Registration Analysis Service; OS: overall survival; PFS: progression-free survival; RCT: randomised controlled trial; RDI: relative dose intensity; SmPC: summary of product characteristics; TTDD: time to treatment discontinuation or death; TTNT: time to next treatment.

B.3.10 Base-case results

B.3.10.1 Base-case incremental cost-effectiveness analysis results

A summary of the probabilistic and deterministic base case results for amivantamab-chemotherapy versus the weighted comparator, comprising chemotherapy and pembrolizumab-chemotherapy, at amivantamab PAS price, are presented in Table 85 and Table 86, respectively.

For the weighted approach used for the cost-effectiveness analysis, total costs and total QALYs for both relevant comparators were weighted by the expected proportional use of the technology in UK clinical practice. The distribution of comparators used in the base case analysis is presented in Table 41 and was informed by expert UK clinicians at an advisory board.⁵ This approach provides an overall ICER versus amivantamab-chemotherapy that represents the group of technologies anticipated to be displaced by the introduction of amivantamab-chemotherapy. This approach was taken due to the lack of clear guidance on the management of, and SoC for, patients with untreated EGFR Exon20 insertion mutation-positive advanced NSCLC, as previously described in Section B.1.3.2 and B.3.2.3. As such, evaluating amivantamab-chemotherapy versus the weighted comparator is considered to be the most appropriate form of comparison, given the management of these patients in the UK.

At amivantamab PAS price, amivantamab-chemotherapy was found to be a cost-effective use of NHS resources when compared to the weighted comparator, resulting in probabilistic and deterministic ICERs of £24,049 per QALY and £24,307 per QALY respectively, within NICE's threshold for cost-effectiveness (£20,000–£30,000). These results incorporate the 1.2x severity modifier, calculated in Section B.3.6.

The clinical outcomes and disaggregated base case cost-effectiveness results are presented in Appendix J.

Table 85: Probabilistic base case results for amivantamab-chemotherapy versus relevant comparators at amivantamab PAS price

	Total			Incremental			ICER (£/QALY)
	Costs (£)	QALYs	LYs	Costs	QALYs	LYs	
Amivantamab-chemotherapy	████	██	3.81	█	█	-	£24,049
Weighted comparator ^a	████	██	2.01	████	██	1.80	

^a The weighted comparator used within the base-case comprises 70% chemotherapy (carboplatin with pemetrexed) and 30% pembrolizumab-chemotherapy (pembrolizumab with carboplatin and pemetrexed)

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; QALYs, quality-adjusted life years; SoC: standard of care.

Table 86: Deterministic base case results for amivantamab-chemotherapy versus relevant comparators at amivantamab PAS price

	Total			Incremental			ICER (£/QALY)
	Costs	QALYs	LYs	Costs	QALYs	LYs	
Amivantamab-chemotherapy	████	██	3.76	█	█	-	£24,307
Weighted comparator ^a	████	██	2.00	████	██	1.76	

^a The weighted comparator used within the base-case comprises 70% chemotherapy (carboplatin with pemetrexed) and 30% pembrolizumab-chemotherapy (pembrolizumab with carboplatin and pemetrexed)

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; QALYs, quality-adjusted life years; SoC: standard of care.

B.3.11 Exploring uncertainty

Parameter uncertainty in the model was assessed via both probabilistic and deterministic sensitivity analyses, the results of which are presented in Sections B.3.11.1 and B.3.11.2. Furthermore, key modelling approaches and assumptions were varied in scenario analyses, the results of which are presented in Section B.3.11.3.

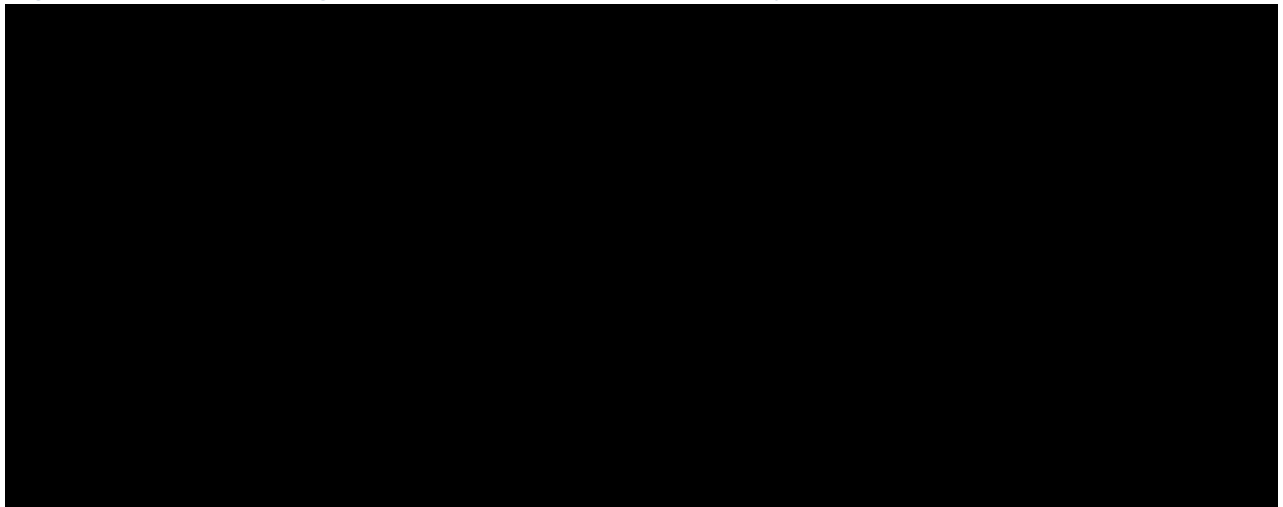
B.3.11.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted in order to assess the simultaneous effect of uncertainty in the different model parameters and to demonstrate whether the model results are robust to those variations. A Monte-Carlo simulation with 500 iterations was performed where model inputs were randomly sampled from the specified probability distributions.

The INHB convergence plot is presented in Figure 49, which incorporates the PAS discount for amivantamab and the 1.2x severity modifier. Additionally, the probabilistic cost-effectiveness plane for amivantamab-chemotherapy versus relevant comparators (amivantamab PAS price, 1.2x severity modifier applied) is presented in Figure 50.

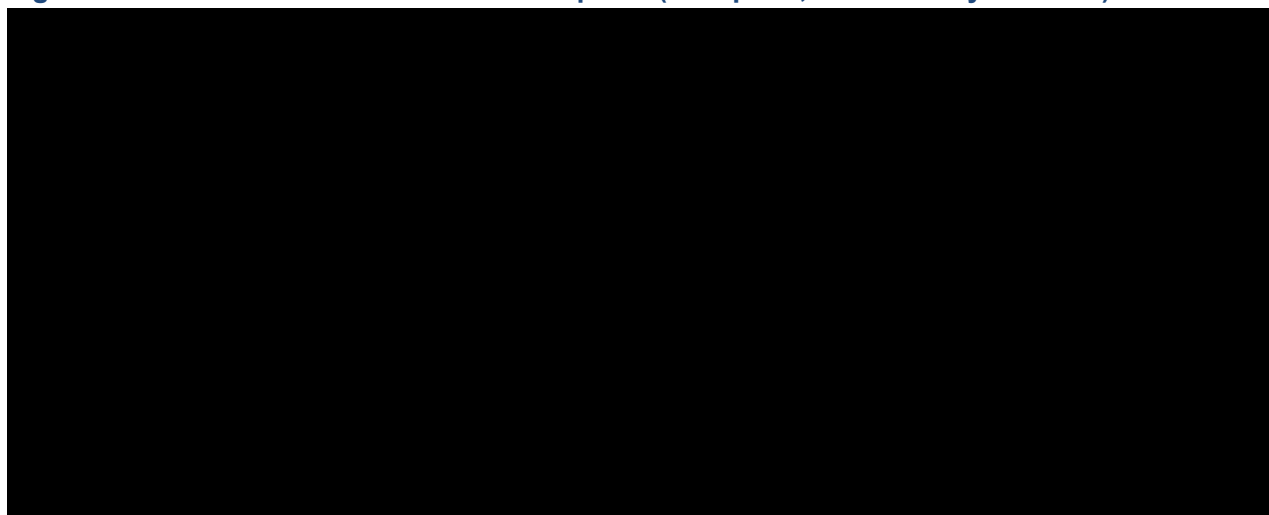
These results indicate that, at a £30,000 WTP threshold, amivantamab-chemotherapy has a superior probability of being cost-effective versus relevant comparators.

Figure 49: INHB convergence plot (PAS price, 1.2x severity modifier)



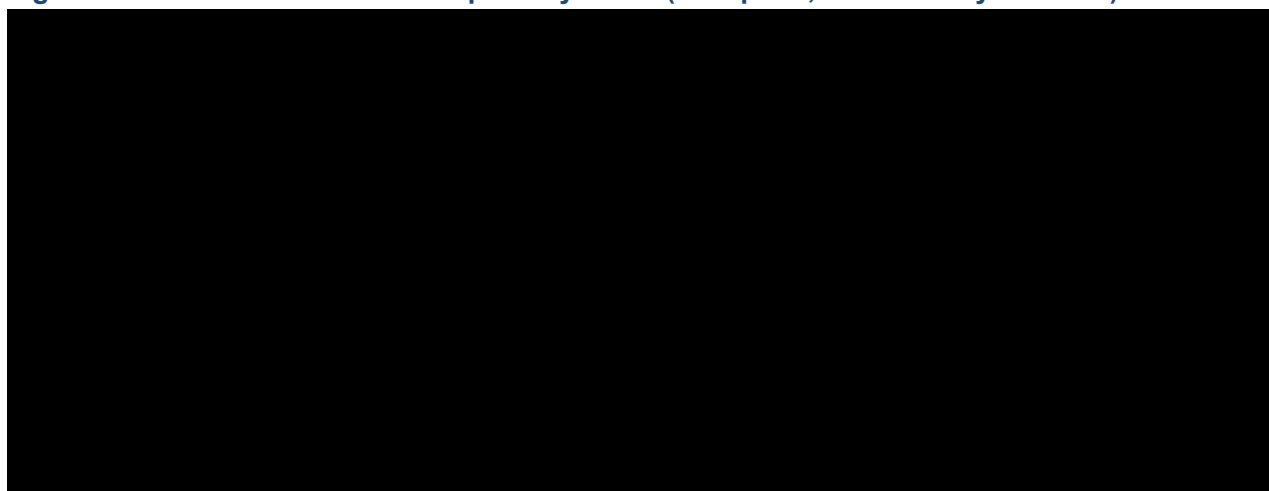
Abbreviations: INHB: incremental net health benefit; PAS; patient access scheme.

Figure 50: Probabilistic cost-effectiveness plane (PAS price, 1.2x severity modifier)



Abbreviations: PAS: patient access scheme; QALY: quality-adjusted life year; WTP: willingness to pay

Figure 51: Cost-effectiveness acceptability curve (PAS price, 1.2x severity modifier)



Abbreviations: PAS: patient access scheme; QALY: quality-adjusted life year.

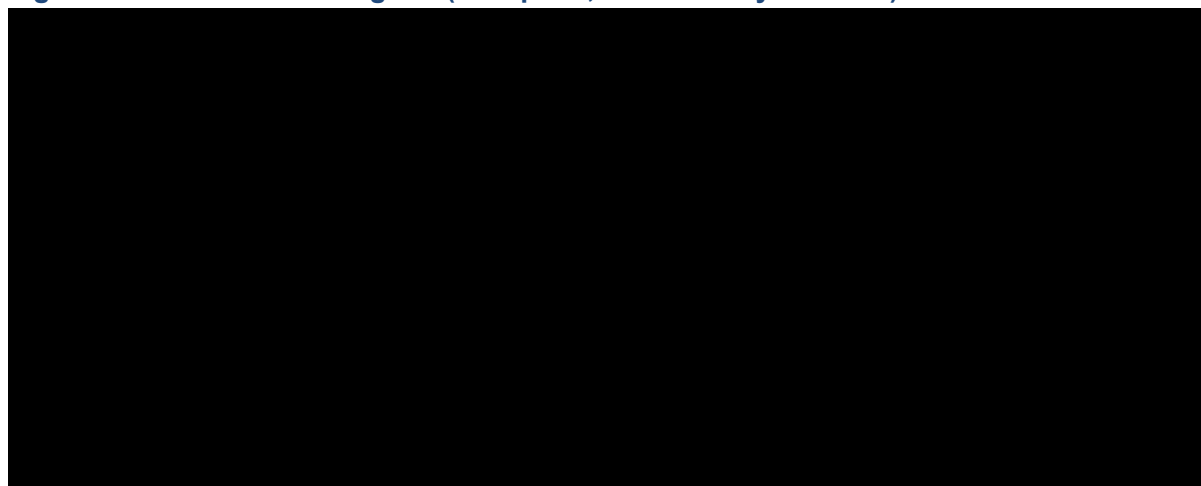
B.3.11.2 Deterministic sensitivity analysis

In order to assess the robustness of the base case cost-effectiveness results, DSAs were conducted by varying the input for each parameter in the model, whilst keeping all other inputs the same.

A tornado diagram showing the top 10 most influential parameters on the ICER for amivantamab-chemotherapy versus relevant comparators is provided in Figure 52. Overall, the parametric extrapolation for OS for amivantamab-chemotherapy is the most influential parameter; the model is otherwise robust to variation in inputs and settings. The tornado diagram illustrates that the parametric function for OS in the amivantamab-chemotherapy arm is the most influential parameter on model results. The limited range in the ICER upon variation of other inputs illustrates the robustness of the model to uncertainty.

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Figure 52: DSA tornado diagram (PAS price, 1.2x severity modifier)



Footnotes: 'p' represent parameters of the survival extrapolations.

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

B.3.11.3 Scenario analysis

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

- Utilising different discount rates
- Exploring alternative survival extrapolations applied to PFS, OS and TTDD for all treatments
- Using TTNT as a proxy for PFS across all treatments
- Utilising alternative approaches for treatment switch adjustment for the chemotherapy treatment arm
- Using differing distributions of comparators in the weighted comparison based on higher usage of pembrolizumab-chemotherapy seen amongst some clinical experts
- Using England specific data from the NCRAS database instead of the pooled data from the NECTAR study to model both efficacy outcomes and alternative distribution of comparator treatments to reflect England clinical practice
- Exploring the inclusion of EGFR testing costs in the model, through the approach suggested in TA850 by multiplying the estimated PCR proportion of testing by the cost of NGS testing.

Probabilistic results for the scenario analyses carried out are presented in Table 87, with deterministic results for the scenario analyses presented in Table 88 for completeness. In all analyses, the resulting ICER remained within the threshold for cost-effectiveness (£20,000–£30,000 per QALY) indicating that the cost-effectiveness of amivantamab-chemotherapy versus relevant comparators remains robust when altering key modelling assumptions and approaches.

Table 87: Summary of scenario analysis results (probabilistic)

Scenario		WITH PAS		
		Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Base case		■	■	24,049
Discount rate				
1	0% costs and effects	■	■	21,956
2	5% costs and effects	■	■	24,945
Treatment switch adjustment method for chemotherapy				
3	TSE with re-censoring	■	■	22,372
4	TSE without re-censoring	■	■	25,537
TTDD parametric extrapolations				
5	Gamma extrapolation for amivantamab and chemotherapy	■	■	25,669
6	Gamma extrapolation for amivantamab; Weibull for chemotherapy	■	■	25,634
7	Weibull extrapolation for amivantamab; gamma for chemotherapy	■	■	24,106
OS parametric extrapolations				
8	Gamma for amivantamab-chemotherapy	■	■	21,447
9	Weibull for chemotherapy (fit to IPCW-adjusted data)	■	■	23,055
PFS parametric extrapolations				
10	TTNT to model PFS	■	■	23,109
Alternative comparator – using NCRAS data				
11	Uses NCRAS data to model comparator efficacy and treatment distribution, using the full dataset ^a	■	■	17,266
12	Uses NCRAS data to model comparator efficacy using the full NCRAS dataset, with costs being calculated for the CP and CP+IO distributions only (removing EGFR TKIs and IO monotherapies) ^b	■	■	25,169
Alternative comparator distributions in the weighted comparison				

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13	90% IO+CP and 10% CP (reflecting insight from some experts in advisory board) ^c	■	■	785
EGFR Exon20 mutation testing costs				
14	EGFR Exon20 insertion mutation testing costs included	■	■	24,397

a. Scenario 11 uses the full NCRAS dataset to model efficacy and the distribution of treatments

b. Scenario 12 uses the full NCRAS dataset to model efficacy data from the full NCRAD dataset but only includes the costs for the distribution of CP (75%) and CP + IO (25%), with the costs of other comparators (EGFR TKIs and IO monotherapies) removed

c. Scenario 13 uses IO + CP data from the NECTAR study and CP data from the PAPILLON trial, as in the base-case, but applies different weightings to these to reflect high usage of IO + chemo which was seen amongst some clinical experts

Abbreviations: BICR: blinded independent central review; EGFR: epidermal growth factor receptor; ICER: incremental cost-effectiveness ratio; ITT: intention to treat; OS: overall survival; PAS: Patient Access Scheme; QALY: quality-adjusted life year; RPSFT: rank preserving structural failure time; TTDD: time to treatment discontinuation or death; TTNT: time to next treatment.

Table 88: Summary of scenario analysis results (deterministic)

Scenario		WITH PAS		
		Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Base case		██████	████	24,307
Discount rate				
1	0% costs and effects	██████	████	22,447
2	5% costs and effects	██████	████	25,116
Treatment switch adjustment method for chemotherapy				
3	TSE with re-censoring	██████	████	22,570
4	TSE without re-censoring	██████	████	25,844
TTDD parametric extrapolations				
5	Gamma extrapolation for amivantamab and chemotherapy	██████	████	25,866
6	Gamma extrapolation for amivantamab; Weibull for chemotherapy	██████	████	25,843
7	Weibull extrapolation for amivantamab; gamma for chemotherapy	██████	████	24,346
OS parametric extrapolations				
8	Gamma for amivantamab-chemotherapy	██████	████	21,943
9	Weibull for chemotherapy (fit to IPCW-adjusted data)	██████	████	23,384
PFS parametric extrapolations				
10	TTNT to model PFS	██████	████	23,358
Alternative comparator – using NCRAS data				
11	Uses NCRAS data to model comparator efficacy and treatment distribution, using the full dataset ^a	██████	████	16,836
12	Uses NCRAS data to model comparator efficacy using the full NCRAS dataset, with costs being calculated for the CP and CP+IO distributions only (removing EGFR TKIs and IO monotherapies) ^b	██████	████	24,636
Alternative comparator distributions in the weighted comparison				

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Scenario		WITH PAS		
		Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
13	90% IO+CP and 10% CP (reflecting insight from some experts in advisory board) ^c	██████	████	1,003
EGFR Exon20 mutation testing costs				
14	EGFR Exon20 insertion mutation testing costs included	██████	████	24,661

^a Scenario 11 uses the full NCRAS dataset to model efficacy and the distribution of treatments

^b Scenario 12 uses the full NCRAS dataset to model efficacy data from the full NCRAD dataset but only includes the costs for the distribution of CP (75%) and CP + IO (25%), with the costs of other comparators (EGFR TKIs and IO monotherapies) removed

^c Scenario 13 uses IO + CP data from the NECTAR study and CP data from the PAPILLON trial, as in the base-case, but applies different weightings to these to reflect high usage of IO + chemo which was seen amongst some clinical experts

Abbreviations: BICR: blinded independent central review; EGFR: epidermal growth factor receptor; ICER: incremental cost-effectiveness ratio; ITT: intention to treat; OS: overall survival; PAS: Patient Access Scheme; QALY: quality-adjusted life year; RPSFT: rank preserving structural failure time; TTDD: time to treatment discontinuation or death; TTNT: time to next treatment.

B.3.12 Subgroup analysis

The PAPILLON trial, which forms the principal clinical evidence base for amivantamab-chemotherapy in this submission, has demonstrated consistent efficacy across all pre-specified endpoints (Section B.2.7).⁷³ Subgroup analyses are not considered necessary and are not considered appropriate given the limited sample size of patients available for analysis in subgroups specified within the NICE final scope (see Table 1). As such, subgroup analyses have not been conducted.

B.3.13 Benefits not captured in the QALY calculation

The economic model presented in this submission captures many of the benefits of amivantamab-chemotherapy compared with current clinical management in the UK. Key benefits include improved PFS and OS versus relevant comparators. A treatment resulting in improved PFS and survival, was identified as a key unmet need by patients with EGFR Exon20 insertion-mutation positive advanced NSCLC during market research conducted by Johnson & Johnson.¹⁴ Furthermore, the economic model results demonstrate that amivantamab-chemotherapy is a cost-effective use of NHS resources, representing good value for money.

However, while the model represents some of the most important aspects of treatment with amivantamab-chemotherapy, there are a number of additional benefits that are not able to be captured in the model.

Amivantamab-chemotherapy is an innovative treatment that will address the lack of targeted treatments currently available in UK clinical practice for EGFR Exon20 insertion mutation-positive advanced NSCLC

As outlined in Section B.1.3.2, there are currently no targeted treatments available in the UK for patients with EGFR Exon20 insertion mutation-positive advanced NSCLC. As confirmed and validated by clinical expert opinion via advisory boards, the EGFR Exon20 insertion mutation induces unique conformational changes in the EGFR protein, which in turn confers *de novo* resistance to EGFR TKIs, as discussed in Section B.1.3.2.1.^{7, 24, 37, 38} Additionally, the lack of targeted treatment options in this patient population was exacerbated by the outcome of the EXCLAIM-2 trial, investigating the safety and efficacy of mobocertinib as a first-line treatment option in patients with EGFR Exon20 insertion mutated NSCLC, which did not meet its primary endpoint.¹⁶

Amivantamab in combination with carboplatin and pemetrexed is an innovative treatment that specifically targets EGFR and MET; as an antibody, amivantamab is able to bind to the extracellular domain of EGFR and is not affected by the conformational changes that affect intracellular TKI binding.³⁹ Results of the PAPILLON trial and the ITC support that amivantamab-chemotherapy is a treatment with superior efficacy versus treatments used in UK clinical practice for an underserved population that currently have no access to targeted treatments and thus face an extremely poor prognosis. The introduction of amivantamab is therefore expected to address the discrepancy in survival currently faced by these patients versus patients with common EGFR mutations, who have a greater range of treatment options available in the first-line setting.^{3, 22, 73}

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In summary, the model does not capture the potential benefit of replacing sub-optimal, limited, generic treatment options with a targeted and effective treatment, which would establish a long sought SoC in this indication.

The impact of societal negative perceptions of lung cancer and the influence on diagnoses is not captured in the QALY calculation

Patients with lung cancer uniquely experience an added burden from developing an illness that the public recognises as directly associated with smoking behaviours, as detailed in B.1.3.1.4.²⁷ This stigma issue is compounded when considering EGFR Exon20 insertion mutations specifically, as these mutations disproportionately affect never-smokers.⁶ This perceived stigma against patients with lung cancer also affects interactions between patients and HCPs, with some patients reporting feeling uncomfortable communicating about their symptoms, which can lead to delays in presentation, diagnosis and treatment.⁶⁹ This perceived stigma therefore may have a direct impact on the timely diagnosis of disease and therefore timely treatment, influencing patient outcomes.

As such, the impact of having a new treatment option available to patients to alleviate this condition should be explicitly considered within the decision-making process, especially as the negative perceptions of lung cancer are not inherently captured within the cost per QALY framework. In addition, stigma is included in the NICE social value judgements principles document.¹³⁷

Wider indirect impacts on patients, caregivers and work productivity

In addition to the results of the economic model which focus on the NHS/PSS perspective, lung cancer (and advanced NSCLC more specifically) is also associated with a substantial indirect economic burden of missed work for patients and carers, and time spent travelling between home and hospital. Although not considered in the presented analysis, the indirect costs displaced by introducing an effective, new treatment like amivantamab should be considered as part of the social value judgement of the treatment. The substantial caregiver burden has been highlighted in market research studies conducted by Johnson & Johnson in 2021 and 2023.¹⁴

Considering these other benefits not being captured within the model, the overall outcomes presented from the CEM are likely to represent a conservative assessment of the overall cost-effectiveness of amivantamab-chemotherapy to the UK NHS.

B.3.14 Validation

B.3.14.1 Validation of cost-effectiveness analysis

Clinical validation

Expert input from UK oncologists was sought during the development of the cost-effectiveness model to ensure that the inputs and assumptions used in the analysis were relevant to UK clinical practice and to validate the clinical plausibility of the outcomes predicted by the model. Feedback was obtained in three advisory boards.^{5, 22, 23}

Expert clinical opinion was sought to validate the following model inputs:

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- The distribution of treatments to be used in the weighted comparator approach, and the feasibility of conducting such a comparison
- The appropriateness of adjusting drug acquisition costs to account for dose reduction and dose skipping
- The proportion and distribution of subsequent treatments
- The most appropriate approach for treatment switch adjustment in the chemotherapy arm
- The most appropriate approach to model PFS, specifically for pembrolizumab-chemotherapy
- Scenario analyses to be explored
- The exclusion of EGFR testing costs in the model

For survival data for amivantamab-chemotherapy and the relevant comparators (chemotherapy and pembrolizumab-chemotherapy) where extrapolation was required, clinical expert opinion on the plausibility of long-term extrapolations was sought, and subsequently considered alongside a combination of statistical goodness of fit criteria and visual inspection when determining the most appropriate selections, as detailed in Section B.3.3.2.

Where available, validation of model outcomes was performed against external data. For example, the long-term extrapolation used in the base case for amivantamab-chemotherapy OS (Weibull) can also be justified by considering long-term data available from the CHRYSALIS trial (Garrido Lopez et al. 2023) for amivantamab monotherapy following progression on chemotherapy as second line treatment, which demonstrates that some patients may experience survival benefits of amivantamab in the long-term, thereby justifying the presence of the ‘tail’ observed for the Weibull extrapolation.⁴³

Technical validation

The model was developed in accordance with ‘Modeling Good Research Practices’ disseminated by the International Society of Pharmacoeconomics and Outcomes Research and the Society for Medical Decision Making (ISPOR-SMDM).¹⁰⁶

An advisory board was held with health economic experts to gain insights and advice regarding the most appropriate assumptions and inputs to consider for the CEM. In total, advice was sought from four health economic experts and feedback was taken into account when developing the CEM for this submission where possible.

B.3.15 Interpretation and conclusions of economic evidence

Advanced NSCLC is a life-limiting disease that has a substantial impact on both patient and caregiver quality of life, negatively affecting both physical and psychosocial health.^{53, 65}

Additionally, patients with EGFR Exon20 insertion mutation-positive advanced NSCLC have a particularly poor prognosis, being worse than those with common EGFR mutations.⁶⁴ This poor prognosis is largely attributed to the lack of approved targeted efficacious treatments for this patient population in the UK, with no SoC or treatment pathway established in current clinical practice.

The lack of a SoC for these patients in clinical practice is evidenced by comprehensive clinical opinion sought by Johnson & Johnson across multiple advisory boards, and RWE, available from

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the NECTAR study and England-specific NCRAS database.^{3, 5, 22} Based on the available evidence, amivantamab-chemotherapy was compared to chemotherapy and pembrolizumab-chemotherapy, considering these treatments as a weighted group of comparators which are anticipated to be displaced upon the introduction of amivantamab-chemotherapy in UK clinical practice.

Clinical evidence for amivantamab-chemotherapy and chemotherapy was informed by the randomised, multicentre Phase 3 PAPILLON trial. In order to ensure outcomes for patients in the chemotherapy arm were aligned with those expected in UK clinical practice, treatment switch adjustment was performed for the chemotherapy arm to account for treatment switching from chemotherapy to amivantamab monotherapy, which was permitted upon BICR-confirmed disease progression.⁷⁹

- The face validity of the treatment switch approach selected in the base-case (IPCW) has been shown given the median OS (██████████) of IPCW-adjusted chemotherapy data from the PAPILLON trial closely align with the median OS (██████████) observed in the ATT-adjusted chemotherapy results from the NECTAR study (which provides long-term RWE data on the survival of patients receiving first-line platinum-chemotherapy, which is not confounded by subsequent amivantamab given it is not available). Further, the OS HR (██████████) calculated following IPCW adjustment of chemotherapy data from PAPILLON closely aligns with the OS HR (██████████) of the ATT-adjusted ITC of amivantamab-chemotherapy from PAPILLON with chemotherapy data from NECTAR.
- The robustness of results is further demonstrated through scenarios 11 and 12 in the Scenario Analyses, with the estimated LYs of the IPCW-adjusted CP OS (1.96) being similar to what is observed in the NCRAS dataset (1.88). This demonstrates the IPCW-adjusted CP OS results are similar to what is seen within a UK population and further demonstrates the robustness of the RWE in both NCRAS and NECTAR through the similar survival seen in both the IPCW-adjusted PAPILLON comparator arm and the real world data.

In the absence of direct evidence for pembrolizumab-chemotherapy, RWE from four systematically identified databases: NCRAS (UK), ESME (France), COTA (US) and ConcertAI (US) were pooled and ITCs were performed as part of the NECTAR study, to investigate the efficacy of amivantamab-chemotherapy versus this treatment. The pembrolizumab-chemotherapy patient population was ATT-weighted to ensure key characteristics were aligned with the amivantamab-chemotherapy arm of the PAPILLON trial.³ Overall, the clinical evidence from PAPILLON and the ITC illustrate the superior efficacy offered by amivantamab-chemotherapy compared to current treatments used in the UK for patients with EGFR Exon20 insertion mutation-positive advanced NSCLC.

The results from the ITC versus pembrolizumab-chemotherapy were further supported by the similarity between the OS HR of chemotherapy from the PAPILLON trial (direct comparison after IPCW-adjustment) and the OS HR of chemotherapy from the NECTAR study (ITC after ATT-weighting). These insights reassure that the results seen in the ITC versus pembrolizumab-chemotherapy can be seen as robust. The ITC versus chemotherapy from the NECTAR study (ITC after ATT-weighting) is further described in section B.3.3.2.1.

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The economic model results demonstrate that amivantamab-chemotherapy is a cost-effective use of NHS resources versus relevant comparators (chemotherapy versus pembrolizumab-chemotherapy) with a probabilistic base case ICER of £24,049 per QALY versus the weighted comparator. Importantly, all scenario analyses conducted remained cost-effective when considering the cost-effectiveness threshold of £20,000–£30,000 per QALY, illustrating the robustness of the model to variation in inputs, and further supporting the cost-effectiveness of amivantamab-chemotherapy to the NHS. The robustness of model results is also supported by the comprehensive validation of key modelling approaches and assumptions described above, considering feedback from clinical and health economist experts and best practice guidance available from ISPOR and the NICE DSU. Finally, through the QALY shortfall analysis, amivantamab-chemotherapy is shown to be eligible for the 1.2x severity modifier, thereby demonstrating the high unmet need faced by patients with EGFR Exon20 insertion mutation-positive advanced NSCLC.

Patients with EGFR Exon20 insertion-mutation positive advanced NSCLC face an extremely poor prognosis in the absence of targeted and efficacious treatment options available via the NHS. As confirmed by UK clinical experts, in the absence of an established SoC, patients in clinical practice receive non-targeted and often expensive treatments that do not address the need for prolonged PFS and OS, as identified by market research conducted by Johnson & Johnson and clinical opinion received in advisory boards. Upon the anticipated introduction of amivantamab-chemotherapy in UK clinical practice, the discrepancy in survival observed between patients with EGFR Exon20 insertion mutated advanced NSCLC and common EGFR mutations is expected to be addressed, in addition to a much-needed disease management pathway being introduced into UK clinical practice.

B.3.15.1 Strengths and limitations of the evidence base

Internal and external validity

The clinical evidence presented as part of the submission has been derived from an SLR that was conducted in accordance with the high-quality standards required by NICE as well as standards set forth in other established guidelines, including PRISMA and the Cochrane handbook. The clinical SLR identified the pivotal clinical trial, PAPILLON, as the primary evidence source for amivantamab in combination with carboplatin and pemetrexed in the population of interest to this submission: adult patients with untreated EGFR Exon20 insertion mutation-positive advanced NSCLC. The results of the quality assessment of the PAPILLON trial demonstrated that it is a methodologically robust and well-reported trial, with results considered to be of low risk of bias in the majority of categories (Table 11).

The PAPILLON trial is a registrational Phase 3 randomised trial providing a direct treatment comparison of amivantamab in combination with chemotherapy to one of the relevant comparators used in clinical practice, chemotherapy, through the control arm of the trial. Additionally, the PAPILLON trial includes a large number of patients (N=308 patients randomised) in the specific patient population relevant to this submission. As a result, this increases the generalisability of the PAPILLON trial to patients with EGFR Exon20 insertion mutation-positive advanced NSCLC in clinical practice. The PAPILLON trial considered a wide range of endpoints (PFS, ORR, DOR, OS, TTST, PFS2 and TTSP) that are all clinically relevant to patients with untreated EGFR Exon20 insertion mutation-positive advanced NSCLC and reflect outcomes assessed in prior appraisals of therapies within both EGFR mutation-positive and wild-type advanced NSCLC.^{17, 19}

Limitations

The SLR did not identify any studies directly comparing amivantamab-chemotherapy versus pembrolizumab-chemotherapy in the population of relevance to this submission. Therefore, an ITC was required to estimate the comparative efficacy of amivantamab-chemotherapy versus pembrolizumab-chemotherapy. Pooled RWE from the NCRAS (England), ESME (France), COTA (US) and ConcertAI (US) databases was used to inform the clinical efficacy for pembrolizumab-chemotherapy. Specifically, the efficacy of pembrolizumab-chemotherapy was informed by patients in the NECTAR pooled RWE who received pembrolizumab in combination with a range of platinum-based chemotherapy regimens to achieve a sufficient sample size for analysis. This was considered a reasonable assumption to maximise sample size. Population weighting was used for the comparison between amivantamab-chemotherapy and platinum chemotherapy-IO to ensure baseline characteristics were balanced. While there are inherent limitations associated with the use of ITCs and RWE, as outlined in Section B.2.9.6, the ITC results demonstrated consistent and promising results indicating the improved efficacy of amivantamab-chemotherapy versus pembrolizumab-chemotherapy.

OS data from the PAPILLON trial was immature with median OS not reached in the amivantamab-chemotherapy arm at either the 3rd May 2023 or additional 31st October 2023 DCO. However, median OS was reached in the chemotherapy arm (at the 31st October 2023 DCO: 28.6 months [95% CI: 24.4-NE]) indirectly supporting the improved efficacy of amivantamab-chemotherapy in prolonging patients' lives. As expanded on below, the comparative efficacy results for amivantamab-chemotherapy versus chemotherapy observed at

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the 31st October 2023 DCO can be considered highly conservative, due to the confounding introduced by treatment switching from the chemotherapy treatment arm to amivantamab monotherapy following BICR-confirmed disease progression. Despite this, a strong trend towards improved survival was observed in patients receiving amivantamab-chemotherapy versus chemotherapy, with splitting and widening of the KM curves observed (Figure 10 and Figure 11). These results are supported by the promising depths and durations of response observed for the amivantamab-chemotherapy treatment arm versus the chemotherapy treatment arm. For example, patients in the amivantamab-chemotherapy arm experienced an ORR of 73.0% versus 47.4% in the chemotherapy arm, which is expected to translate into a survival benefit for patients in the amivantamab-chemotherapy arm.⁷³

The impact of treatment switching is expected to be substantial, given that, at the 31st October 2023 DCO, 78/█ (█%) patients in the chemotherapy-arm had received subsequent amivantamab monotherapy after BICR confirmed disease progression.⁷⁶ Given that treatment with amivantamab monotherapy is not currently recommended in UK clinical practice for patients with EGFR Exon20 insertion mutated advanced NSCLC who have progressed following first-line therapy, the chemotherapy OS data was adjusted for treatment switching in line with methods included in NICE DSU TSDs 16 and 24.^{81, 117}

The treatment switching methods explored included TSE, RPSFT and IPCW, with further detail on these methods presented in Section B.3.3.2.1. The IPCW method, which was used in the base case analysis, was selected based on validation of core assumptions associated with each methodology, health economist input and face validity of the resulting OS estimates, when compared with the results of the ITC for amivantamab-chemotherapy versus chemotherapy, which is presented as supplementary evidence.⁷³ Following adjustment via IPCW, a clear survival benefit was observed for amivantamab-chemotherapy versus chemotherapy, with clear separation of the OS KM curves explored and an improved OS HR (█ [95% CI: █-█; p=█]) observed. As such, the adjusted OS results demonstrate that amivantamab-chemotherapy would be a valuable treatment option in UK clinical practice given the survival benefit imparted on treated patients with EGFR Exon20 insertion mutation-positive advanced NSCLC, who otherwise face an extremely poor prognosis on currently used treatments.

The OS benefit observed in the PAPILLON trial is reinforced by results from the IT) between amivantamab-chemotherapy (from PAPILLON) versus chemotherapy (from the NECTAR study) using ATT-weighting of individual patient level data, which estimated an OS HR of █ Median OS (█) of chemotherapy in PAPILLON (following adjustment for cross-over), has high face validity as closely aligns with median OS (█) of chemotherapy in RWE (after ATT-weighting).

The results from the ITC vs pembrolizumab-chemotherapy can be considered robust and reassuring given the similarity between the OS HR of amivantamab-chemotherapy vs chemotherapy from the PAPILLON trial (direct comparison after IPCW-adjustment for subsequent amivantamab monotherapy) and the OS HR of amivantamab-chemotherapy vs chemotherapy from the NECTAR study (ITC after ATT-weighting of RWE data). This is further described in section B.3.3.2.1.

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Conclusions

The registrational Phase 3 PAPILLON trial is a robust and well-reported trial, with the results demonstrating that amivantamab-chemotherapy achieves higher, more durable response rates and prolongs the time until disease progression compared with chemotherapy in adult patients with EGFR Exon20 insertion mutation-positive advanced NSCLC. Such benefits are expected to translate to survival benefits in patients treated with amivantamab-chemotherapy versus currently used treatments, supported by the treatment switch adjusted OS data for amivantamab-chemotherapy versus chemotherapy, and the supportive results from the NECTAR study.³ Furthermore, amivantamab-chemotherapy has a tolerable and manageable safety profile, with the safety profiles consistent with the individual treatment components. Pembrolizumab-chemotherapy also represents a relevant comparator in UK clinical practice, and results of the ITC, utilising data from the NECTAR study, consistently demonstrate the superior efficacy of amivantamab-chemotherapy versus this treatment in terms of OS and TTNT.³

The cost-effectiveness analysis demonstrates that amivantamab-chemotherapy represents value for money for the NHS. A positive NICE recommendation for amivantamab-chemotherapy will prevent the need for underserved patients with EGFR Exon20 insertion-mutation positive advanced NSCLC in the UK to use non-targeted, sub-optimal treatments, which contribute to the poorer outcomes these patients face versus individuals with more common EGFR mutated NSCLC. In conclusion, amivantamab-chemotherapy is anticipated to fulfil the substantial unmet need for a targeted treatment option in patients with EGFR Exon20 insertion mutation-positive advanced NSCLC, for whom no such options currently exist in UK clinical practice, whilst representing a cost-effective use of NHS resources.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Summary of Information for Patients (SIP)

September 2024

Template version	Date amended	Changes since previous version
2.0	Dec 2023	Clarifications made to guidance notes in section 3i regarding inclusion of statements on cost effectiveness.

File name	Version	Contains confidential information	Date
ID5110_Amivantamab in Econ20 NSCLC_SIP_12Sept24	1.0	No	12 th September 2024

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the [Health Technology Assessment International – Patient & Citizens Involvement Group](#) (HTAi PCIG). Information about the development is available in an open-access [IJTAHC journal article](#)

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Amivantamab (Rybrevant®)

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

To receive this treatment, patients must be 18 years or older and have non-small cell lung cancer (NSCLC) in the advanced setting. NSCLC is a common type of lung cancer and advanced NSCLC means the cancer has spread from the lung and is difficult to cure or control.¹ Patients must also have a specific mutation (a type of change in the DNA of the cells) called an epidermal growth factor receptor (EGFR) Exon20 insertion mutation and this must be the first treatment patients receive in the advanced setting.¹ In this patient population, amivantamab is given in combination with carboplatin and pemetrexed (a form of chemotherapy).

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

The Medicines and Healthcare products Regulatory Agency (MHRA) granted approval (marketing authorisation) for amivantamab in combination with carboplatin and pemetrexed on the 15th July 2024. This shows that the medicine has been tested and deemed effective with acceptable safety.²

Amivantamab is indicated:

- in combination with carboplatin and pemetrexed for the first-line treatment of adult patients with advanced non-small cell lung cancer with activating epidermal growth factor receptor Exon 20 insertion mutations.

The link to the MHRA approval is here:

<https://mhraproducts4853.blob.core.windows.net/docs/25163952a8714ce40eae4ecfa6ccff74e74677a7>

The link to the Great Britain SMPC is here:³

<https://www.medicines.org.uk/emc/product/13084/smpc#gref>.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

The collaborations with patient groups relevant to amivantamab is detailed in Table 1.		
Table 1: Engagement and financial support provided to patient groups		
Patient Group	Engagement/Activity (correct as of 12/09/24)	Financial Support Provided
EGFR Positive UK	Grant towards the refresh of their website	£3508 (2024)
	Grant to support the design, development, and running of two day-long patient information events	£8800 (2023)
	Grant to cover two of their membership events which provide information and support to patients	£5000 (2022)
	Fees for involvement in a Janssen Oncology event	£270 (2022)
	Travel costs for involvement in a Janssen Oncology event	£115 (2022)
Roy Castle Lung Cancer Foundation	Grant for the 'Let go of the labels' Campaign provided by Johnson and Johnson Innovative Medicine	£20,000 (2024)
	Sponsorship towards the 'Be Unforgettable' lung cancer awareness campaign	£5000 (2023)
	Fee for participation in a Lung Cancer Working Group	£600 (2023)
	Grant to understand the needs of lung cancer patients and adapt their information and resource	£24,000 (2022)
	Core funding support for their information and advocacy services for people living with lung cancer	£15,000 (2021)
	Consultancy fee to support the development of a value story	£60 (2021)
	Core funding to help support their Ask the Nurse helpline for people living with lung cancer	£25,000 (2021)
	Fee for participation in an advisory board	£240 (2021)
	Core funding support towards their information and support services for people living with lung cancer	£7000 (2020)
	Fee for participation in two advisory boards	£300 (2020)
	Fee for advocates reviewing a NICE patient-centric submission	£960 (2020)
Macmillan Cancer Support	Core funding towards their genomics information and support for people living with cancer	£20,000 (2021)
	Core funding to help deliver online information and support for people living with cancer	£10,000 (2020)
Asthma and Lung UK	Grant to support the work of the Taskforce for Lung Health	£10,000 (2024)
	Grant to support the work of the Taskforce for Lung Health	£10,000 (2023)
	Grant to support the work of the Taskforce for Lung Health	£10,000 (2022)
Cancer52	Fee to chair a Janssen meeting plus expenses for travel and accommodation (£654.40) and conference pass (£135)	£765 (2023)
	Sponsorship of Cancer 52's Corporate Supporter Programme	£10,000 (2023)

	Grant to support delivery of their core activities	£10,000 (2022)
	Funding towards their core activity	£9000 (2021)

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Overview of Condition

NSCLC is the most common type of lung cancer, accounting for about 85% of all cases.⁴ It is categorised based on changes in the tumour, with one type of change being an EGFR mutation, which happens in about 10% of all advanced NSCLC.⁵ Across Europe, around 0.3%-1.3% of patients with NSCLC have a specific type of EGFR mutation called an Exon20 insertion mutation.^{6, 7 8}

Patients living with EGFR Exon20 insertion mutations have very poor outcomes. Compared to patients with more common EGFR mutations, their survival is a lot worse.⁹ The poor survival rate is shown in real world data (data collected from patients outside a clinical trial, within normal clinical practice), with this patient population typically living for only 16.2 months compared to 25.5 months for patients with more common EGFR mutations.¹⁰

Impact on Patients and Carers Quality of Life

Patients with EGFR Exon20 insertion mutation-positive advanced NSCLC experience symptoms that impact their quality of life. They may feel tired all the time, have pain in their bones, struggle with constipation and feeling sick, and get recurring and constant infections. They might also have problems with their skin and eyes, have trouble thinking clearly, and find it difficult to concentrate. As well as the physical impact, there is also a negative impact on their mental health and emotional wellbeing which impacts their quality of life. This includes anxiety around the results of the next scan, the mental load of planning life around NSCLC, the lack of hope for the future and losing their sense of identity/self-esteem.¹¹

There is also an impact on caregivers/supporters of patients with EGFR mutated NSCLC, as 94% of caregivers also experience an impact of their quality of life, having both an emotional impact and affecting their ability to participate in everyday life.¹²

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

Diagnosis of the condition

In most cases, lung cancer is detected when it has already reached an advanced stage with about half of patients in England and Wales being diagnosed with NSCLC in the advanced stage.¹³ To determine if someone has lung cancer, doctors can use different tests. These tests include:¹⁴

1. A chest X-ray: A scan which uses X-rays to take a picture of the chest to check for any abnormalities in the lungs.
2. Computed tomography (CT) scan: This type of scan uses X-rays and a computer to create detailed pictures of the inside of the body. It can provide a more thorough view of the lungs than a chest X-ray.

3. Magnetic Resonance Imaging (MRI) scan: Like a CT scan, an MRI scan also creates detailed images of the lungs using powerful magnets and radio waves.
4. Bronchoscopy: During this procedure, a thin, flexible tube with a camera on the end is inserted through the nose or mouth and into the lungs. It allows doctors to examine the airways and collect samples if needed.
5. Ultrasound scan: This involves using high-frequency sound waves to create images of the lungs. It helps doctors identify any abnormalities or areas of concern.
6. Biopsies: A biopsy involves taking a small sample of lung tissue to be examined under a microscope. This helps determine if cancer is present and provides essential information about its type and stage.

Genomic testing

Patients will also undergo genomic testing. This test looks for specific changes in the genes and it helps doctors to guide appropriate treatment options.

There are two types of specialised genomic tests that can find out if a person has the specific EGFR mutation. These tests are called polymerase chain reaction (PCR) and next-generation sequencing (NGS):

1. PCR: This test looks for a specific gene mutation by making copies of the genetic material and examining it. It helps determine if a person has an EGFR mutation in their DNA.
2. NGS: This test looks at a person's DNA in more detail and can identify multiple gene mutations at once. It is a more comprehensive and accurate way to find specific genomic changes, like the EGFR mutation. NGS is considered the more accurate and most appropriate method of testing and therefore is predominately used.

This testing is important for deciding the best treatment for patients with lung cancer. With the introduction of amivantamab in combination with carboplatin and pemetrexed, there is no need for additional diagnostic tests as the testing is already part of routine lung cancer care in the UK.¹⁵

2c) Current treatment options:

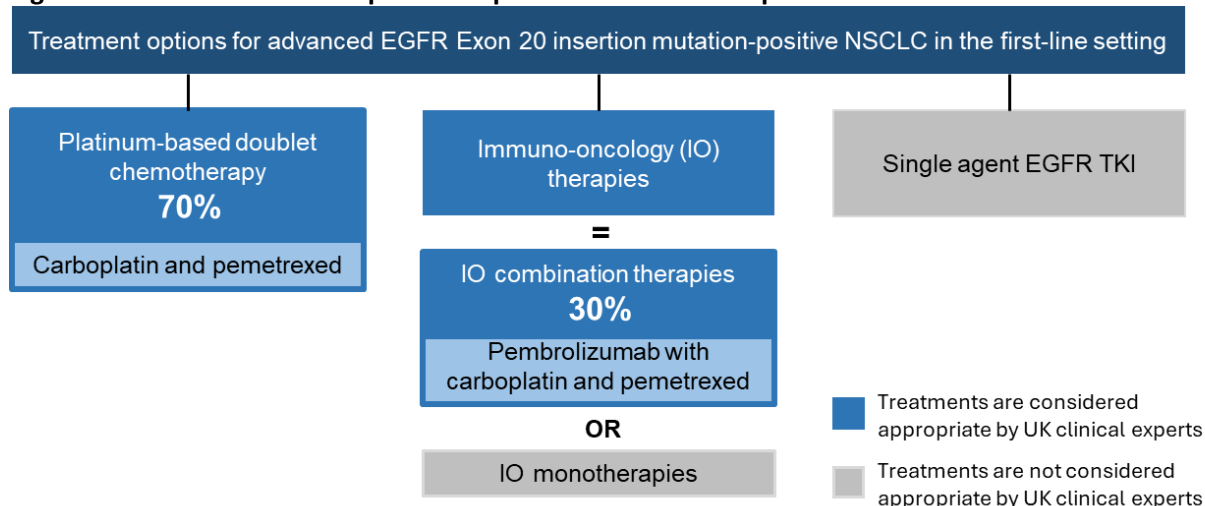
The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
 - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
 - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

The goal of treatment in advanced NSCLC is to delay the disease getting worse, increase survival and to maintain quality of life. For patients with EGFR Exon20 insertion mutation-positive advanced NSCLC there are no UK-specific treatment guidelines published by the National Institute of Health and Care Excellence (NICE) and no targeted therapies (treatments which specifically target cancers associated with a particular mutation) are recommended or reimbursed (available on the NHS).¹⁶

Unfortunately, patients with EGFR Exon20 insertion mutations do not respond to treatments which work for “common” EGFR mutations – a different type of EGFR mutation for which there are targeted treatments available on the NHS.^{10, 17-19} For this reason, these patients are generally treated in a similar way to those without a mutation. The types of treatment that patients with EGFR Exon20 insertions mutations currently receive are shown in Figure 1.

Figure 1: Current treatment options for patients in UK clinical practice



As Figure 1 shows, most patients with EGFR Exon20 insertion mutation-positive advanced NSCLC receive a form of platinum-based chemotherapy. Chemotherapy uses anti-cancer drugs to destroy cancer cells and platinum-based chemotherapy (in the form of carboplatin and pemetrexed) is a common treatment used for many cancers. Patients may also receive an immuno-oncology (IO) combination therapy. IO therapies are treatments that help the body's own immune system fight against the cancer, and this is given in the form of pembrolizumab in combination with carboplatin and pemetrexed. Both these treatments however, do not work well in this patient population as explained in section 2a, meaning there is an unprecedented high unmet need for new treatments.¹⁰

Advisory boards conducted with UK Oncologists confirmed that carboplatin and pemetrexed is given to approximately 70% of patients and around 30% would receive pembrolizumab with carboplatin and pemetrexed. UK Oncologists highlighted that there is limited to no use of IO monotherapy or EGFR TKIs and that using these treatments in this population is against best-practice, as such, these treatments should not be considered as comparators in this appraisal.²⁰

As there are no UK specific guidelines or recommended treatments for this patient population, there is no clearly defined standard of care, with treatment differing across different centres, and the split between treatments varying. Some experts state the use of pembrolizumab with carboplatin and pemetrexed could be as high as 80-90%.²⁰²¹

Contraindications and drug-drug interactions

No drug-drug interaction studies have been performed for amivantamab but the way amivantamab works should not interfere with how other medications work or how they are broken down in the body.³

Contraindications include hypersensitivity to the active substance or to any of the excipients listed below:

- Ethylenediaminetetraacetic acid (EDTA) disodium salt dihydrate
- L-Histidine
- L-Histidine hydrochloride monohydrate
- L-Methionine
- Polysorbate 80
- Sucrose
- Water for injection

2d) Patient-based evidence (PBE) about living with the condition

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

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Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

The physical and emotional challenges faced by patients with EGFR Exon20 insertion mutation-positive advanced NSCLC and their caregivers were explored in a Johnson & Johnson funded patient led research in 2023 via in depth interviews (n=6) and online surveys (n=3).¹¹

Emotional Impact

All patients in the online survey reported an overall negative impact on their mental health/emotional wellbeing and the highest contributors were anxiety around the results of next scans, the mental load of planning life around NSCLC, the lack of hope for the future and losing their sense of identity/self-esteem. The in-depth interviews stated patients live in a constant state of general anxiety, stress and worry which was heightened around the time of scans. Stress and anxiety were cited as having the biggest impact of NSCLC or its treatment on quality of life.

Physical Impact

Both the online surveys and in-depth interviews showed that treatments impact the ability to carry out patients' usual day-to-day activities. Their treatment often results in a reduction in social activities, travel, everyday activities and exercise, as well as loss of relationships, independence and identity.

Side effects

The research also suggested side effects of current treatments have a negative impact on quality of life. Fatigue was a common symptom which had a negative impact on quality life, as well as skeletal pain, constipation, feeling sick, recurring and ongoing infections, skin and eye symptoms, brain fog and lack of concentration. Breathlessness was also noted as a symptom in the in-depth interviews.

Additional patient-based evidence

A Johnson & Johnson study investigating the impact of a broader EGFR mutated NSCLC population (including patients with "common EGFR" mutations) on quality of life and experiences of stigma was conducted in 2021. This also found the physical and emotional impact had a negative impact on the quality of life of the patients. The physical symptoms included fatigue, coughing, choking, wheezing, breathlessness and pain, with 72% of patients' activity being limited by lung cancer. There was also an emotional burden, with the fear of death, fear of disease progression and the loss of interest in living all contributing to worsening of quality of life. Additionally, 75% of patients felt sad and anxious or worried, and 53% felt fearful.¹²

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

How amivantamab works

Amivantamab is a type of treatment called a bispecific antibody. This means it targets two proteins that are present on cancer cells, one is called EGFR and the other is mesenchymal epithelial transition (MET). Amivantamab works in three different ways: ^{3, 22, 23}

- 1) It blocks certain substances that make cancer grow and advance.
- 2) It helps remove receptors that are already present in the body, which further reduces the growth of cancer cells.
- 3) It works with the immune system to identify and help destroy cancer cells within EGFR.

Amivantamab is not chemotherapy, but works with it:

- Chemotherapy is a key part of the treatment that stops cancer cells from dividing and growing.
- Amivantamab and chemotherapy are effective together because they destroy cancer cells in different ways.

Innovation

Amivantamab is innovative as described above in the way amivantamab works, as it is the first approved targeted therapy specifically designed to improve outcomes for adult patients with EGFR Exon20 insertion mutation-positive advanced NSCLC.²⁴ There are no other targeted therapies available on the NHS for this group of patients. Therefore, if reimbursed, amivantamab would provide hope for patients and their caregivers as it would be the first targeted treatment available as a first-line option.

The SMPC for amivantamab can be found here:

<https://www.medicines.org.uk/emc/product/13084/smpc#about-medicine>

The Patient Information leaflet can be found here:

<https://www.medicines.org.uk/emc/product/13084/pil#about-medicine>

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Yes, amivantamab is given in combination with carboplatin and pemetrexed (referred to here onwards as amivantamab-chemotherapy) in this indication.

Carboplatin is a type of chemotherapy and works by sticking to one of the cancer cell's DNA strands. DNA is the genetic code that is in the nucleus of all cells, and it controls everything the cell does. The cell cannot then grow and divide into new cells. The most common side effects from carboplatin (which occur in more than 10% of people) include: increased risk of getting an infection, breathlessness and looking pale, bruising, bleeding gums and nosebleeds, feeling or being sick, changes to how your liver works, kidney damage, tummy cramps and pain and low level of minerals in blood.²⁵

Pemetrexed is a type of chemotherapy, known as an anti-metabolite. It stops cancer cells making and repairing DNA so they can't grow and multiply. The most common side effects from pemetrexed include an increased risk of getting an infection, breathlessness and looking pale, diarrhoea or constipation, feeling or being sick, mouth sores and ulcers, loss of appetite, fatigue, skin problems, numbness or tingling in fingers or toes, kidney damage or sore throat.²⁶

Carboplatin and pemetrexed (referred to here onwards as chemotherapy) is one of the most common treatments in current clinical practice for this group of patients, as described in section 2c.

Amivantamab-chemotherapy is effective together because they destroy cancer cells in different ways. The effectiveness has been demonstrated in the randomised controlled trial PAPILLON, which is further described in Section 3d.²⁴

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Amivantamab is given to patients through a vein using a drip called an intravenous (IV) infusion. This means that it is given in a hospital setting like carboplatin and pemetrexed which are also given as an IV infusion. The combination therapy is given on a 21 day cycle and the impact of this for patients is explained below.³

The dosing schedule for amivantamab depends on a patient's weight. For patients who weigh less than 80kg, amivantamab is given as follows:

- The first infusion is split between Day 1 (350mg) and Day 2 (1050mg) of week 1. This is to allow the patient to tolerate the treatment and reduce the risk of infusion-related reactions (IRRs, which is one of the very common adverse events associated with treatment with amivantamab detailed in Section 3g).
- During weeks 2 to 4, the patient will be given 1400mg once weekly.
- From week 7 onwards, the patient will be given 1750mg of amivantamab every three weeks.

For patients weighing 80kg or more, amivantamab is given in a similar way, although the dose will change:

- The first infusion is split between Day 1 (350mg) and Day 2 (1400mg) of week 1, also to allow the patient to tolerate the treatment and reduce the risk of IRRs.
- During weeks 2 to 4, the patient will be given 1750mg once weekly.
- From week 7 onwards, the patient will be given 2100mg of amivantamab every three weeks.

The change in dosing between the different weeks is to allow for amivantamab to be given on a 3-week cycle together with carboplatin and pemetrexed to avoid too many hospital visits. All patients will receive pemetrexed and carboplatin first, followed by amivantamab. Based on the dosing schedule, patients need to go to the hospital more frequently during the first three weeks of treatment but starting from week 4, the visits to hospital reduce and will be the same as for pemetrexed.

Pemetrexed is given as an IV 500mg/m² on day 1 of each 21-day cycle (week 1, 4 and 7 onwards). Carboplatin IV is given area under the concentration-time curve 5 mg/mL per minute (AUC5) on day 1 of cycles 1-4 and is then stopped. Amivantamab-chemotherapy is given until there is evidence of the cancer getting worse, which is referred to as disease progression, which will be determined by a healthcare professional (HCP).

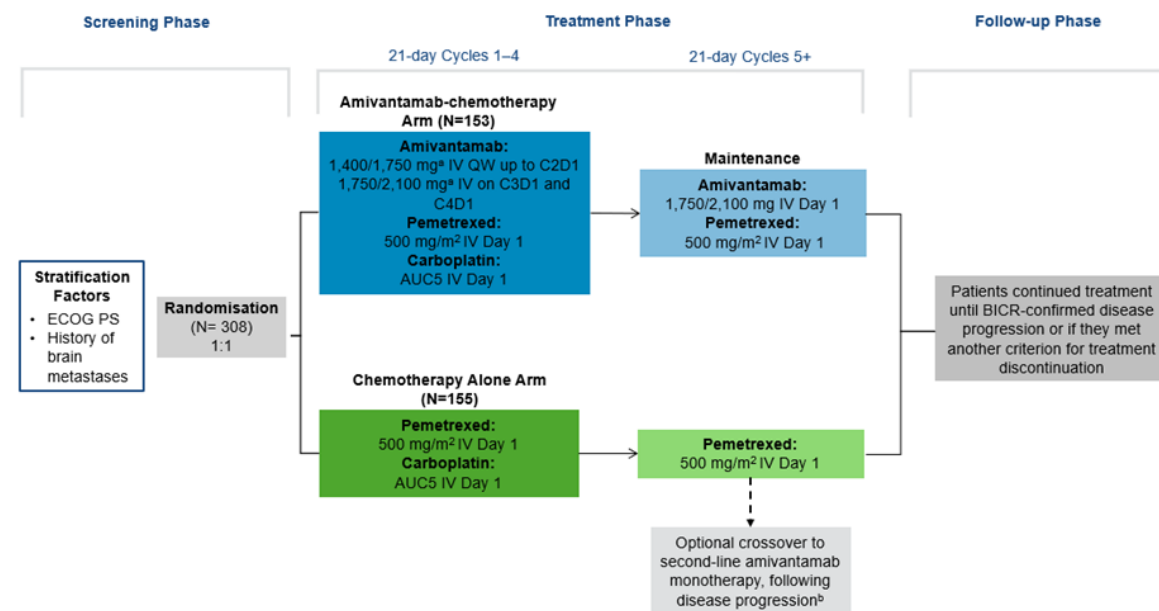
3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

PAPILLON

Amivantamab in combination with carboplatin and pemetrexed is now fully licensed in the UK following the positive results from a clinical trial called 'PAPILLON' (clinical trial number NCT04538664). This is a phase 3, open-label trial where patients were randomised to receive either a) amivantamab-chemotherapy or b) chemotherapy. A phase 3 trial means the trial tests the effectiveness of a new treatment and the open label trial design means patients know what treatment they were receiving. The trial recruited 306 patients who were evenly split between each arm. The study was conducted in North America, Asia, Australasia and Europe (including three sites in the UK). Figure 2 below demonstrates the study design.²⁷

Figure 2: Overview of PAPILLON study design:



a Doses are shown by body weight (<80 kg/≥80 kg).

b Treatment switching was only permitted following confirmation of disease progression by blinded independent central review; dosing for second-line amivantamab monotherapy is the same as in the main treatment phase of the study.

Abbreviations: AUC: area under the curve; BICR: blinded independent central review; C: Cycle; D: Day; ECOG: Eastern Cooperative Oncology Group; IV: intravenous; PS: performance status.

Source: Adapted from Zhou et al., 2023

Some key criteria for participants being included in the trial include: Patients aged 18 years and older, histologically or cytologically confirmed locally advanced or metastatic non-squamous NSCLC with documented primary EGFR Exon20 insertion mutations, an Eastern Cooperative Oncology Group (ECOG) score of 0 or 1 and adequate organ and bone marrow function.

Some of the key exclusion criteria included: participants had received prior systemic treatment for locally advanced or metastatic disease (with minor exceptions), evidence of synchronous NSCLC disease and untreated or active brain metastases. Further details can be found on the clinical trial website.

The PAPILLON trial met its primary endpoint of Progression-Free Survival (PFS, the length of time from starting treatment until the cancer gets worse) by Blinded Independent Committee Review (BICR, a panel of independent clinical experts) as presented at the European Society for Medical Oncology (ESMO, a medical conference for cancer specialists to share their research) conference in October 2023 with a subsequent publication in the New England Journal of Medicine. The study is still ongoing, and its estimated completion date is in January 2026.

Further information about the trial can be found using the following links:

- Clinical trial: <https://classic.clinicaltrials.gov/ct2/show/NCT04538664>
- Publication: <https://www.nejm.org/doi/full/10.1056/NEJMoa2306441>

Other amivantamab trials

There are additional trials investigating amivantamab; however, these are in a different patient population and in combination with different therapies. A single arm trial investigating amivantamab as monotherapy in the second-line setting (after platinum based chemotherapy) for the same mutation was previously conducted with a marketing authorisation granted by the MHRA in November 2021.²⁸ The indication for that population is:

- as monotherapy for treatment of adult patients with advanced NSCLC with activating EGFR Exon 20 insertion mutations, after failure of platinum-based therapy.

Amivantamab is also being investigated as a subcutaneous (SC) injection (a type of injection that is given just below the skin) in a phase 2 open label trial named 'PALOMA 2' where one cohort explores amivantamab as a SC injection in combination with carboplatin and pemetrexed in EGFR Exon20 insertion-mutated NSCLC. The clinical trial number is NCT05498428. The key primary endpoint for this cohort is Overall Response Rate (ORR) and the expected primary completion date is October 2025.²⁹ Depending on the results of this trial, amivantamab may in future be available as a SC injection. This means that patients would need to spend less time in hospital as the SC injection will reduce the administration time compared to amivantamab given as an IV infusion.

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Results from the PAPILLON trial were published in 2023.

Progression Free Survival

PFS by BICR was the primary endpoint in the PAPILLON trial. At a median follow up time of 14.9 months, the median PFS by BICR was 11.4 months for amivantamab-chemotherapy vs 6.7 months for chemotherapy (hazard ratio [HR]: 0.40; 95% Confidence Interval (CI, the CI is a term that shows the range of values that likely contains the true value): 0.30, 0.53; $p < 0.0001$). This shows that amivantamab-chemotherapy increased the amount of time before the cancer got worse by 4.7 months and resulted in a 60% reduction in the risk of disease progression or death compared to chemotherapy. This benefit was shown to be consistent when looking at different subgroups (e.g., age, sex, race, weight).²⁴

Overall Survival

Overall survival (OS) is the length of time patients remain alive after starting treatment. Based on an updated data-cut, with median follow up of 20.9 months, the amivantamab-chemotherapy arm had not yet reached median OS compared to 28.6 months OS in the chemotherapy arm (HR: 0.76; 95% CI: 0.50, 1.14; $p = 0.1825$). This represents a 24% reduction in the risk of death with amivantamab-chemotherapy compared to chemotherapy.³

Overall Survival Interpretation

As the PAPILLON trial was conducted globally, it is not fully consistent with what happens in UK clinical practice. The trial design shown in **Figure 2** demonstrated that patients in the chemotherapy arm were allowed to switch to amivantamab monotherapy as a second-line therapy (so once their cancer had progressed and they go onto a next treatment), this is referred to either as "crossover" or "treatment switching".

However, in the UK amivantamab (which has better outcomes compared to other second-line treatments) is not reimbursed as a second-line therapy which means that patients would not be able to receive this treatment on the NHS. Therefore, the OS results above are conservative as 50% of the patients in the chemotherapy arm crossed over to receive amivantamab monotherapy once their disease got worse. Therefore, a type of statistical analysis was conducted to explore what the survival of patients in the chemotherapy arm would have been had they followed what happens in UK clinical practice (by adjusting for the patients who switched to receive amivantamab monotherapy). The results from this analysis are confidential but can be found in Section B.3.3.2.1 of the company submission.²⁴

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs)**.

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

EQ-5D-5L

EuroQol 5-Dimension 5-level (EQ-5D-5L) is a way to measure the quality of life for patients and helps doctors understand how patients feel and how their health is affected before and during treatment. The results showed that the scores for patients receiving amivantamab-chemotherapy compared to chemotherapy alone were similar, demonstrating that adding amivantamab does not negatively impact the quality of life of patients. The exact scores are confidential but can be found in Section B.2.6.3.2 of the company submission.

EORTC-QLQ-C30³⁰

EORTC-QLQ-C30 is a measurement tool that helps assess the symptoms and overall functioning of patients with cancer. This tool compares the scores from the start of treatment and tracks changes over time. The results demonstrated that patients felt better physically and emotionally with amivantamab-chemotherapy compared to chemotherapy. This was shown through:

- A higher percentage of patients with improved or stable physical functioning (54% vs 41%), emotional functioning (63% vs 47%), cognitive functioning (47% vs 38%), role functioning (50% vs 41%) and global health status (51% vs 42%) compared to the start.
- A higher percentage reporting 6 months no dyspnea (shortness of breath) (43% vs 25%), no pain (35% vs 31%) and no fatigue (18% vs 8%).

Normally adding more drugs to a patient's treatment can increase side effects and reduce their quality of life. However, the results show that amivantamab-chemotherapy improved or maintained the patient's HRQoL functioning without adding lung cancer related symptoms compared to chemotherapy alone.

Patient preference information

Patient preference information was sought in market research led by Johnson & Johnson and showed the desire amongst patients for treatments which increase life or keep the disease stable with minimal impact on their everyday life. A new treatment with the dosing schedule the same as amivantamab, was considered acceptable if it offered an additional five months before the cancer got worse (aligning with the improvement in PFS with amivantamab-chemotherapy compared to chemotherapy demonstrated in PAPILLON).²⁴ Side effects, which are manageable, are expected to some extent by patients, and manageable side effects were those that were predictable, so the patient has control over

them, or they had a limited effect on quality of life (meaning the patient was not constantly in hospital or unable to leave the house). Although patients cited a preference for an oral treatment, efficacy (e.g., delaying the cancer getting worse and increasing survival) was seen as more important than the route of administration.¹¹

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

The safety profile of amivantamab-chemotherapy was similar with the safety profile of the separate individual treatments based on the data from the PAPILLON trial. Adverse events (AEs) are side effects that occur during treatment. The PAPILLON trial showed that all patients (100%) in the amivantamab-chemotherapy arm experienced an AE and 152 patients (98%) had an AE in the chemotherapy arm. The occurrence of serious AEs was similar between treatment arms with 56 patients (37%) in the amivantamab-chemotherapy arm and 48 patients (31%) in the chemotherapy arm reporting them.²⁴

AEs which led to discontinuation were seen in 36 patients (24%) in the amivantamab-chemotherapy arm compared to 16 patients (10%) in the chemotherapy arm. Dose reductions also occurred in both arms with 73 patients (48%) in the amivantamab-chemotherapy arm receiving a dose reduction and 35 patients (23%) in the chemotherapy arm. Dose interruptions were reported in 104 patients (69%) in the amivantamab-chemotherapy arm compared to 56 patients (36%) in the chemotherapy arm. AEs which led to death occurred in 7 patients (4.6%) in the amivantamab-chemotherapy arm compared to 4 patients (2.6%) in the chemotherapy arm.²⁴

Table 2 presents the most commonly reported AEs in the PAPILLON trial. The AEs are graded according to severity, with Grade ≥ 3 AEs being more serious. The total number of Grade ≥ 3 AEs was 114 (75%) in the amivantamab-chemotherapy arm compared to 83 (54%) in the chemotherapy arm.²⁴ The Grade ≥ 3 AEs associated with amivantamab-chemotherapy were manageable with dose reductions and interruptions.

Table 2: Adverse events reported in $\geq 15\%$ of patients in either group

Adverse events reported in $\geq 15\%$ of patients in either group	ACP (n=151)		CP (n=155)	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Neutropenia	89 (59)	50 (33)	70 (45)	35 (23)
Paronychia	85 (56)	10 (7)	0	0
Rash	81 (54)	17 (11)	12 (8)	0
Anemia	76 (50)	16 (11)	85 (55)	19 (12)
Infusion-related reaction	63 (42)	2 (1)	2 (1)	0
Hypoalbuminemia	62 (41)	6 (4)	15 (10)	0
Constipation	60 (40)	0	47 (30)	1 (1)
Leukopenia	57 (38)	17 (11)	50 (32)	5 (3)
Nausea	55 (36)	1 (1)	65 (42)	0
Thrombocytopenia	55 (36)	15 (10)	46 (30)	16 (10)
Decreased appetite	54 (36)	4 (3)	43 (28)	2 (1)
Increased alanine aminotransferase	50 (33)	6 (4)	56 (36)	2 (1)
Increased aspartate aminotransferase	47 (31)	1 (1)	51 (33)	1 (1)
Dermatitis acneiform	47 (31)	6 (4)	5 (3)	0

Peripheral edema	45 (30)	2 (1)	16 (10)	0
Stomatitis	38 (25)	2 (1)	9 (6)	0
Covid-19	36 (24)	3 (2)	21 (14)	1 (1)
Diarrhea	31 (21)	5 (3)	20 (13)	2 (1)
Hypokalemia	32 (21)	13 (9)	13 (8)	2 (1)
Vomiting	32 (21)	5 (3)	29 (19)	1 (1)
Asthenia	30 (20)	8 (5)	29 (19)	4 (3)
Pyrexia	24 (16)	0	9 (6)	0
Fatigue	23 (15)	1 (1)	32 (21)	2 (1)
Increased γ -glutamyltransferase	21 (14)	4 (3)	26 (17)	6 (4)
Cough	21 (14)	0	24 (15)	0

Abbreviations: ACP; amivantamab, carboplatin and pemetrexed, CP; carboplatin and pemetrexed.

Source: Zhou et al. 2023

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

Amivantamab-chemotherapy has demonstrated several benefits to patients when compared to chemotherapy. This includes:

- The first licensed targeted treatment for adult patients with untreated EGFR Exon20 insertion mutation-positive advanced NSCLC.³
- If reimbursed, the only specifically targeted treatment to be available for patients with EGFR Exon20 insertion mutation-positive advanced NSCLC in the UK on the NHS.¹⁶
- A dual mechanism of action (a bispecific antibody that targets two key receptors).^{22, 23}
- A trend towards increasing overall survival, with a reduction in the risk of death of 24% compared to carboplatin and pemetrexed.³
- Delaying the cancer progression by an additional 4.7 months compared to carboplatin and pemetrexed.²⁴
- Quality of life being similar between both amivantamab-chemotherapy and chemotherapy arms at different points in time when patients are receiving treatment.³⁰
- Safety profile consistent with the individual treatments without new adverse events.^{3, 24}

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

The safety profile of amivantamab as described in Section 3g demonstrated that amivantamab-chemotherapy sees more grade ≥ 3 AEs (75% vs 54%) and serious AEs (37% vs 31%) compared to chemotherapy although the AEs associated with amivantamab-chemotherapy were manageable with dose reductions and interruptions. Notably the rate of IRRs is greater in the amivantamab-chemotherapy arm (42%) compared to chemotherapy (1%) although most of these were grade 1-2 AEs (therefore not too serious) and associated with the first infusion on the first day of treatment.²⁴

Amivantamab-chemotherapy has an additional administrative burden in the first cycle of treatment. Patients require weekly visits to hospital for the first 21 days of treatment (with the first dose needing to be split over 2 days) compared to chemotherapy requiring one visit in the first 21 days. This may have an impact on both the patient and their caregiver who may need to accompany the patient to hospital. However, the amivantamab dosing decreases to once every 3 weeks from week 4 onwards (therefore the same as the chemotherapy dosing).

There are no other targeted treatments available for this patient population at present; and with the potential licensing of the subcutaneous formulation, the administration disadvantages from the IV infusions for amivantamab during the first cycle should be reduced in future.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Johnson & Johnson has developed an economic model to understand the cost-effectiveness of amivantamab-chemotherapy vs the main comparators of chemotherapy and pembrolizumab in combination with carboplatin and pemetrexed (pembrolizumab-chemotherapy). The economic model helps understand if the new treatment is an effective use of NHS resources (good value for money) compared to the other treatments available and does this through considering resources and costs, as well as the impact on quality of life and survival of patients on the potential treatment options.

The model simulates a patient's progression over a 30-year time horizon through a set of different health states (before disease progression, after disease progression, and death). Each health state is associated with relevant costs and a specific quality-of-life benefit.

The following health states were used in this cost-effectiveness model:

- **Progression-free:** This means a patient's disease is stable or responding to treatment and not actively getting worse. Quality of life is higher compared to patients with progressed disease but is also affected by adverse events.
- **Progressed disease:** This means a patient's disease has progressed. Quality of life is lower compared to patients with progression-free disease.
- **Death:** This state includes costs associated with palliative care and end-of-life costs.

The model uses PFS, time to next treatment, treatment discontinuation, OS, AE and QoL data (the EQ-5D questionnaire) from the PAPILLON trial for amivantamab-chemotherapy and chemotherapy. Real-world evidence is used to inform the efficacy estimates for the pembrolizumab-chemotherapy as there are no randomised controlled trials investigating pembrolizumab in patients with EGFR Exon20

insertion mutations. The time spent in each health state is then adjusted by the HRQoL of a patient in that health state, to estimate the total number of quality-adjusted life years (QALYs) gained by a patient for each treatment. A QALY is therefore a measure of health that combines both the length of life and the quality of life.

The costs considered includes treatment acquisition, administration, monitoring, subsequent treatment, adverse event, healthcare resource use and end-of-life costs. By comparing the costs with the expected QALYs gained for each treatment, the model considers the economic value of the new treatment compared to the existing treatment.

As there are no reimbursed treatments for patients with EGFR Exon20 insertion mutation-positive advanced NSCLC, there is not one standard of care that would be displaced with the introduction of amivantamab-chemotherapy. Treatments that would be displaced collectively comprise carboplatin and pemetrexed and pembrolizumab-chemotherapy. The model therefore uses a weighted comparator meaning the result for each comparator is weighted based on its expected use in UK clinical practice. As identified by UK Oncologists in advisory boards, this weighting is 70% for chemotherapy and 30% for pembrolizumab-chemotherapy.

The model demonstrates that amivantamab-chemotherapy results in more life years (LYs) and QALYs compared to the weighted comparator. This is mainly from the improvement in both PFS and OS compared with the comparators in the model. The model also shows higher costs with the introduction of amivantamab-chemotherapy compared with chemotherapy alone due to the drug costs of treatment and the time spent on treatment being higher with amivantamab-chemotherapy. When comparing the costs and the estimated health benefits (in the form of QALYs) between amivantamab-chemotherapy and the weighted comparator, the model demonstrates amivantamab-chemotherapy is cost effective at a willingness to pay threshold that NICE uses.

Uncertainty

There is some uncertainty in the model, specifically in relation to the data maturity. The latest data from the trial has 14.9 months follow up for all outcomes (except for OS where the follow up is 20.9 months), and it is used to model outcomes over 30 years. Therefore, there is some uncertainty if the modelled outcomes follow exactly what will happen in the trial.

There is also uncertainty for the comparison with pembrolizumab-chemotherapy as there is no clinical trial data for this patient population. Therefore, the comparison is between amivantamab-chemotherapy in a clinical trial setting compared to real world data for pembrolizumab-chemotherapy. Ideally head-to-head data or data from only clinical trials would be used, but this data does not exist as there have been no investigational trials of pembrolizumab-chemotherapy in patients with EGFR Exon20 insertion mutation-positive advanced NSCLC.

The chemotherapy survival and how long patients stay in the progressed disease state is also uncertain due to having to adjust for patients who crossed over to amivantamab monotherapy at disease progression (as detailed in section 3e). There are different ways to 'adjust' for patients who receive second-line amivantamab, and the different methods lead to different model results.

Severity modifier

NICE looks at how severe a disease is when it evaluates a medicine. The modifier gives more value to the health benefits by multiplying the QALYs by a value to upweight them, which essentially increases the amount the NHS is willing to pay for severe conditions. For amivantamab-chemotherapy, a modifier of 1.2 is used meaning the QALYs are multiplied by this value. This highlights the severity of disease in this group and the level of high unmet need.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations. If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Amivantamab is innovative in the way it works based on its mechanism of action, as detailed in section 3a. It also represents a large step-change in treatment as it improves health outcomes for patients with EGFR Exon 20 insertion mutation-positive advanced NSCLC by significantly improving PFS and trending towards increasing OS while maintaining their HRQoL. It will also give hope to patients as being the potential first and only approved targeted treatment for EGFR Exon20 insertion mutation-positive advanced NSCLC, offering patients a chance of a treatment specific for their needs rather than untargeted chemotherapy.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme
Find more general information about the Equality Act and equalities issues here

There is an important equality consideration with respect to the stigma of lung cancer. Lung cancer patients often face stigma due to people associating smoking with lung cancer, therefore blaming the patient. EGFR Exon20 insertion mutations are more likely than other NSCLC mutations to be associated with women, never-smokers, and Asian heritage, showing the issue of stigma is higher for EGFR Exon20 insertion mutations specifically which makes it especially difficult for these patients. There is also some evidence that symptoms of lung cancer are stigmatised in Asian communities, which could reinforce the treatment delaying behaviour seen in lung cancer more generally.¹²

If amivantamab-chemotherapy is made available on the NHS, patients with EGFR Exon20 insertions (an extremely rare form of lung cancer, even amongst EGFR mutated NSCLC) will have an opportunity to receive an efficacious targeted therapy option. This would narrow the gap between the clinical benefit that patients could achieve with within this rare population and the clinical benefit that patients with common EGFR mutations already achieve (where efficacious treatment options are routinely available).

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.

Where possible, please provide open access materials or provide copies that patients can access.

Patient groups and charities:

- EGFR Positive UK: <https://www.egfrpositive.org.uk/>
- Roy Castle Lung Cancer Foundation: <https://roycastle.org/>

Clinical trial and data:

- Clinical trial: <https://clinicaltrials.gov/study/NCT04538664>
- SMPC: <https://www.medicines.org.uk/emc/product/13084/smpc>

- Amivantamab plus Chemotherapy in NSCLC with EGFR Exon 20 Insertions: <https://www.nejm.org/doi/full/10.1056/NEJMoa2306441>
- Patient relevant endpoints from PAPILLON: amivantamab plus chemotherapy vs chemotherapy as first-line treatment of EGFR exon 20 insertion-mutated (Ex20ins) advanced NSCLC: <https://oncologypro.esmo.org/meeting-resources/european-lung-cancer-congress-2024/patient-relevant-endpoints-from-papillon-amivantamab-plus-chemotherapy-vs-chemotherapy-as-first-line-treatment-of-egfr-exon-20-insertion-mutated>

Further information on NICE and the role of patients:

- Public Involvement at NICE [Public involvement](#) | [NICE and the public](#) | [NICE Communities](#) | [About | NICE](#)
- NICE's guides and templates for patient involvement in HTAs [Guides to developing our guidance](#) | [Help us develop guidance](#) | [Support for voluntary and community sector \(VCS\) organisations](#) | [Public involvement](#) | [NICE and the public](#) | [NICE Communities](#) | [About | NICE](#)
- EUPATI guidance on patient involvement in NICE: <https://toolbox.eupati.eu/resources/patient-toolbox/guidance-for-patient-involvement-in-regulatory-processes/>
- EFPIA – Working together with patient groups: <https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf>
- National Health Council Value Initiative. <https://nationalhealthcouncil.org/issue/value/> INAHTA: <http://www.inahta.org/>
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: <https://eurohealthobservatory.who.int/publications/i/health-technology-assessment-an-introduction-to-objectives-role-of-evidence-and-structure-in-europe-study>

4b) Glossary of terms

Advanced cancer: Cancer that is unlikely to be cured or controlled with treatment. The cancer may have spread from where it first started to nearby tissue, lymph nodes, or distant parts of the body. Treatment may be given to help shrink the tumour, slow the growth of cancer cells, or relieve symptoms.

Adverse event/side effect: An unexpected medical event that arises during treatment with a drug or other therapy. Adverse events can be classified as mild, moderate or severe.

Antibody: a protein produced by the immune system in response to the presence of a foreign substance, called an antigen.

Bispecific antibody: A type of antibody that can bind to two different antigens at the same time.

Diagnosis: The process of identifying a disease, condition, or injury from its signs and symptoms. A health history, physical exam, and tests, such as blood tests, imaging tests, and biopsies, may be used to help make a diagnosis.

Disease progression: Cancer that continues to grow or spread.

Clinical guidelines: Guidelines developed to help health care professionals and patients make decisions about screening, prevention, or treatment of a specific health condition.

Clinical trial: A type of research that studies new tests and treatments and evaluates their effects on human health outcomes.

Disease progression: Cancer that continues to grow or spread

Eligibility criteria: In clinical trials, requirements that must be met for a person to be included in a trial. These requirements help make sure that participants in a trial are like each other in terms of specific factors such as age, type and stage of cancer, general health, and previous treatment. When all participants meet the same eligibility criteria, it is more likely that results of the study are caused by the intervention being tested and not by other factors or by chance.

Endpoint: In clinical trials, an event or outcome that can be measured objectively to determine whether the intervention being studied is beneficial. The endpoints of a clinical trial are usually included in the study objectives. Some examples of endpoints are survival, improvements in quality of life, relief of symptoms, and disappearance of the tumour.

Immuno-oncology therapy: A type of therapy that uses substances to stimulate or suppress the immune system to help the body fight cancer, infection, and other diseases. Some types of immunotherapy only target certain cells of the immune system, others affect the immune system in a general way.

Intravenous (IV): Into or within a vein. Intravenous usually refers to a way of giving a drug or other substance through a needle or tube inserted into a vein.

Performance status: A measure of how well a patient is able to perform ordinary tasks and carry out daily activities.

QALY: A measure of health outcomes pertaining to disease burden and is used to assess the value of medical interventions. As health can be defined as the length of life and the quality of life, the QALY combines the two factors into a single figure.

Quality of life: An individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns.

Real-world data: Data relating to patient health or experience or care delivery collected outside the context of a highly controlled clinical trial.

Reimbursement: In the pharmaceutical industry, reimbursement refers to the process by which drug costs are covered by health insurance providers or national healthcare systems. A successful reimbursement strategy ensures that a drug is included on the list of drugs that are covered by insurance companies or national health systems, making it accessible to patients.

Serious Adverse Events: a reaction that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, is a suspected transmission of any infectious agents or is a birth defect

4c) References

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Clarification questions

October 2024

File name	Version	Contains confidential information	Date
ID5110_Amivantamab Clarification Letter_Company response_21Oct24 [Redacted]	V1	Yes	Monday 21 st October 2024

Updated base case results

As it relates to a number of clarification question responses throughout this document, Johnson & Johnson would like to inform the external assessment group (EAG) that the cost-effectiveness model (CEM) used in the company submission (CS) has been updated to include the most recent National Health Service (NHS) 2022/2023 reference costs.¹ These were published on the NHS costing website after the CS was made and before receipt of the EAG clarification questions. Therefore, the cost-effectiveness results in the base case are different to those cited within the CS. An updated model is attached alongside the responses to the clarification questions, and the updated probabilistic plus deterministic ICERs are presented in Table 1 and Table 2 respectively.

Table 1. Updated probabilistic base case results for amivantamab-chemotherapy versus relevant comparators at amivantamab PAS price using NHS 2022/2023 reference costs

	Total			Incremental			ICER (£/QALY)
	Costs (£)	QALYs	LYs	Costs	QALYs	LYs	
Amivantamab-chemotherapy	████	██	3.92	-	-	-	24,044
Weighted comparator ^a	████	██	2.03	████	██	1.88	

^a The weighted comparator used within the base-case comprises 70% chemotherapy (carboplatin with pemetrexed) and 30% pembrolizumab-chemotherapy (pembrolizumab with carboplatin and pemetrexed)

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

Table 2: Updated deterministic base case results for amivantamab-chemotherapy versus relevant comparators at amivantamab PAS price using NHS 2022/2023 reference costs

	Total			Incremental			ICER (£/QALY)
	Costs (£)	QALYs	LYs	Costs	QALYs	LYs	
Amivantamab-chemotherapy	████	██	3.76	-	-	-	24,839
Weighted comparator ^a	████	██	2.00	████	██	1.76	

^a The weighted comparator used within the base-case comprises 70% chemotherapy (carboplatin with pemetrexed) and 30% pembrolizumab-chemotherapy (pembrolizumab with carboplatin and pemetrexed)

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

Section A: Clarification on effectiveness data

Literature searches

- A 1. Please confirm the issue searched for the Cochrane Library databases (CDSR and CENTRAL) for the June 2024 update (documented in Section D.1.1.1 and Appendix D; Table 19). The EAG assumes that the issue given (Issue 2 of 12, June 2024) is a typographical error.

The issue given (Issue 2 of 12, June 2024) for the Cochrane Library databases searched as part of the June 2024 update was incorrect and was a copying error. The footnote should read as follows: “**Databases:** Cochrane Database of Systematic Reviews, Issue 6 of 12, June 2024; Cochrane Central Register of Controlled Trials. Issue 5 of 12, May 2024”.

- A 2. Please correct the Embase search strategy provided in Appendix G; Table 35. Lines #58 - #67 are incorrect due to a typographical error in line #58 (this should read ‘or/38-57’, not ‘or/38-58’), and this has led to errors in subsequent lines.

The Embase search strategy originally provided in Table 35 was missing a line (#55). Johnson & Johnson thank the EAG for pointing out this error. The correct Embase search strategy is presented below, with the additional line in bold text. This was a copying error and Johnson & Johnson confirm that the line was included in the searches when they were run.

Table 3: Embase search strategy for clinical effectiveness data, June 2024

Dates searched: Original, 4 th May 2020; Update 1, 2 nd August 2022; Update 2, 4 th October 2023; Update 3, 12 th March 2024; Update 4, 1 st July 2024							
Term group	#	Search terms	Results 04.05.20	Results 02.08.22	Results 04.10.23	Results 12.03.24	Results 01.07.24
Disease area: Metastatic NSCLC	1	NSCLC.ti,ab,kw.	81003	100580	112025	116915	119564
	2	exp Lung/ and (exp Neoplasm/ or exp squamous cell carcinoma/ or exp Adenocarcinoma/ or exp large cell carcinoma/)	66534	76748	85943	87781	88914
	3	(lung\$ and (non small cell or nonsmall cell) and (carcinoma\$ or adenocarcinoma\$ or cancer\$ or tumor\$ or neoplasm\$)).ti,ab,kw.	104930	128034	142033	147654	150869
	4	exp Metastasis/ or exp Advanced cancer/ or (metastat\$ or metastas\$ or advanced or stage IIb or stage 3b or stage IIc or stage 3c or stage IV or stage 4 or unresectable or non-resectable or nonresectable or inoperable or progressive).ti,ab,kw.	1791865	2110877	236121	244173	248796
	5	1 or 2 or 3	177029	212214	2299304	2370659	2421325
	6	4 and 5	88298	106947	119056	123311	125515
Study design: Economic evaluations	7	Cost benefit analysis/ or exp economic evaluation/ or cost effectiveness analysis/ or cost minimization analysis/	303435	336917	356845	364768	370628
	8	Economics/ or health economics/ or socioeconomics/ or economic aspect/	486779	518125	534374	539760	544411

Dates searched: Original, 4th May 2020; Update 1, 2nd August 2022; Update 2, 4th October 2023; Update 3, 12th March 2024; Update 4, 1st July 2024

Term group	#	Search terms	Results 04.05.20	Results 02.08.22	Results 04.10.23	Results 12.03.24	Results 01.07.24
	9	(cost\$ adj (effective\$ or utilit\$ or consequence\$ or benefit\$ or minimi\$)).tw.	199469	237522	264234	273614	280672
	10	(economic evaluation\$ or economic analysis or life year\$ gained or ICER or QALY\$ or DALY\$ or quality adjusted or adjusted life year\$ or disability adjusted life or qald\$ or qale\$ or qtime\$).tw.	50848	62268	71322	74120	76009
	11	quality adjusted life year/	26129	32115	35440	36871	37821
	12	or/7-11	823304	908688	959354	978039	992676
Study design: Utilities and HRQoL	13	(health utilit\$ or health state\$1 or illness state\$1 or HSUV or HSUVs or health state\$ value\$ or health state\$ preference\$ or utility assessment\$ or utility measure\$ or preference based or utility based).tw.	15785	19122	21137	21901	22344
	14	((index adj3 wellbeing) or (quality adj3 wellbeing) or qwb).tw.	1139	1549	1849	1922	2008
	15	(multiattribute\$ or multi attribute\$).ti,ab.	1105	1337	1507	1569	1605
	16	utility.ab. /freq=2	26942	33464	37148	38654	39727
	17	(utilities or disutilit\$).tw.	11956	14446	16082	16626	16974
	18	(euro qual or euro qual5d or euro qol5d or eq-5d or eq5-d or eq5d or eq 5d or euroqual or euroqol or euro qol or euroqual5d or euroqol5d or eq-sdq or eqsdq).tw.	20158	26771	30728	32150	33092
	19	(short form\$ or shortform\$).ti,ab.	44797	55096	60516	62415	63829
	20	(sf36\$ or sf 36\$ or sf thirtysix or sf thirty six).tw.	37196	42724	46148	47100	47789
	21	(sf6 or sf 6 or sf6d or sf 6d or sf six D or sfsixD or sf six or sfsix or sf8 or sf 8 or sf eight or sfeight).tw.	4444	5107	5497	5609	5695
	22	(sf12 or sf 12 or sf twelve or sftwelve).tw.	7971	9683	10697	10993	11196
	23	(sf16 or sf 16 or sf sixteen or sfsixteen).tw.	55	60	62	65	65
	24	(sf20 or sf 20 or sf twenty or sftwenty).tw.	339	368	380	386	391

Dates searched: Original, 4 th May 2020; Update 1, 2 nd August 2022; Update 2, 4 th October 2023; Update 3, 12 th March 2024; Update 4, 1 st July 2024							
Term group	#	Search terms	Results 04.05.20	Results 02.08.22	Results 04.10.23	Results 12.03.24	Results 01.07.24
	25	(15D or 15-D or 15 dimension).tw.	6556	7299	7738	7874	7984
	26	visual analog\$ scale\$.tw.	77073	94749	151036	155757	159427
	27	(standard gamble\$ or sg).tw.	15939	19360	21633	22449	23078
	28	(time trade off\$1 or time tradeoff\$1 or tto or timetradeoff\$1).tw.	2729	3232	3576	3682	3754
	29	(health\$1 year\$1 equivalent\$1 or hye or hyes).tw.	151	167	202	209	214
	30	(hui or hui1 or hui2 or hui3 or rosser).tw.	2369	2941	3302	3428	3518
	31	*quality of life/ and (quality of life or qol or hrqol).tw.	93710	114991	128696	133118	136449
	32	quality of life/ and ((quality of life or qol or hrqol) adj (score\$1 or measure\$1)).tw.	28988	35249	38836	40188	41141
	33	quality of life/ and health-related quality of life.tw.	55917	69511	78903	81853	83858
	34	quality of life/ and ec.fs.	41876	53145	61677	64715	67181
	35	quality of life/ and (health adj3 status).tw.	15303	18458	21003	21795	22303
	36	((qol or hrqol or quality of life).ti. or *quality of life/) and ((qol or hrqol\$ or quality of life) adj2 (increas\$ or decrease\$ or improv\$ or declin\$ or reduc\$ or high\$ or low\$ or effect or effects or worse or score or scores or change\$1 or impact\$1 or impacted or deteriorat\$)).ab.	49333	61277	77793	80658	82724
	37	or/13-36	360679	443397	540055	559363	573753
Study design: Cost and resource use studies	38	Cost control/	67800	73557	76593	77747	78582
	39	Cost of illness/	19052	20668	21351	21579	21781
	40	Drug cost/	76863	83021	86719	87924	88901
	41	Hospital cost/	21232	23979	25532	26037	26432
	42	exp Budget/	28786	31953	33678	34414	34874
	43	Financial management/	112403	118235	122308	123325	123836
	44	health care cost/	187668	212005	227737	232911	236748
	45	health care financing/	13232	13716	13960	14062	14126
	46	health expenditure/	169305	165612	165232	164684	165698
	47	(low adj cost).mp.	64946	85313	97328	101248	104063
	48	(high adj cost).mp.	18850	23554	26387	27433	28243
	49	((health?care) adj cost\$.mp.	20011	26013	29484	30903	32077

Dates searched: Original, 4 th May 2020; Update 1, 2 nd August 2022; Update 2, 4 th October 2023; Update 3, 12 th March 2024; Update 4, 1 st July 2024							
Term group	#	Search terms	Results 04.05.20	Results 02.08.22	Results 04.10.23	Results 12.03.24	Results 01.07.24
	50	(fiscal or funding or financial or finance).tw.	194350	258066	299241	317788	330943
	51	(cost adj estimate\$).mp.	3374	3947	4192	4295	4373
	52	(cost adj variable\$).mp.	260	303	324	331	340
	53	(unit adj cost\$).mp.	4446	5196	5537	5674	5752
	54	(economic\$ or pharmaco-economic\$ or price\$ or pricing).tw.	382371	467804	529930	548626	561442
	55	((resource\$ or healthcare\$ or service\$) adj3 (use\$ or utilis\$ or utiliz\$ or consume\$ or consuming or consumption\$)).tw.	141176	177066	200358	207984	213912
	56	((patient\$ or caregiver\$ or carer\$ or social\$ or society\$ or family\$) adj2 (burden\$ or productiv\$)).tw.	25438	33896	39579	41672	43088
	57	("length of stay" or utilization or "economic burden" or "cost-of-illness" or nursing cost\$ or physician cost\$ or physician visit\$ or "out of pocket").tw.	383728	478368	542522	564972	582572
	58	(absenteeism or presenteeism or employment or unemployment).tw. or exp presenteeism/ or exp absenteeism/ or exp unemployment/ or exp employment/	143634	174350	191864	199672	203849
	59	or/38-58	1470365	1780571	1979445	2051793	2104521
	60	limit 59 to yr="2015-2020"	505524	646779	832791	904768	956810
Exclusion terms	61	(conference abstract or conference review).pt.	3779855	4495317	4926726	5088192	5211834
	62	limit 61 to yr="1946-2017"	3030409	3829861	4438524	4458984	4477972
	63	exp animals/ not exp humans/	4623263	4978294	5148291	5221821	5274091
	64	(comment or editorial or "case reports" or "clinical trial, phase I").pt.	650801	732634	781233	798278	810830
	65	(case stud\$ or case report\$).ti.	355781	428946	472233	488256	499865
	66	or/62-65	8334193	9544816	10374721	10499200	10593181
Combination	67	6 and (12 or 37 or 60)	4695	6447	8046	8797	9100
	68	67 not 66	3048	4047	4280	5013	5310

Decision problem

A 3. 8Priority question. In terms of the rationale which was provided for not assessing subgroups of patients based on histology type, the company submission (CS) stated that “*The PAPILLON trial excludes squamous non-small cell lung cancer (NSCLC) and, since 99% of the trial population was of adenocarcinoma histology type, these subgroups could not be explored*”. However, the population defined in the NICE final scope was “*Adults with untreated, locally advanced or metastatic NSCLC with an epidermal growth factor receptor (EGFR) exon 20 insertion mutation*.”

a) Please provide further justification for the exclusion of squamous NSCLC in the CS, given that this was not specified in the NICE final scope.

The pivotal, Phase 3 PAPILLON clinical trial included patients with histologically or cytologically confirmed, locally advanced or metastatic, non-squamous NSCLC with documented primary EGFR Exon20 insertion activating mutations.² The trial excluded patients with squamous histology as EGFR mutations are very rare in squamous-cell lung cancer.³ A European real-world study (assessing patients from 2015 to 2020) using data collected from the ESME database showed that, out of 19,759 patients screened, only 602 has squamous histology (3.05%).⁴ Non-squamous and adenocarcinoma of the lung are used interchangeably, and it is in this patient population where EGFR Exon20insertion mutations have been identified. Hence the PAPILLON trial only included patients with non-squamous histology.⁵

Johnson & Johnson have therefore aligned the CS to the population in the pivotal PAPILLON trial and as such, excluded patients with squamous histology.

b) Please adapt the decision problem to exclude squamous histology or provide clinical and cost effectiveness evidence for this population.

Squamous histology is excluded from the decision problem as patients with squamous lung cancer were not included in the PAPILLON trial population. Johnson & Johnson can therefore confirm that the decision problem excludes patients with squamous histology, in line with the population within the CS.

A 4. Priority question. The decision problem (Table 1) lists pembrolizumab monotherapy as a comparator, but this is not included in the cost effectiveness analysis. Table 1 also includes carboplatin with pemetrexed, but excludes any other chemotherapy on the basis of clinical expert opinion. EGFR tyrosine kinase inhibitors (TKIs) are also

excluded on the basis of clinical expert opinion. However, the English data from the NECTAR study (Table 3 of the Study Report) showed 21.7% immuno-monotherapy and 8.7% TKI use, and three clinical expert opinions (included in the June 2023 advisory board) stated that atezolizumab, bevacizumab, carboplatin and paclitaxel (ABCP) combination therapy was used (10%-20%). On the basis that limited use is not the same as no use and that any treatment used in clinical practice should be a comparator, please include pembrolizumab monotherapy and all forms of chemotherapy in clinical practice in all clinical and cost effectiveness analyses.

All forms of chemotherapy

In the June 2023 advisory board, none of the seven oncologists involved cited use of any other chemotherapy regimen aside from carboplatin plus pemetrexed when completing the pre-meeting survey, as illustrated in Table 4.⁶ Further, no other forms of chemotherapy aside from carboplatin plus pemetrexed were discussed during the meeting.

Table 4: Pre-meeting survey responses regarding first-line therapy regimens for patients with EGFR Exon20 insertion mutations from the June 2023 advisory board

Pre-meeting survey feedback - Approximate proportion (%) of patients with NSCLC and <i>EGFR</i> exon20ins mutations receiving each first-line therapy regimen (N=7)	
One advisor:	• Carboplatin + pemetrexed: 70% • Pembrolizumab + carboplatin + pemetrexed: 30%
One advisor:	• Carboplatin + pemetrexed: 60% • Pembrolizumab + carboplatin + pemetrexed: 30% • ABCP: 10%
One advisor:	• Pembrolizumab + carboplatin + pemetrexed: 60% • Carboplatin + pemetrexed: 20% • ABCP: 20%
One advisor:	• Pembrolizumab + carboplatin + pemetrexed: 80% • Carboplatin + pemetrexed: 10% • Best supportive care: 10%
One advisor:	• Carboplatin + pemetrexed: 80% • ABCP: 20%
One advisor:	• Carboplatin + pemetrexed: 70% • Pembrolizumab + carboplatin + pemetrexed: 30%
One advisor:	• Carboplatin + pemetrexed: 90% • Pembrolizumab + carboplatin + pemetrexed: 10%

Although limited use of ABCP was included in some responses from individual advisors, no use of ABCP was mentioned or discussed during the advisory board meeting itself when reaching a consensus on the set of relevant comparators. As well as not being mentioned on the June 2023 advisory board, no use of the ABCP regimen was mentioned during the more recent May 2024 or August 2024 advisory boards.

In the May 2024 advisory board with six oncologists, advisors aligned on a consensus that, for patients receiving platinum-based chemotherapy without any other treatment, carboplatin plus pemetrexed was the only prescribed regimen and was used in all patients.⁷ Similarly, carboplatin plus pemetrexed was the only chemotherapy regimen used for patients receiving an immuno-oncology therapy (IO) with chemotherapy.

In the August 2024 advisory board, the clinical experts highlighted that the cisplatin plus pemetrexed chemotherapy regimen can be excluded as a comparator.⁸

Given clinical opinion from the three advisory boards provided a unanimous consensus that carboplatin plus pemetrexed is the only chemotherapy regimen used in practice, Johnson & Johnson do not consider that other forms of chemotherapy are relevant comparators and, as such, no comparative data has been provided versus other forms of chemotherapy.

Pembrolizumab monotherapy

The English data included within the NECTAR study, showing 21.7% of patients received a form of IO monotherapy ('IO alone'), were sourced from the National Cancer Registration and Analysis Service (NCRAS) database.⁹ This covered patients in England who were diagnosed with NSCLC between 2016 to 2021, with follow-up of patients ending in March 2023. While these data are specific to England, there are limitations associated with using these data to inform what current treatments are prescribed to patients with EGFR Exon20 insertion mutations in the United Kingdom (UK), and associated treatment splits. The first limitation of the data is the small sample size of 23 patients from the NCRAS dataset being assessed as part of the NECTAR study. The small sample size can be partially attributed to the rarity of the mutation, as well as the limitations associated with polymerase chain reaction (PCR) in successfully identifying EGFR Exon20 insertion mutations, given mutation testing with next generation sequencing (NGS) did not enter routine clinical practice testing until 2021. The small sample size can also be attributed to the group of patients included within the NCRAS dataset needing to be matched with the PAPILLON trial through applying the inclusion and exclusion criteria of the trial to this real-world population. This, however, does not represent the full population of patients who have untreated EGFR Exon20 insertion mutations as the license is broader than the trial population. The second limitation is the fact that the data collection period of the NCRAS dataset only covers patients diagnosed up to 2021. Since then, changes to the testing landscape have resulted in clinicians being better able to identify EGFR Exon20 insertion mutations. There has also been an increase in awareness and education of oncologists as to how best to treat these patients (e.g., if using an immuno-oncology agent it should be given in combination with platinum-based chemotherapy, not as a single agent). Therefore, the dates of collection of the NCRAS dataset mean it likely does not fully reflect the treatments patients would receive in 2024.

Given the small sample size and data collection dates, only some information can be extracted from the NCRAS data alone and the proportions of therapies reported from the NCRAS data may not fully reflect current UK clinical practice. Therefore, the choice of comparators used in the CS), and their associated proportional uses, was driven by expert clinical opinion obtained across the advisory boards. These insights showed that the standard first-line therapy for patients with EGFR Exon20 insertion mutation-positive advanced NSCLC is platinum-based chemotherapy with or without pembrolizumab.

Insight from the advisory boards has confirmed that it is against best practice to prescribe IO monotherapies within patients with EGFR Exon20 insertion mutations. This is mainly driven by the fact that there is no demonstrated benefit from IO monotherapies within this population.

- At the June 2023 advisory board, no advisor reported any use of IO monotherapy for patients with untreated EGFR Exon20 insertion mutation-positive advanced NSCLC.⁶
- At the May 2024 advisory board, all advisors aligned on a consensus that IO monotherapy was not used in practice and should not constitute a comparator to amivantamab.⁷
- At the August 2024 advisory board, clinical experts highlighted that well-informed clinicians would not use IO monotherapy and prescribing this to patients with EGFR Exon20 insertion mutation-positive advanced NSCLC is against best practice.⁸

Therefore, Johnson & Johnson maintain that pembrolizumab monotherapy is not a relevant comparator. As such, results from a comparison versus pembrolizumab monotherapy are not provided here.

However, although there is limited to no use of pembrolizumab monotherapy observed across the UK (as it is against best practice), Johnson & Johnson have aligned with the EAG request and provided a scenario within the cost-effectiveness model where pembrolizumab monotherapy is included as a standalone comparator (deterministic and probabilistic cost-effectiveness results for amivantamab with chemotherapy versus pembrolizumab monotherapy can be found in the 'HTA outputs sheet' of the updated model).

Systematic review

A 5. Please provide details on how the discrepancies between the two reviewers were resolved for quality assessment of the included studies.

The quality assessment for each included study was completed by one individual and verified by a second independent reviewer. If necessary, any discrepancies were resolved by a third independent individual.

A 6. Please confirm whether the process of study selection, data extraction and quality assessment (outlined in Appendix D) was the same for each updated version of the systematic review.

Johnson & Johnson can confirm that the process of study selection, data extraction and quality assessment, as outlined in Appendix D of the CS, was identical in each updated version of the systematic review.

Clinical effectiveness evidence

A 7. Priority question: In the PAPILLON trial, a total of 65 patients (out of 155 patients) had treatment switched from the chemotherapy arm to receive amivantamab monotherapy.

a) Please provide the details of reasons for the large number of patients in the control group who switched to the intervention group.

Johnson & Johnson would like to clarify there is no crossover during the interventional phase in PAPILLON study. Patients in the control group (chemotherapy arm) could transition to amivantamab monotherapy (administered every three weeks at the dose specified in the protocol) as a subsequent therapy upon disease progression, which is distinct from switching to the intervention arm.

The PAPILLON study included an intervention arm of amivantamab in combination with carboplatin plus pemetrexed (amivantamab with chemotherapy) and a comparator arm of carboplatin plus pemetrexed (chemotherapy). According to the protocol, those randomised to the chemotherapy arm could receive amivantamab monotherapy following blinded independent central review (BICR)-confirmed disease progression. Amivantamab monotherapy was not part of the intervention but was offered as a potential subsequent treatment for patients who experienced progression in the chemotherapy arm.

The use of amivantamab monotherapy was determined by BICR-confirmed disease progression, with investigators choosing to prescribe it as a subsequent treatment option (as detailed in Section B.3.3.2.1 of the CS).

b) Please explain whether patients' baseline characteristics between the amivantamab monotherapy and the chemotherapy group remain balanced after crossover.

The baseline characteristics of patients within the amivantamab with chemotherapy arm as well as the chemotherapy arm (before and after the chemotherapy overall survival (OS) data had been adjusted for treatment switching) are presented in Table 5.

The results show that the baseline characteristics of patients within the chemotherapy arm before and after adjustment are consistent with regards to age (median age = 62 years vs 62.5 years), proportion of female patients (60% vs 56.4%), proportion of patients with a weight < 80kg (82.6% vs 83.3%), and proportion of patients of non-Asian ethnicity (40% vs 34.6%).

Table 5: Baseline characteristics between patients receiving chemotherapy before and after switching

	Amivantamab with chemotherapy arm (N=153)	Chemotherapy arm (N=155)	Patients in the chemotherapy arm who crossed over (N=78)
Age			
Mean (SD)	██████████	██████████	██████████
Median	61	62	████
Range	(27; 86)	(30; 92)	██████████
Age categories			
<65	97 (63.4%)	92 (59.4%)	██████████
>=65	56 (36.6%)	63 (40.6%)	██████████
Gender			
Male	68 (44.4%)	62 (40%)	██████████
Female	85 (55.6%)	93 (60%)	██████████
Weight (kg)			

Mean (SD)			
Median	61.8	66.5	
Range	(39; 126.8)	(36.5; 112)	
Weight (kg)			
<80	132 (86.3%)	128 (82.6%)	
>=80	21 (13.7%)	27 (17.4%)	
Height (cm) at Baseline			
Mean (SD)			
Median			
Range			
Body Mass Index (kg/m2) at Baseline			
Mean (SD)			
Median			
Range			
Race			
Asian	97 (63.4%)	89 (57.4%)	
No-Asian	53 (34.6%)	62 (40%)	
Unknown	3 (2%)	4 (2.6%)	
Baseline ECOG score			
0	54 (35.3%)	55 (35.5%)	
1	99 (64.7%)	100 (64.5%)	
History of smoking			
No	88 (57.5%)	91 (58.7%)	
Yes	65 (42.5%)	64 (41.3%)	
Location of metastasis at screening			
Bone			
Liver			
Brain	35 (23.2%)	36 (23.5%)	
Lymph node			
Adrenal gland			
Lung			
Other			

Footnote: The imbalances detailed in the above table are adjusted for in the IPCW (base-case) and two stage estimation (scenario) methodologies for treatment switch adjustment.

Abbreviations: ACP: amivantamab in combination with carboplatin and pemetrexed; CP: carboplatin and pemetrexed; ECOG: Eastern Cooperative Oncology Group; SD: standard deviation.

c) If there is a large proportion of crossover during the process of the trial, this may suggest that the chemotherapy therapy in the control group is associated with poor treatment outcome and thus does not correspond to real-world conditions. This may limit the degree of external validity of the results of the trial. Please explain whether

these results can be generalised, given that there is a large proportion of crossover in the trial.

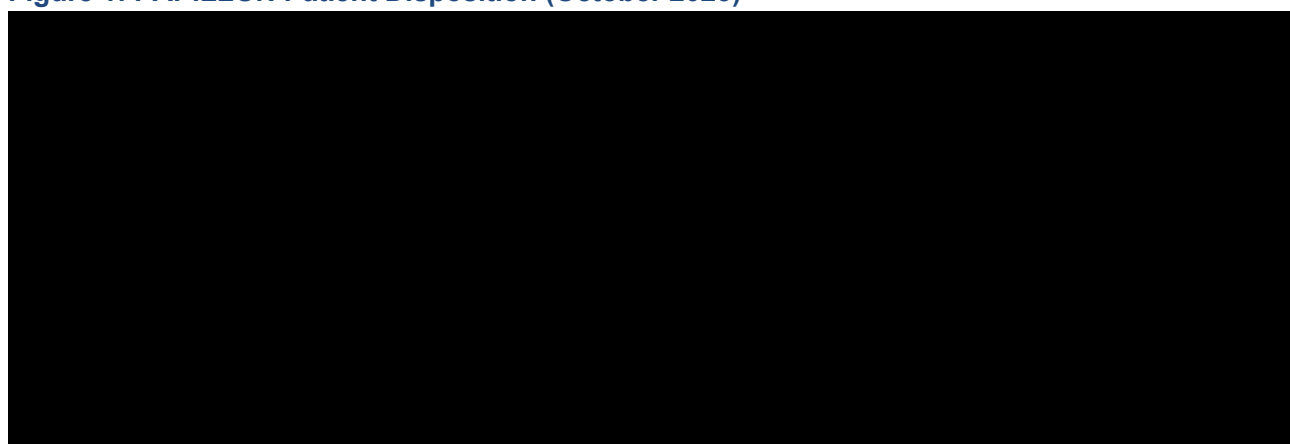
Johnson & Johnson are aligned with the statement from the EAG regarding the poor outcomes observed for patients with EGFR Exon20 insertion mutation-positive advanced NSCLC receiving first-line chemotherapy. As a result of the poor outcomes associated with chemotherapy, many patients experienced progression and then received amivantamab monotherapy as a subsequent treatment, which does not reflect UK clinical practice. Therefore, Johnson & Johnson corrected for the treatment switching to amivantamab monotherapy as a subsequent therapy, to make chemotherapy OS data more accurately reflect real-world conditions in the UK.

It is known that patients with EGFR Exon20 insertion mutation-positive advanced NSCLC receiving first-line chemotherapy have poor treatment outcomes, with a median survival of less than two years. This was demonstrated through results from the NECTAR study which showed that the median OS of patients receiving platinum-based chemotherapy was [REDACTED] months (95% confidence interval [CI]; [REDACTED], [REDACTED]).

The large proportion of patients within the control arm (chemotherapy) who received amivantamab monotherapy as a subsequent therapy after disease progression is indeed related to the limited efficacy of first-line chemotherapy. The proportion of patients who switched to receive amivantamab monotherapy as a subsequent treatment can be attributed to BICR-confirmed disease progression and is a testament to more patients progressing earlier compared with the intervention arm. However, it is not a testament to the underperformance of chemotherapy in the PAPILLON trial compared to real-world conditions.

At the October 2023 data cut-off (DCO), [REDACTED]% of patients in the chemotherapy arm who experienced BICR-confirmed disease progression (78 out of [REDACTED]) received subsequent treatment with amivantamab monotherapy. This is detailed in Figure 1 below.

Figure 1: PAPILLON Patient Disposition (October 2023)



Source: Treatment switch adjustment technical report (figure 1, page 4)¹⁰

Amivantamab monotherapy is not recommended by the National Institute of Health and Care Excellence (NICE) for the treatment of adult patients with advanced NSCLC with activating EGFR Exon20 insertion mutations after failure of platinum-based therapy (TA850) and is not therefore available to patients in UK clinical practice via the NHS.¹¹ As such, Johnson & Johnson believe that the presence of treatment switching in the PAPILLON study is expected to confound the OS results for chemotherapy, resulting in an over-estimation of the survival compared to what would be expected in UK clinical practice. This is due to the positive results of the CHRYSALIS

study which investigated amivantamab-monotherapy in patients with advanced NSCLC with activating EGFR Exon20 insertion mutations after platinum-based therapy. This ultimately reduces the generalisability of the chemotherapy intention to treat (ITT) data to UK practice.

Therefore, Johnson & Johnson adjusted the OS results for chemotherapy to account for the observed treatment switching in the PAPILLON study. The adjusted OS data within the chemotherapy arm more accurately reflect the survival if patients had followed UK clinical practice and are therefore more generalisable to UK practice.

The generalisability of the adjusted chemotherapy data is demonstrated through the close alignment between the OS hazard ratio (HR) for the Inverse Probability of Censoring Weighting (IPCW)-adjusted chemotherapy data (0.76 [CI: 0.50-1.14]) and the OS HR (0.76 [CI: 0.50-1.14]) for the average effect of the treated (ATT)-adjusted indirect comparison of chemotherapy data from the NECTAR study with amivantamab-chemotherapy data from PAPILLON, which did not include subsequent amivantamab monotherapy. The alignment between OS HRs and survival curves is shown in Table 6.

Table 6: Comparative efficacy of amivantamab-chemotherapy versus chemotherapy for OS

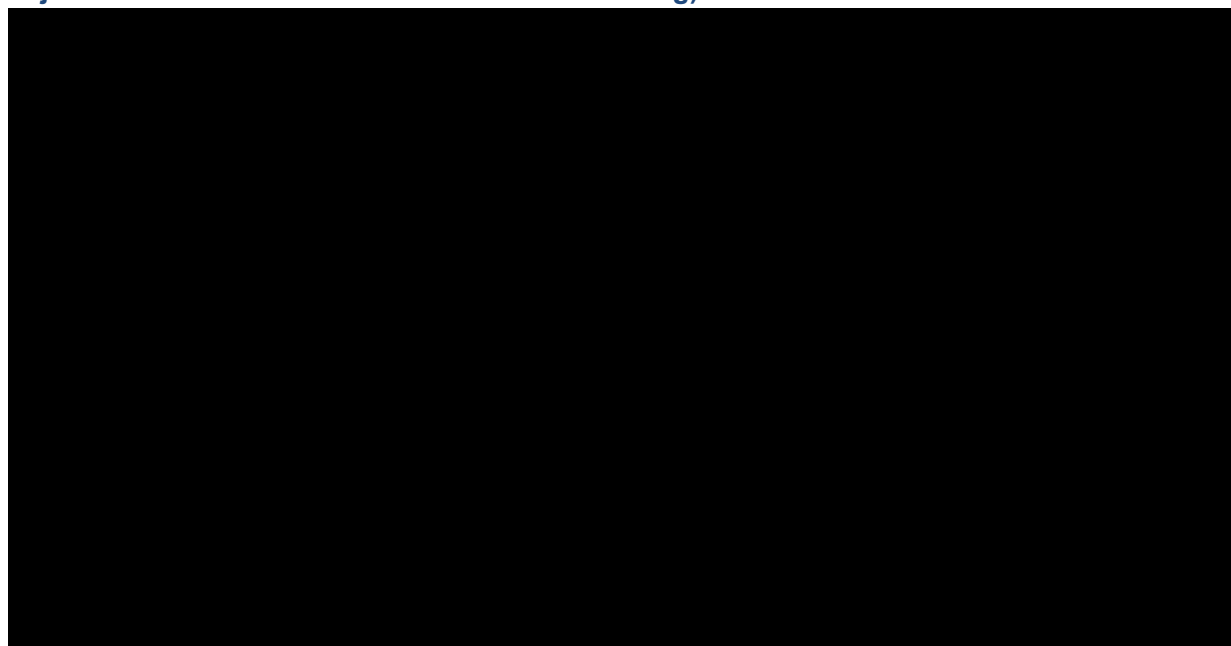
Method	Median OS (months)	OS HR (95% CI)	P-value	Setting
PAPILLON trial (ITT)	28.86	0.76 (0.50-1.14)	0.1825	No adjustment for switching
PAPILLON trial (IPCW)	28.86	0.76 (0.50-1.14)	0.1825	Censor at time of switch and reweight; stabilized weight
RWE (NECTAR study) ^a	28.86	0.76 (0.50-1.14)	0.1825	ATT-Adjusted Analysis Oct 23 data cut; n=230

^a n=70 subjects. Data leveraged from four RW datasets (NCRAS, ESME, US [ConcertAI and COTA]) between 2012 and 2023

Abbreviations: ATT: average treatment effect for the treated; CI: confidence interval; HR: hazard ratio; IPCW: inverse probability of censoring weighting; ITT: intention to treat; OS: overall survival; RWE: real-world evidence

The generalisability of the chemotherapy OS data after treatment switch adjustment via two methodologies (blue curve for two-stage estimation [TSE] and red curve for IPCW in Figure 2), and the limited generalisability of the chemotherapy OS data with no adjustment for treatment switching (green curve in the figure below) to real-world evidence (RWE) is also shown in Figure 2. This figure shows that, compared to chemotherapy with no treatment switch adjustment (green curve), the Kaplan-Meier (KM) curve for chemotherapy OS after adjustment for treatment switching (using two switching methodologies, the IPCW and TSE without recensoring, blue and red curves) better aligns with the KM curve for chemotherapy OS from the NECTAR study where no subsequent amivantamab monotherapy was observed (black curve) and the English-specific RWE from the NCRAS sample (black dotted curve).

Figure 2: Comparison of OS data for chemotherapy from the PAPILLON trial (with/without adjustment via IPCW and TSE without re-censoring) versus RWE sources



Abbreviations: ATT; average effect of the treated; CP: carboplatin + pemetrexed; IPCW: inverse probability of censoring weighting; NCRAS: National Cancer Registration and Analysis Service; TSE: two-stage estimation.

In summary, Johnson & Johnson agree that patients receiving chemotherapy often have poor outcomes. However, Johnson & Johnson have introduced a treatment-switching adjustment (via the IPCW methodology in the base case) to make the chemotherapy data from the PAPILLON trial more representative of UK clinical practice. This adjustment enhances the study's external validity and corrects for treatment switching. The outcomes from the IPCW-adjusted chemotherapy arm align closely with real-world data from the NECTAR and NCRAS studies. Therefore, contrary to the EAG's suggestion, the findings from the PAPILLON study demonstrate strong consistency with NCRAS and NECTAR data, supporting its generalisability to UK clinical practice.

A 8. Priority question: Please provide subgroup analyses for the overall survival outcome of the PAPILLON trial.

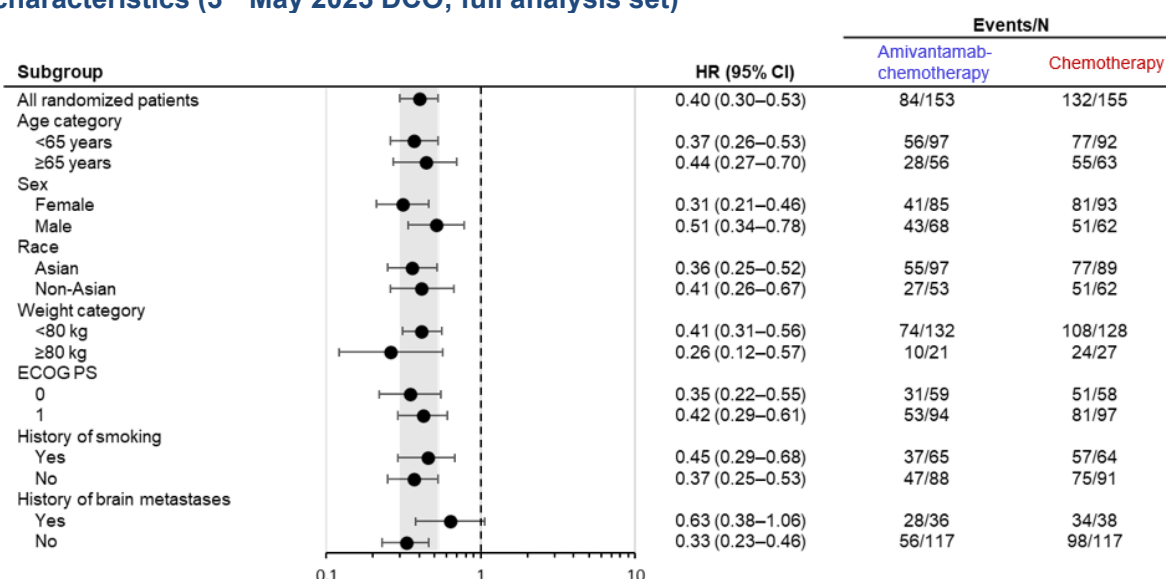
Subgroup analyses are not considered appropriate given the limited sample size of patients available for analysis in the subgroups specified within the NICE final scope (e.g., based on histology, disease stage, and type of EGFR Exon20 alteration).

Further, it is important to note that randomisation was not stratified according to the suggested subgroups in the final scope. Rather, it was stratified based on the performance status score (0 or 1) on the Eastern Cooperative Oncology Group (ECOG) scale, history of brain metastases (yes or no), and prior receipt of an EGFR tyrosine kinase inhibitor (yes or no). Consequently, as the specific subgroups identified during the final scoping were not stratified, the resulting findings may be less reliable and more susceptible to bias. Additionally, OS data from the October 2023 DCO were not assessed by subgroup and these data are therefore not available.

The progression-free survival (PFS) benefit of amivantamab-chemotherapy compared to chemotherapy (based on the primary analysis at the May 2023 DCO) was consistent across all predefined subgroups of brain metastases at study entry (yes or no), age (< 65 or ≥ 65), sex

(male or female), race (Asian or non-Asian), weight (< 80 kg or ≥ 80 kg), ECOG performance status (0 or 1), and smoking history (yes or no). This is illustrated in Figure 3.

Figure 3: Forest plot of BICR-assessed PFS for subgroups defined by baseline disease characteristics (3rd May 2023 DCO; full analysis set)



Abbreviations: BICR: blinded independent central review; CI: confidence interval; DCO: data cut-off; ECOG: Eastern Cooperative Oncology Group; HR: hazard ratio; PFS: progression-free survival; PS: performance status

Further, data presented by Goldman JW, et al, at the WCLC 2024 conference showed that amivantamab with chemotherapy reduced the risk of progression or death by >60% over chemotherapy in patients with analysable plasma ctDNA NGS samples (HR, 0.35; $P < 0.0001$) and patients with site of insertion data (HR, 0.39; $P < 0.0001$).¹² The consistent PFS benefit across these subgroups indicates that these are representative of the ITT population. Goldman JW, et al., also showed that amivantamab with chemotherapy significantly prolonged PFS in patients with or without TP53 co-mutations, indicating that these subgroups were also representative of the ITT population.

The consistent PFS benefit across all assessed subgroups is expected to be replicated for OS and there is no evidence available to suggest that there is a subgroup in which amivantamab with chemotherapy is expected to have a better or worse survival benefit.

Indirect treatment comparison (ITC)

A 9. Priority question. In the CS it is mentioned that: “Efficacy data for pembrolizumab-chemotherapy were informed by the pooled RWE databases from the NECTAR study”.

- a) Please clarify how the NECTAR data were pooled and whether this was done in a methodologically correct way i.e. considering the multi-level structure of the data given the multiple countries/sources of data.

Direct access to Individual Patient Data (IPD) allowed for the pooling of data at the patient level from UK (NCRAS) and US (COTA and ConcertAI). For France (ESME), IPD were accessed remotely. To perform a comparative analysis using inverse probability weighting (IPW), IPD including baseline characteristics and outcomes data from PAPILLON ACP arm were shared with ESME. Having data for both cohorts in one place enabled the estimation of propensity scores (PS), which represent the probability of belonging to the ACP cohort rather than to the RWCP cohort, conditional on baseline characteristics. The same PS model was applied for ESME and for the combined US and UK data. PS were converted into IPW-ATT weights, using the ACP cohort as the target population (and thus keeping as observed, with ATT weight of 1). This ensures exchangeability, under the assumption of no unmeasured confounding, that the PAPILLON ACP arm and RWPC cohorts are exchangeable with respect to patient characteristics at baseline. ESME subsequently shared the unadjusted and ATT-weighted Kaplan-Meier data for each outcome. From this aggregated data, ESME's patient-level outcome data could be reconstructed along with the derived ATT weights. This information was then pooled with the unadjusted or weighted outcome IPD from the US plus UK cohorts. A weighted Cox proportional hazards regression analysis was fitted to this pooled dataset, yielding the estimated IPW-ATT adjusted hazard ratio and confidence interval using the robust sandwich variance estimator.

b) If a multilevel approach has not been adopted then please conduct analyses that do use this approach.

The IPW-ATT treatment effect, described in Question A9, part a, carries a population-averaged (marginal) interpretation, reflecting an average across all data sources. While the Cox model is known to provide a consistent estimate of the population hazard ratio, the corresponding standard error may not be reliable due to potential correlations in survival times within clusters. In the table below, we present an adjustment for the standard error, taking into account the correlation within data source (cluster).

A multilevel approach was not employed in this analysis to address the potential clustering of patients within data sources. Multilevel modelling incorporates cluster-specific random effects to account for the homogeneity of outcomes within clusters. Including random effects in the Cox proportional hazards model yields a database-specific (conditional) interpretation, which indicates an increased or decreased hazard for each database. This model was considered for thoroughness; however, akin to findings from multicentre clinical trials, a site-specific interpretation is generally not of primary interest.

A comparison between the unadjusted and IPW-ATT-adjusted TTNT and OS data is provided in Table 7.

Table 7: Comparison between unadjusted and IPW-ATT-adjusted TTNT and OS data

	TTNT		OS	
	Unadjusted	IPW-ATT	Unadjusted	IPW-ATT
Pembrolizumab + IO				
Accounting for correlation within patient due to weights				
Accounting for correlation within data source				
Platinum-based chemotherapy				

Accounting for correlation within patient due to weights				
Accounting for correlation within data source				

Abbreviations: ATT: average treatment effect of the treated; IO: immunotherapy; IPW: inverse probability weighting; OS: overall survival; TTNT: time to next treatment.

A 10. Priority question. The indirect treatment comparison (ITC) uses propensity score weighting (PSW) to estimate the average treatment effect for the treated (ATT) in the comparison of amivantamab plus chemotherapy with pembrolizumab plus chemotherapy. Eight baseline characteristics were listed for consideration in estimating the PS, but summary data were only provided for four (Tables 28 and 29 in the CS). For the ITC analysis:

a) Please follow Decision Support Unit (DSU) Technical Support Document (TSD) 17 in showing all tests of validity of the individual patient data (IPD) analysis, including overlap assessment.

The balance in covariates across both cohorts, before and after IPW adjustment, was assessed by computing the standardised mean differences (SMD) for each covariate. The SMDs, together with the distribution of PS scores, confirmed that the ATT weighted RW cohort was well balanced across all baseline characteristics versus the observed ACP cohort.

b) Please clarify which baseline characteristics were used to estimate the PS.

i. Please also provide a table showing which baseline characteristics were included from the systematic literature review (SLR), which by clinical experts and which were available in the individual patient data (IPD) for the ITC.

ii. Please conduct sensitivity analyses using any characteristics for which IPD are available and that were either included from the SLR or recommended by clinical experts.

Most prognostic variables identified as clinically important were available in the external data sources and were therefore adjusted for in the analyses. However, adjusting for available, clinically important, prognostic variables cannot entirely exclude bias due to residual confounding, as with any non-randomised comparison. The set of potential confounders was pre-specified following recommendations from the systematic literature review (SLR) and further validated through feedback from clinical experts. The individual participant data (IPD) received

from participating sites were limited to these pre-specified variables, as detailed in the table below.

All variables identified in the SLR that were commonly available across databases were included in the analysis. Consequently, a sensitivity analysis was deemed unnecessary.

Table 8: Comparison of baseline characteristics within the analysis

Baseline characteristics (SLR and clinical experts)	US	NCRAS	ESME	Included in the analysis	Reason for exclusion
Functional status ECOG at baseline	I	I	I	I	I
Presence of brain metastases	I	I	I	I	I
Presence of liver metastases	I	I	I	I	I
Any other metastatic locations	I	I	I	I	
Age at baseline	I	I	I	I	I
Asian ethnicity	I	I	I	I	
Smoking history	I	I	I	I	
Gender	I	I	I	I	I

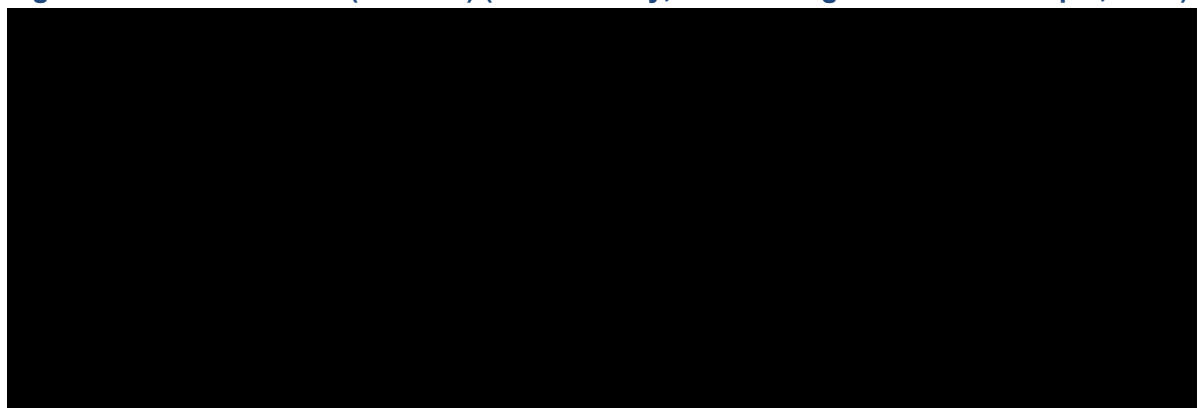
Abbreviations: ECOG: Eastern Cooperative Oncology Group; ESME: Epidemiological Strategy and Medical Economics; NCRAS: National Cancer Registration And Analysis Service; SLR: systematic literature review; US: United States.

c) Please conduct sensitivity analyses as recommended in TSD 17, such as using regression adjustment and/or a doubly robust method.

Covariate adjustment and doubly robust regression require centralized pooling of all individual patient data (IPD). Due to the remote access setup of the IPD in ESME, these analyses could not be performed on the pooled NECTAR data. However, these methods can be applied using the UK data independently with results for both methods shown in the plot below.

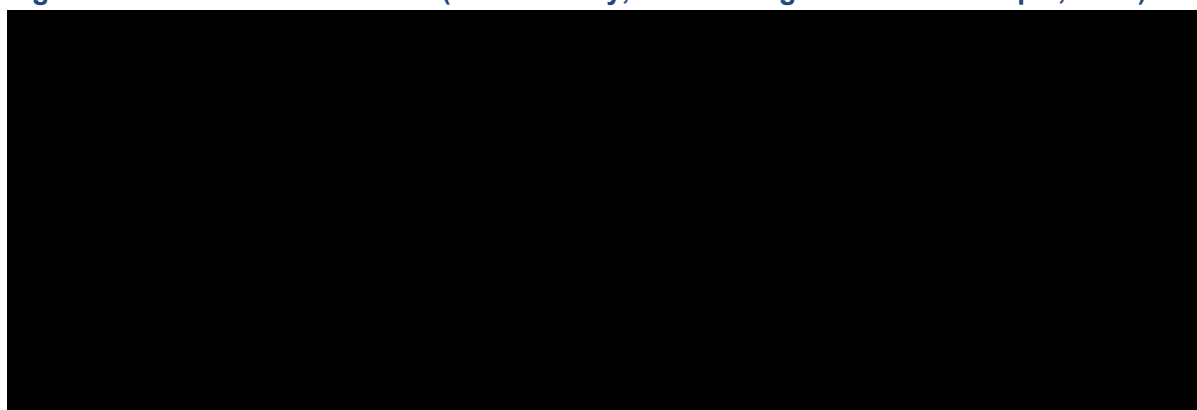
Using only the UK data, an analysis for a specific treatment class is not feasible due to a limited patient sample (4 patients for pembrolizumab + IO) class. However, it was feasible when taking into account all available UK RW data (RWCP) from 23 patients (i.e., the full NCRAS dataset included within the NECTAR study). The results of this analysis demonstrate consistency across various methods, as illustrated in the Figure 4 and Figure 5 below.

Figure 4: Overall survival (October) (UK data only, considering full NCRAS sample, n=23)



Abbreviations: ACP: amivantamab in combination with carboplatin and pemetrexed; ATC: average treatment effect in the control; ATT: average treatment effect of the treated; CI: confidence interval; HR: hazard ratio; RW: real world; UK: United Kingdom.

Figure 5: Time to next treatment (UK data only, considering full NCRAS sample, n=23)



Abbreviations: ACP: amivantamab in combination with carboplatin and pemetrexed; ATC: average treatment effect in the control; ATT: average treatment effect of the treated; CI: confidence interval; HR: hazard ratio; RW: real world; UK: United Kingdom.

d) Please conduct sensitivity analyses using the UK data only.

Please see combined response in part c.

e) Please provide justification for the ATT on the basis of the generalisability of the patient data to UK clinical practice. Please also conduct sensitivity analyses to estimate the average treatment effect by adjust to better match the UK real-world data i.e. UK real-world data receive a PS of 1.

The ATT approach has been selected given it ensures patient data from real-world evidence sources have a similar distribution of confounders as the PAPILLON amivantamab with chemotherapy arm (with data within the PAPILLON trial remaining unchanged). Ensuring the PAPILLON trial data remain unchanged was the driving factor behind why the ATT weighting approach was selected over others (e.g., ATC weighting).

However, as detailed in Figure 4 and Figure 5, Johnson & Johnson have also conducted a scenario using the average treatment in the control (ATC) approach. This involves weighting the data from the amivantamab with chemotherapy arm of the PAPILLON trial to provide a similar distribution of confounders to patients within the UK RWE data from NCRAS (i.e., UK RWE cohort remains unchanged and receives a PS of 1). The OS and TTNT HRs between the ATT-weighting and ATC-weighting approaches are similar (ATT-weighted OS HR: 0.38 vs ATC-weighted OS HR: 0.39). As such, ATT-weighted real-world data are generalisable to data from the UK real-world cohort. Johnson & Johnson also performed the scenarios looking at the doubly robust and Covariate adjustment, which provided a larger relative benefit with lower HR than the ATT or ATC-weighted scenarios.

For all scenarios presented above, the hazard ratios are similar, and the confidence intervals do not cross 1, showing statistical significance in the results. The wide confidence intervals can be attributed to the UK-specific analysis being based on a small number of patients (n=23).

f) In line with question A3, please provide ITCs for comparisons with all relevant comparators.

Johnson and Johnson maintain the position provided in the CS, and detailed within the response to question A3, that the only relevant comparators (i.e., treatments likely to be displaced by the introduction of amivantamab with chemotherapy, if reimbursed) are carboplatin with pemetrexed and pembrolizumab with carboplatin plus pemetrexed. This is based on clinical opinion obtained across three advisory boards (June 2023, May 2024, and August 2024), as well as RWE (English RWE from the NCRAS database and pooled RWE from four databases within the NECTAR study).⁶⁻⁹

However, Johnson & Johnson acknowledge that, despite being against best practice, pembrolizumab monotherapy had previously been shown to be used to a limited extent in practice. Therefore, ITC results from the NECTAR study for the IO alone treatment class are presented below. These are also detailed within the full NECTAR study report which was included within the reference pack of the CS.

Due to a small number of patients within the IO alone treatment class, ATT-adjustment was not possible. Therefore, only unadjusted results are presented which should be interpreted with caution. Results for the IO alone treatment class from the NECTAR study are expected to be representative of patients receiving pembrolizumab monotherapy given █% (█/█) of patients within the IO alone treatment class were receiving pembrolizumab monotherapy. Full results from the ITC can be found in the NECTAR study report, included within the reference pack of the CS.⁹

OS

Based on unadjusted HR estimates of OS, amivantamab with chemotherapy demonstrated statistically significantly better OS compared with IO alone (Wald-p < 0.05). The unadjusted median OS for patients receiving IO alone was █ months (95% CI: █-█) whereas the median OS was █ for patients receiving amivantamab with chemotherapy. The unadjusted OS HR for IO alone versus amivantamab with chemotherapy was █ (95% CI: █-█; Wald p-value = █). The results are presented in Table 9 and Figure 6.

Table 9: Unadjusted HR estimates of OS: ACP versus IO alone treatment class (Oct 2023 OS data)

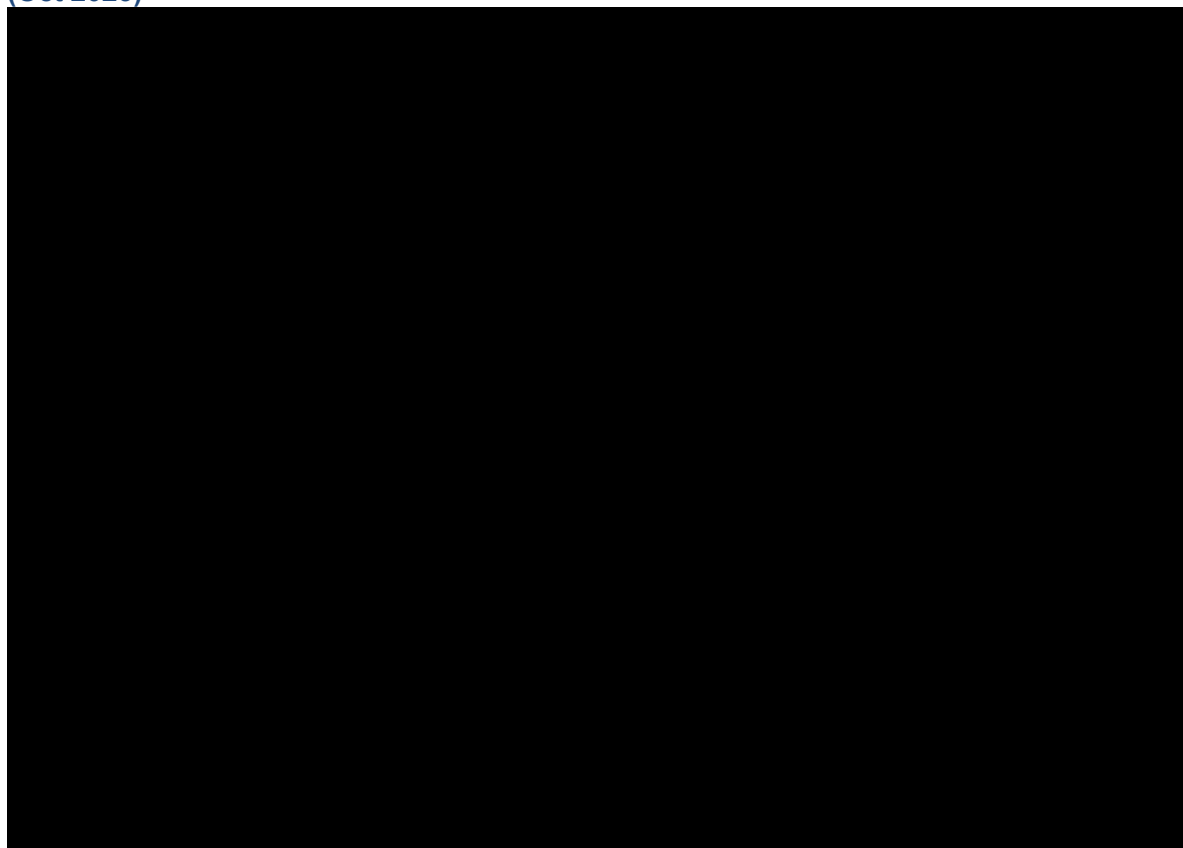
OS	Unadjusted Analysis

	N	Median, months (95% CI)	HR (95% CI)	Wald-p-value
ACP vs:	153	NE (28.32, NE)	■■■■■	■■■
IO ^a	20	■■■■■		

^a ATT adjustment not performed due to small sample size.

Abbreviations: ACP: amivantamab with carboplatin plus pemetrexed (PAPILLON active arm); HR: hazard ratio; IO: immunotherapy; OS: overall survival

Figure 6: Kaplan-Meier curve of OS for ACP versus RWD IO alone – unadjusted results (Oct 2023)



Footnotes: ATT adjustment was not performed due to small sample size. RWD datasets were ENG-NCRAS, FR-ESME, US-ConcertAI, and US-COTA.

Abbreviations: ACP: amivantamab with carboplatin plus pemetrexed (PAPILLON active arm); ATT: average treatment effect in the treated; CI: confidence interval; ENG: England; ESME: Epidemiological Strategy and Medical Economics; FR: France; HR: hazard ratio; IO: immunotherapy; NA: not applicable; NCRAS: National Cancer Registration and Analysis Service; OS: overall survival; RWD: real-world data; US: United States.

TTNT

In the unadjusted HR analysis, amivantamab-chemotherapy demonstrated statistically significantly favourable TTNT compared with IO alone (Wald-p < 0.05).

The unadjusted median TTNT for patients receiving IO alone was ■■ months (95% CI: ■■-■■) whereas the median TTNT was ■■ months (95% CI: ■■-■■) for patients receiving amivantamab-chemotherapy. The unadjusted TTNT HR for IO alone versus amivantamab-chemotherapy was ■■■ (95% CI: ■■-■■; Wald p-value ■■■). The results are presented in Table 10 and Figure 7.

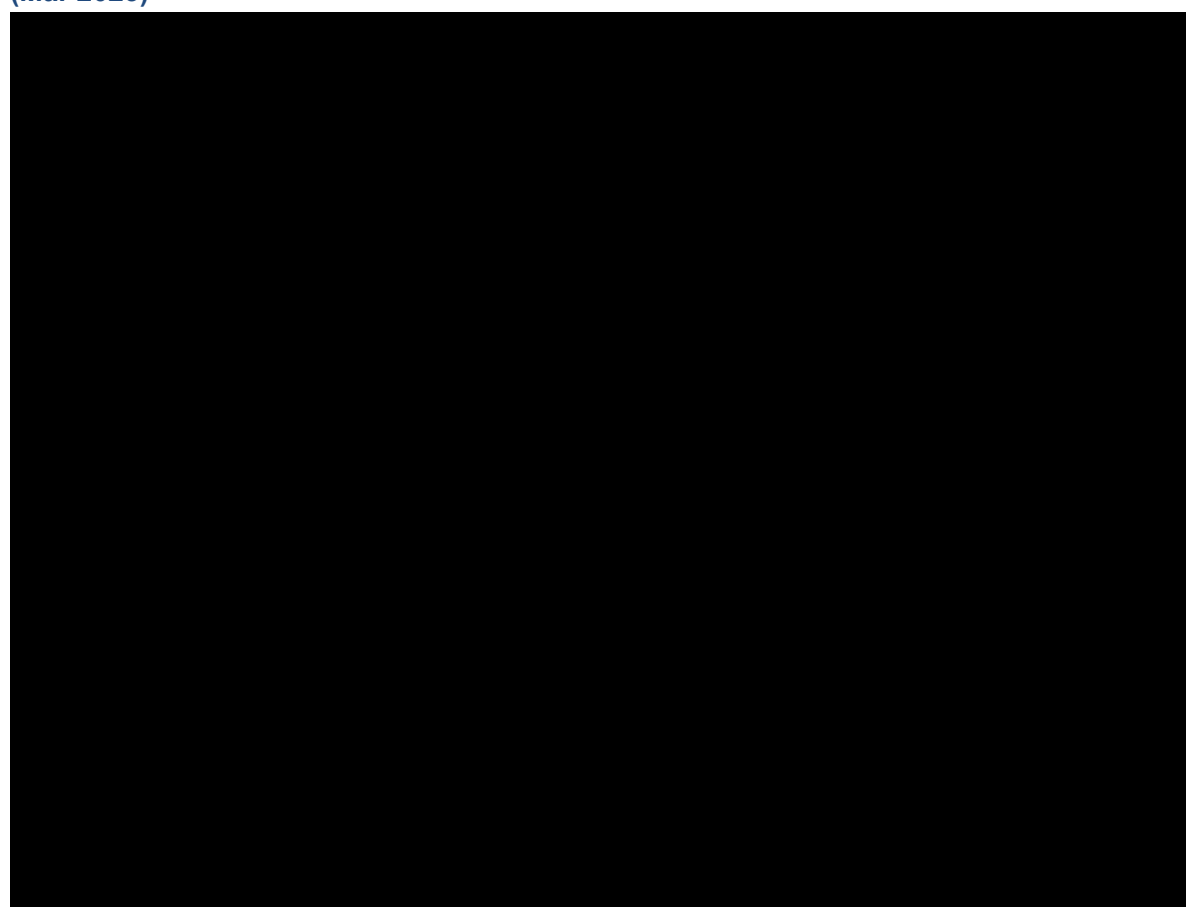
Table 10: Unadjusted and ATT-Adjusted HR Estimates of TTNT: ACP Versus Pooled RWD Treatments and Classes (Mar 2023)

TTNT	Unadjusted analysis			
	N	Median, months (95% CI)	HR (95% CI)	Wald-p-value
ACP vs:	153	17.7 (13.67, NE)		
IO ^a	20			

^aATT adjustment not performed due to small sample size.

Abbreviations: ACP: amivantamab with carboplatin plus pemetrexed (PAPILLON active arm); HR: hazard ratio; IO: immunotherapy; OS: overall survival

Figure 7: Kaplan-Meier Curve of TTNT for ACP Versus RWD IO Alone –Unadjusted Results (Mar 2023)



Footnotes: ATT adjustment was not performed due to small sample size. RWD datasets were ENG-NCRAS, FR-ESME, US-ConcertAI, and US-COTA.

Abbreviations: ACP: amivantamab with carboplatin plus pemetrexed (PAPILLON active arm); ATT: average treatment effect in the treated; CI: confidence interval; ENG: England; ESME: Epidemiological Strategy and Medical Economics; FR: France; HR: hazard ratio; IO: immunotherapy; NA: not applicable; NCRAS: National Cancer Registration and Analysis Service; RWD: real-world data; TTNT: time to next treatment; US: United States.

- g) The adjusted outcomes for pembrolizumab plus platinum-based chemotherapy are worse than the unadjusted outcomes. However, the change in effect for platinum-based chemotherapy alone is in the opposite direction (see Figure 14, NECTAR Study Report). Given that**

the population in PAPILLION seems to have a worst prognosis according to a comparison of baseline characteristics (see Table 28, CS), please explain this discrepancy.

Johnson & Johnson would like to highlight that the observed differences between unadjusted and adjusted analyses for both chemotherapy and for pembrolizumab with chemotherapy are minor (curves closely align). The ATT-adjusted group shows small deviations compared with the naïve population in both comparisons. Whilst the trend between the unadjusted and adjusted analyses for chemotherapy is opposite to the trend seen with pembrolizumab with chemotherapy, the results should be interpreted with caution due to the limited sample size of the patient population which restricts the interpretability of the findings.

The Kaplan-Meier curves exhibit similar shapes, while the HRs are closely aligned with one another and accompanied by broad overlapping confidence intervals. Consequently, the significance of the observed differences is minimal. This suggests that the variability present may primarily result from random chance rather than a genuine difference in treatment efficacy.

In the analysis of treatment classes, each class was compared separately to the ACP arm, with a distinct PS model fitted for each comparison. While ACP in PAPILLION may appear to have a worse prognosis compared to pembrolizumab plus platinum-based chemotherapy, this may not hold true for other treatment classes. Further, the differences in baseline characteristics between treatment classes may not necessarily indicate the direction of outcomes observed given these also depend on the prognostic impact of the variables for each specific outcome (i.e., TTNT and OS).

Section B: Clarification on cost-effectiveness data

Intervention and comparator

B 1. Priority question. As highlighted in CS Table 84, a weighted comparator comprising chemotherapy (70%) and pembrolizumab in combination with carboplatin and pemetrexed (30%) was included in the base case. This approach is not in line with best practices and is inconsistent with the preferences reported in the company's advisory board report from August 2024. A 'blended' comparator approach can hide important differences in estimated cost-effectiveness, as illustrated in the current case ('blended' ICER [REDACTED], all without disease modifier). Please provide further clarification on the following points, as this will help ensure the appraisal process is fully informed.

a) Please provide all results presented in CS Sections B.3.10 and B.3.11, while considering chemotherapy and pembrolizumab in combination with carboplatin and pemetrexed as separate comparators.

Johnson & Johnson believe that weighting the individual ICERs of each relevant comparator (chemotherapy and pembrolizumab with chemotherapy) based on their expected use in UK clinical practice is an appropriate approach to the cost-effectiveness analysis, given the treatment landscape for patients with Exon20 insertion mutation-positive advanced NSCLC. Although Johnson & Johnson acknowledge that a weighted comparator is unusual, robust justification for this approach has been provided in Section B.3.2.3 of the CS, in the response that follows and in part c below. Specifically, there is no established SoC for patients with EGFR Exon20 insertion mutation-positive advanced NSCLC in the UK, and the expectation is that amivantamab with chemotherapy would displace both chemotherapy and pembrolizumab with chemotherapy collectively in UK clinical practice in lieu of a single dominant comparator. Indeed, variation in use of these two comparators across the UK is expected given the lack of treatment guidance for this patient population; for example, Johnson & Johnson would like to emphasise that numerous hospitals and clinicians within the UK administer pembrolizumab with chemotherapy in up to 90% of their patients (also see response to part b below). Johnson & Johnson have therefore employed a weighted comparator to more accurately reflect these treatment practices, with the company base case conservatively setting use of pembrolizumab-chemotherapy at 30%.

b) According to the company's June 2023 advisory board report (second page), the weighing, i.e. the approximate proportions (%) of patients receiving each of the first-line therapy regimen (reported by seven advisors), does vary considerably (e.g. for pembrolizumab in combination with carboplatin and pemetrexed the proportion varied between 10%-80%). Please clarify how this uncertainty is reflected in the CS base-case analyses and elaborate on the implications of this variation, in advisors' responses, for the 'blended' comparator approach.

Johnson & Johnson acknowledge there is substantial variation in the proportional use of different first-line therapies cited by individual advisors in the June 2023 advisory board.⁶ Further, the proportional use of first-line therapies varies across different advisory boards and is different to the proportions of first-line therapies observed within the NCRAS dataset (likely due to timing of the data collection in NCRAS and the small sample size).¹³ This variation further supports the lack of an established SoC and a single dominant comparator within this population.

The model is flexible to allowing changes to the weightings assigned to the comparators to reflect different proportional uses in practice. Indeed, the CS provided several scenarios where the proportional use of relevant comparators was varied (Section B.3.11.3). In scenario 13, the proportional use of pembrolizumab plus chemotherapy is increased to 90% (reflecting the upper bound of individual responses elicited from the May 2024 advisory board).⁷ To address this uncertainty further, Johnson & Johnson also incorporated two scenarios informed by the NCRAS data (scenarios 11 and 12). Scenario 11 modelled the costs and efficacy of all treatments

identified, weighted by their corresponding observed use in NCRAS, whilst scenario 12 modelled the efficacy of treatments (to avoid reducing the small sample size further) but modelled the costs solely for chemotherapy and IO with chemotherapy. Accordingly, uncertainty in the proportional use of the relevant comparators has been carefully explored through these scenario analyses, which all led to a cost-effective ICER.

c) According to the company's August 2024 advisory board report "The HE experts agreed that strong justification for use of a weighted comparator approach would be required in the submission, noting that precedence for this approach in previous appraisals fails to provide a strong rationale by itself". A strong justification for this approach is currently missing in the CS. Please provide strong justification supporting the 'blended' comparator approach.

As described in Section B.1.3 of the CS, there is currently no NICE treatment pathway for patients with EGFR Exon20 insertion mutation-positive advanced NSCLC. Although NICE lung cancer diagnosis and management guidelines (NG122) previously included guidance for these patients, this guidance has been removed following the withdrawal of mobocertinib (recommended after prior chemotherapy) by the manufacturer in March 2024.^{14, 15} Following the withdrawal of the NICE guidance for mobocertinib, there are currently no NICE-recommended therapies for patients with EGFR Exon20 insertion mutation positive NSCLC at any line. The absence of a clear SoC was further reflected in the NICE final scope, with over 20 treatments being suggested.¹⁶

In lieu of an established treatment pathway or any NICE-recommended therapies, multiple first-line treatments are prescribed to patients with untreated EGFR Exon20 insertion mutation-positive advanced NSCLC in UK practice. To understand the treatments most commonly used in UK clinical practice that would constitute relevant comparators, Johnson & Johnson examined English RWE sourced from the NCRAS database and conducted three advisory boards.

As discussed in response to Question A4, the RWE obtained from NCRAS is associated with a number of limitations, including sample size and the timing of data collection. Therefore Johnson & Johnson conducted three advisory boards to gain further, and more accurate, insight into the proportional use of first-line treatments in UK clinical practice. From the advisory boards, detailed below, the two predominant regimens being prescribed were carboplatin plus pemetrexed and pembrolizumab with carboplatin plus pemetrexed, used in approximately 70% and 30% of patients, respectively.

- At the June 2023 advisory board, the average proportional use across the seven advisors, based on responses from a pre-meeting survey, was 57% (10%–90%) for carboplatin plus pemetrexed, 34% (0%–80%) for pembrolizumab with carboplatin plus pemetrexed, and 7% (0%–20%) for atezolizumab in combination with bevacizumab plus carboplatin plus pemetrexed (ABCP), with the remaining 2% attributed to best supportive care. It should be noted that ABCP was not listed as a comparator with the NICE final scope and, during both the May 2024 and August 2024 advisory boards, the ABCP combination was not mentioned as a relevant comparator.⁶

- At the May 2024 advisory board, advisors aligned on a consensus that platinum-based chemotherapy was used in approximately in 70% of patients and that practically all patients (95%–100%) would receive carboplatin plus pemetrexed. Advisors also aligned on a consensus that 30% of patients would receive immunotherapy in combination with chemotherapy and that practically all patients (100%) would receive pembrolizumab plus carboplatin and pemetrexed. Additionally, advisors aligned on a consensus that IO monotherapy should not be used in practice.⁷
- At the August 2024 advisory board, the clinical advisors agreed that the predominant treatments being prescribed are chemotherapy (carboplatin with pemetrexed) and IO combination therapies (pembrolizumab with chemotherapy).⁸

As noted in the details above and discussed in part b, use of the two relevant comparators varies in clinical practice, there is no single dominant comparator within this population, Johnson & Johnson therefore consider use of a weighted comparator in the economic analysis to be appropriate.

B 2. Priority question. In line with question A4, the CS base-case does not consider all comparators listed in the final NICE scope.

a) Pembrolizumab monotherapy is listed in CS Table 1 as “addressed in the company submission”. Please provide analyses, as well as an updated economic model, including pembrolizumab monotherapy as comparator.

As discussed in Section B.1.1 of the CS and in response to Question A4, Johnson & Johnson maintain that pembrolizumab monotherapy is not a relevant comparator to amivantamab with chemotherapy in this evaluation. Given the lack of licensed treatments and clinical guidelines specifically for patients with EGFR Exon20 insertion mutation-positive advanced NSCLC, there is no standard of care for these patients in the UK. Expert clinical opinion was therefore sought to understand which therapies are prescribed to patients in the UK in the absence of an effective treatment.

Clinical expert opinion supports that there is limited to no use of pembrolizumab monotherapy in clinical practice. Clinical experts participating in the August 2024 advisory board confirmed that use of immunotherapy monotherapy in this patient population is against best practice, and that well-informed clinicians would not use this treatment.⁸

Furthermore, use of pembrolizumab monotherapy for any EGFR mutation is not within licence, as this only covers first-line treatment of adults with metastatic NSCLC whose tumours express PD-L1 with a $\geq 50\%$ tumour proportion score (TPS), with no EGFR or ALK positive tumour mutations.¹⁷ As such its use within the population in this submission would be off-label. In line with this, pembrolizumab monotherapy is not a treatment option recommended by NICE for patients with EGFR Exon20 insertion mutation-positive advanced NSCLC in the UK.

For the above reasons, Johnson & Johnson maintain the position within the CS that pembrolizumab monotherapy is not a relevant comparator and have not provided results comparing to this comparator.

However, Johnson & Johnson have included pembrolizumab monotherapy within the updated cost-effectiveness model (as a standalone comparator). Despite it being viewed as irrelevant, the EAG can use the updated model to obtain results of amivantamab with chemotherapy versus pembrolizumab monotherapy (deterministic and probabilistic results within 'HTA outputs' sheet of the model).

b) Atezolizumab is listed in the final scope. Please provide analyses, as well as an updated economic model, including atezolizumab as comparator.

Johnson & Johnson maintain that atezolizumab is not a relevant comparator to this decision problem and have not included this in the economic model.

Firstly, as described in response to part a) and Question A4, use of immunotherapy monotherapy for the patient population of interest is considered against best practice by UK clinical experts. This is supported by RWE from the NCRAS dataset showing no usage of atezolizumab in patients with EGFR Exon20 insertion mutation-positive advanced NSCLC.¹³

NICE recommends atezolizumab treatment exclusively for patients without an established EGFR mutation. Consequently, atezolizumab is not recommended for the population addressed in this decision problem.

c) TKIs are listed in the final scope. Please provide analyses, as well as an updated economic model, including TKIs as comparator.

Johnson & Johnson maintain that EGFR TKIs are not relevant comparators within this evaluation. EGFR TKIs are not specifically recommended by NICE for patients with EGFR Exon20 insertion mutations at any treatment line.¹⁴ Importantly, EGFR Exon20 insertion mutations are associated with *de novo* resistance to EGFR TKIs, rendering their use ineffective in this patient population.^{5, 18} This is a result of conformational changes in the EGFR protein that diminish TKI binding affinity.^{5, 19} Clinical expert opinion highlighted that any use of EGFR TKIs in UK clinical practice is against best practice, given their lack of efficacy in this patient population.⁸ RWE supporting the lack of efficacy of EGFR TKIs in patients with Exon20 insertion mutation-positive NSCLC is also discussed in Section B.1.3.1 of the CS.

The response from the British Thoracic Oncology Group (BTOG) on the draft scope for this evaluation further highlighted that use of standard EGFR TKIs in this population was inappropriate.²⁰ Additionally, in the appraisal of the second-line indication of amivantamab for treating EGFR Exon20 insertion mutation-positive advanced NSCLC after platinum-based chemotherapy (TA850), clinical experts explained that EGFR TKIs have limited efficacy when there are EGFR Exon20 insertion mutations and, because of this, are rarely and inappropriately used in this population.

Given the above Johnson & Johnson do not consider EGFR TKIs relevant comparators and have not included these in the economic model.¹¹

d) Please provide the results of a fully incremental analysis (and updated economic model used for this analysis) with all comparators listed in the scope as comparators modelled separately.

As described in the CS and the responses to parts a–c above and Question A4, Johnson & Johnson do not consider that any other comparators, aside from carboplatin with pemetrexed (chemotherapy) and pembrolizumab with carboplatin plus pemetrexed (pembrolizumab with chemotherapy), are relevant.

As described in response to Question A1, there is no standard of care within EGFR Exon20 insertion mutation-positive advanced NSCLC, and as a result, no single dominant comparator to amivantamab-chemotherapy; chemotherapy and pembrolizumab with chemotherapy represent the two relevant comparators in this population. In lieu of a single dominant comparator, Johnson & Johnson maintain that the weighted comparator approach used in the CS is appropriate. Therefore, individual comparisons would not reflect the therapies on the NHS that would be displaced by the introduction of amivantamab with chemotherapy. As such, a fully incremental analysis has not been conducted.

B 3. Priority question. According to the 2024 Advisory Board Report:

“ [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED] ”

- a) Please provide analyses, as well as an updated economic model, adjusting the population characteristics, used in the economic model, to the population as expected in UK clinical practice (including weight [also the % of patients above 80kg] and BSA).

Table 11 shows the baseline characteristics available from the following sources: PAPILLON (base case), NECTAR (US and UK only [access to the ESME data is currently unavailable – see part b]), and NCRAS (using available IPD).

Johnson & Johnson have provided a scenario analysis whereby the baseline characteristics reflect the NCRAS dataset. The baseline characteristics within the NCRAS dataset align to the characteristics within the PAPILLON study, albeit with a slightly older mean age and a slightly higher proportion of female patients.

Table 11: Baseline characteristics used in the economic model based on PAPILLON, NECTAR (US and UK) and NCRAS

Baseline characteristics	PAPILLON	NECTAR (US and UK) n= 139	NCRAS – n=23
Age (mean), years	[REDACTED]	[REDACTED]	65 (sd = 6.74)
Proportion of female, %	58	[REDACTED]	69.57%
Body weight (mean), kg	[REDACTED]	[REDACTED]	66.945 (sd = 17.15)
Body surface area (mean), m ²	[REDACTED]	[REDACTED]	NA

Proportion of patients <80 kg, %	84	■	80

Footnote: Estimates from the NCRAS database are from unadjusted analyses. Body weight data is unavailable from US databases.

Abbreviations: NA: not applicable; NCRAS: National Cancer Registration And Analysis Service; sd: standard deviation; UK: United Kingdom; US: United States.

Source: Johnson & Johnson PAPILLON CSR 2023,²¹ Johnson & Johnson, The NECTAR Study 2024,⁹ and Johnson & Johnson RWE NCRAS Data 2024.¹³

Results from the scenario analysis whereby the population characteristics have been adjusted to reflect the NCRAS dataset are presented in Table 12. It is important to acknowledge that the NCRAS dataset only included a small number of patients (n=23) from England. Therefore, any comparisons or analyses requested specifically for this subgroup are likely to yield limited information and should be interpreted with caution.

As highlighted at the start of the company response to the clarification questions, the cost-effectiveness results in the base case are different to those cited within the company submission due to the inclusion of the updated NHS reference costs.

Table 12: Scenario analysis results (alternative data source for baseline characteristics used in the economic model)

	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Base case	■	■	24,839
Baseline characteristics from NCRAS	■	■	25,151

Abbreviations: ICER: incremental cost effectiveness ratio; NCRAS: National Cancer Registration and Analysis Service; QALY: quality adjusted life year.

- b) Please provide analyses, as well as an updated economic model using the NECTAR study population characteristics in the economic model.

Table 11 presented in part a, shows the baseline characteristics used in the economic model based on PAPILLON (base case) as well as the baseline characteristics from the NCRAS dataset (using available IPD)

It should be noted that, since the conclusion of the NECTAR study, access to the ESME database has been withdrawn. Consequently, additional analyses using the full IPD set from the NECTAR study, such as calculating the median age from the pooled data, is not possible. As such, the baseline characteristics within the current NECTAR dataset are different compared with the dataset used at the time of the CS. Additionally, using baseline characteristics from the NECTAR dataset would not represent patients within England. Therefore, Johnson & Johnson do not view an analysis based on the NECTAR baseline characteristics as appropriate.

Population

B 4. : Johnson & Johnson PAPILLON CSR 2023. The CS base-case does not consider all subgroups listed in the final NICE scope.

- a) Disease stage is listed in the final scope as subgroup. Please provide analyses, as well as an updated economic model, including disease stage as subgroup.
- b) Histology is listed in the final scope as subgroup. Please provide analyses, as well as an updated economic model, including histology as subgroup.
- c) Type of exon 20 alteration present and presence of co-mutations is listed in the final scope as subgroup. Please provide analyses, as well as an updated economic model, including type of exon 20 alteration present and presence of co-mutations as subgroup.

As per the response to Question A8, subgroup analyses for the populations specified within the NICE final scope (based on histology, disease stage, and type of EGFR Exon20 alteration) are not considered appropriate given the limited sample size of patients available for analyses and the fact that randomisation to the PAPILLON study was not stratified by these factors.

- **Histology:** The PAPILLON trial excluded patients with squamous NSCLC and, since 99% of the trial population was of adenocarcinoma histology type, these subgroups could not be explored.
- **Disease stage:** Subgroup based on disease stage could not be explored as efficacy data stratified by this group are not available.
- **Type of EGFR Exon20 alteration or presence of co-mutations:** Subgroups based on mutation alteration could not be explored as available sample sizes do not permit such analyses.

Model structure

B 5. The National Institute for Health and Care Excellence (NICE) DSU TSD 19 recommended the use of state transition models (STMs) alongside partitioned survival models (PSMs) to verify the plausibility of PSM extrapolations and explore key clinical uncertainties in the extrapolation period.

- a) According to the SLR described in CS Section B.3.2.2, 17 out of 50 (34%) identified economic evaluations for patients with advanced common EGFR mutation positive NSCLC, used a STM (described as Markov in the CS) approach. This illustrates that the STM approach should be considered as relevant option. Please provide further insight into the decision to adopt a PSM instead of an STM. Please discuss the rationale and explore the

implications of this choice, particularly in light of the issues highlighted in NICE DSU TSD 19.

As described in Section B.3.2.2 of the CS, a partitioned survival model (PSM) is an appropriate model structure for this decision problem as it captures the natural history and clinical pathway for NSCLC. At the advanced stage of NSCLC, patients may only progress through the health states in one direction and cannot return to the progression-free state once progressed. Use of a PSM was validated as the most suitable modelling approach by a global advisory board conducted by Johnson & Johnson in November 2023.²²

The model structure aligns with prior technology appraisals in patients with advanced NSCLC, including TA850 (amivantamab for treating EGFR exon20 insertion mutation-positive advanced NSCLC after platinum-based chemotherapy), TA855 (mobocertinib for treating EGFR exon20 insertion mutation-positive advanced NSCLC after platinum-based chemotherapy), and TA683 (pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic NSCLC).^{11, 23, 24} Therefore, the PSM approach aligns with the model structure used for decision-making in Exon20 mutation-positive NSCLC populations as well as for a relevant comparator therapy to this evaluation. As supported by the economic SLR, a PSM is the most frequent structure utilised for oncology models (used in 21/50 identified cases) due to the simplicity of model structure and ease of interpretation.²⁵

In response to the question, as described in NICE DSU TSD 19, the computational, statistical and data requirements of a state transition model (STM) are substantially greater than those of a PSM. Accordingly, the complexity associated with an STM approach is anticipated to introduce greater uncertainty into the cost-effectiveness analysis than might be offset in the long-term survival predictions through use of this structure. The following complexities of an STM relative to a PSM with regards to the modelling of amivantamab vs relevant comparators are particularly highlighted:

- The PSM approach requires estimates of the PFS and OS curves for each treatment, whereas a corresponding STM (as shown in Figure 3 of TSD 19) requires time-to-event data on each of three individual transition probabilities, as well as estimates of the effects of each treatment on each transition probability
- As noted by TSD 19, trial PFS and OS data, as available from PAPILLON, cannot be used to derive the time-to-event data required for state transition modelling in a straightforward manner, meaning additional analysis and assumptions are required to calculate the transition probability inputs. The TSD in particular highlights the complexity of the methods to calculate time-dependency in transition probabilities for STMs
- A key source of comparator data (pembrolizumab-chemotherapy) in the submission was the NECTAR study, which represents a rich source of real-world individual patient data for patients with advanced Exon20 insertion-positive NSCLC.⁹ However, in line with Section B.2.9.3 of the CS, the clinical outcomes collected in the databases would not have been sufficient to fulfil the significant data requirements of an STM, leading to need for a greater set of assumptions compared to those used for the PSM. More generally, a STM structure is not flexible enough to incorporate ITC data from non-trial comparators
- As described in Section B.3.3.2 of the CS, the IPCW was (clinically) validated as the most appropriate methodology to adopt with regards to adjusting for treatment switching

in the PAPILLON trial. However, as noted by TSD 19, the outputs of the IPCW cannot be used to inform an STM

Whilst state transition modelling allows event rates and treatment effects on these event rates to be specified for individual components of the disease process (e.g. the transition from post-progression to death), model inputs are still ultimately informed by the same set of data (whether this be trial-based or RWE), as caveated in recommendation 11 of TSD 19. Accordingly, the TSD is clear that neither use of a PSM nor an STM is able to resolve uncertainty associated with immature trial data. Indeed, the immaturity of the PAPILLON trial does not provide sufficiently mature data to populate model transitions beyond progression. As such, the survival inputs included in the PSM adopted by Johnson & Johnson were reviewed for their long-term clinical validity by UK clinical experts, as described in Section B.3.3.2 of the CS, with scenario analyses performed exploring alternative survival extrapolations to ensure the robustness of the model to uncertainty in long-term survival estimations.

- b) Please justify the use of a PSM given the issues highlighted in NICE DSU TSD 19, particularly regarding the extrapolation of progression-free survival (PFS) and overall survival (OS) while assuming structural independence between these endpoints.

As described in response to part a), whilst a STM structure is able to granularly model individual stages of the disease, with OS subsequently informed by the culmination of all individual transitions in the model, as opposed to a PSM, where the interdependency of PFS and OS is not explicitly modelled, the uncertainty introduced from the additional complexity with the STM approach is expected to outweigh any reduction in uncertainty in long-term survival predictions. As discussed above, the PSM remains the most frequently adopted structure choice in oncology models, and was deemed suitable by prior NICE Committees for decision-making in applicable advanced NSCLC (including EGFR Exon20 insertion mutations) evaluations.^{11, 23}

Additionally, as described above, the immaturity of the PAPILLON trial does not provide sufficiently mature data to populate model transitions beyond progression and an STM structure is not flexible enough to incorporate ITC data from non-trial comparators.

- c) Please use state transition modelling to assist in verifying the plausibility of the PSM extrapolations and to address uncertainties in the extrapolation period (NICE DSU TSD 19, recommendation 11).

As discussed above in Question B5 a) and b), Johnson & Johnson maintain that their use of the PSM approach is robust, is supported by expert opinion, has been used previously in similar and relevant submissions (TA683, TA850 and TA855) and has a well-established precedent within the disease area. Therefore, the PSM structure will be retained and a STM analysis will not be provided.^{11, 23, 24}

Effectiveness - assumptions for pembrolizumab-chemotherapy

B 6. Priority question. Progression-free survival (PFS) data were not available for pembrolizumab-chemotherapy. Time to next treatment (TTNT) was used to approximate PFS for pembrolizumab-chemotherapy. This was done by: “*applying the per cycle HR of amivantamab-chemotherapy TTNT vs BICR-assessed PFS in the PAPILLON trial to the selected TTNT extrapolation for pembrolizumab-chemotherapy, informed by the RWE*”. It was also stated in CS Table 84 that: “*Independent extrapolations were subsequently fitted to the estimated PFS data, and a loglogistic curve was selected in the base case.*”

- a) It is stated in the CS that “*details on the exact date of disease progression were not available from several of the relevant databases*”. Please clarify what this means (i.e. why ‘exact’ was added) and provide an overview of all data related to progression that were available from the NECTAR study.**

Only the France ESME database has a detailed documentation of progression data while other participating databases have minimal to no recorded progression information, hence the exact date of progression is unavailable.

- b) Providing a detailed explanation is essential to ensure that the assumptions made in the economic model can be replicated and validated independently. Please clarify the approach to estimate PFS for pembrolizumab-chemotherapy in detail by providing step-by-step instructions.**

Step-by-step calculations for estimating PFS for pembrolizumab with chemotherapy is provided within the reference pack of the responses.²⁶ .

- c) Please explicitly state what assumptions are made by adopting this approach.**

The approach assumes that the *ratio* of the per cycle probability of a patient starting the next treatment or dying before starting the next treatment to per cycle probability of pre-progression death or progression, as observed in the amivantamab with chemotherapy arm, also holds for the pembrolizumab-chemotherapy arm.

The approach was adopted given the lack of PFS data available for pembrolizumab with chemotherapy in NECTAR study, with the intention to have as comparable endpoints across comparators as possible in order to inform the economic model.

d) Please elaborate on the implications of this approach, i.e. is it likely to result in over- or underestimation of PFS for pembrolizumab-chemotherapy and why, similarly for the estimated ICER.

Johnson & Johnson believe that using TTNT for pembrolizumab with chemotherapy would overestimate the time that patients spend in the progression-free health state. This is because the TTNT curve for pembrolizumab with chemotherapy is expected to sit above the PFS curve given a delay between patients progressing and initiating their next line of active therapy (due to adverse events or delays to treatment changes following progression). The inappropriateness of assuming TTNT to be a valid proxy to PFS, owing to the delay between PFS and TTNT, was validated by clinical experts at the August 2024 advisory board.

A delay between PFS and TTNT is observed within the PAPILLON trial for both amivantamab with chemotherapy and chemotherapy, as detailed within Table 13 below. The median value, as well as the 6-month, 12-month, and 18-month event-free rate at consistently higher for TTNT compared with PFS across both treatment arms. There is no evidence to suggest that pembrolizumab with chemotherapy in patients with EGFR Exon20 insertion mutation-positive advanced NSCLC would follow a different trend to that observed for amivantamab with chemotherapy and chemotherapy within the PAPILLON trial.

Table 13: Summary of PFS and TTNT data from the PAPILLON trial for amivantamab with chemotherapy and chemotherapy (03rd May 2023 DCO)

	Amivantamab-chemotherapy (N=153)		Chemotherapy (N=155)	
	PFS	TTNT	PFS	TTNT
Median (95% CI)	11.37 (9.79-13.70)		6.70 (5.59-7.33)	
6-month event-free rate (95% CI)	77% (69-83%)		51% (43-59%)	
12-month event-free rate (95% CI)	48% (39-56%)		13% (8-19%)	
18-month event-free rate (95% CI)	31% (22-40%)		3% (1-9%)	

Abbreviations: CI: confidence interval; DCO: data cut-off; ECOG: Eastern Cooperative Oncology Group; HR: hazard ratio; NE: not estimable; PFS: progression-free survival; PS: performance status; TTNT: time to next treatment

Sources: Company submission, section B.2.6.1 (PFS) and B.2.6.2.4 (TTNT). PFS data are presented in Johnson & Johnson PAPILLON CSR (Table 14, page 57). TTNT data are presented in Johnson & Johnson PAPILLON CSR 2023 (Table 21, Page 73)

Using TTNT to model PFS for pembrolizumab with chemotherapy would overestimate PFS and the time patients spend in the progression-free state. For that reason, Johnson & Johnson have followed an approach to down-weight the TTNT extrapolation of pembrolizumab with chemotherapy by applying the per cycle HR of amivantamab with chemotherapy TTNT vs BICR-assessed PFS (from PAPILLON) to the selected TTNT extrapolation. The down-weighting of the PFS TTNT extrapolation, to more accurately reflect what the PFS should be, can be visualised in Figure 8 below (part f).

Using TTNT to model PFS for the intervention and all comparators (i.e., applying this approach to amivantamab with chemotherapy, chemotherapy, and pembrolizumab with chemotherapy) disproportionately affects amivantamab with chemotherapy, given the longer TTNT. Thus, using

this approach decreases the ICER for amivantamab with chemotherapy versus the weighted comparator. The difference between the two approaches is given in Table 14 below. The results of using TTNT to model PFS for the intervention and all comparators has been provided as a scenario within the model and this shows the base case is a conservative approach, as using TTNT to model PFS results in a decrease to the ICER.

Table 14: Scenario analysis results (TTNT used to model PFS for all comparators)

	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Base case (per cycle HR used to model PFS for pembrolizumab with chemotherapy)	■	■	24,839
Scenario (TTNT used to model PFS for all comparators)	■	■	23,898

Note: In this scenario, TTNT has been used to model the PFS of all comparators to ensure parity between the efficacy data used for the comparator and intervention

Abbreviations: HR: hazard ratio; ICER: incremental cost-effectiveness ratio; PFS: progression-free survival

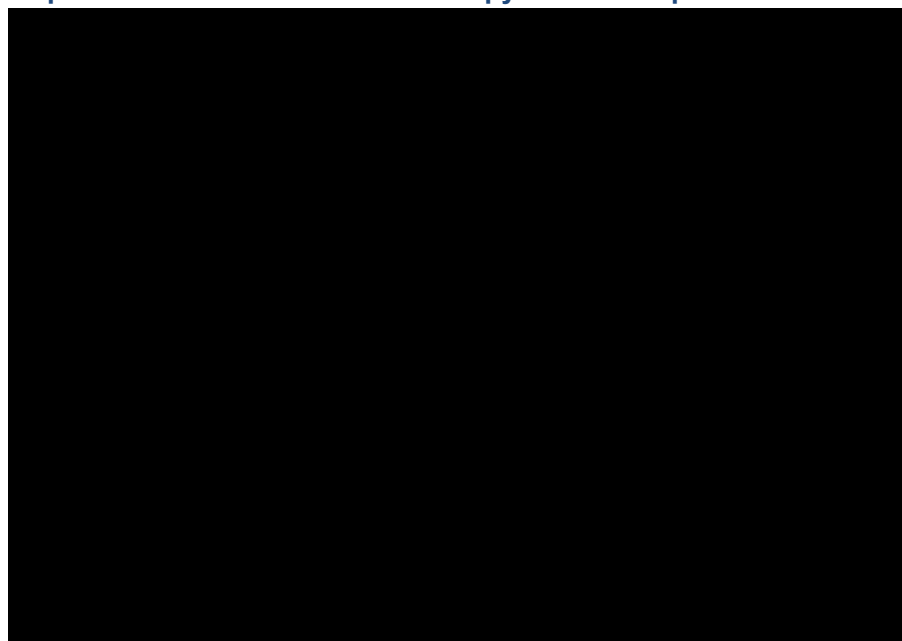
- e) According to the 2024 Advisory Board Report: “it was noted that TTNT could not serve as a valid proxy for progression-free survival (PFS) due to its standard definition in clinical trials.”. Given the description above, TTNT is used to approximate PFS. Please justify the approach given the expert input indicating TTNT could not serve as a valid proxy for PFS.**

From insight gained in the August 2024 advisory board,⁸ Johnson & Johnson are using BICR-assessed PFS from the PAPILLON study for both amivantamab with chemotherapy and chemotherapy within the model. Johnson & Johnson are using an alternative approach to estimate PFS for pembrolizumab with chemotherapy. To provide clarity on the question, TTNT is not used as a proxy alone, instead it is adjusted as per the process described in Part b above to elicit data that captures the expected PFS for pembrolizumab-chemotherapy in the patient population under consideration.

- f) Please justify that the described approach provides a valid approximation of PFS for pembrolizumab-chemotherapy.**

The approach of applying the per cycle hazard ratio of amivantamab with chemotherapy TTNT versus BICR-assessed PFS to the selected TTNT extrapolation for pembrolizumab with chemotherapy ensures that the estimated PFS is shorter than the estimated TTNT. The resulting PFS curve for pembrolizumab-chemotherapy (derived from applying the per cycle hazard ratio) compared with the TTNT extrapolation is shown in Figure 8.

Figure 8: Pembrolizumab with chemotherapy PFS extrapolation curve (after adjustment*) vs pembrolizumab with chemotherapy TTNT extrapolation curve

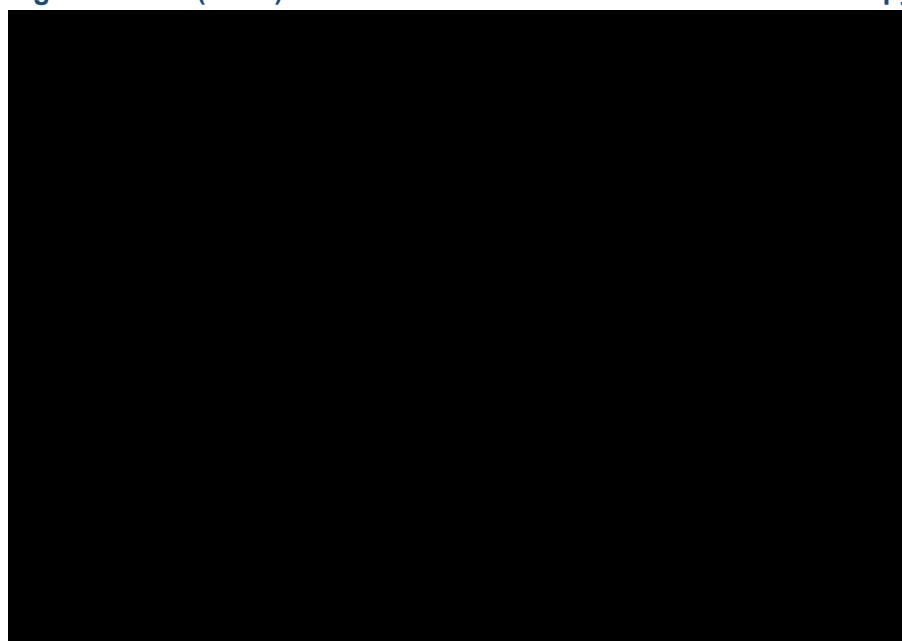


Note: *The PFS curve has been derived by applying the per cycle HR of amivantamab-chemotherapy TTNT versus BICR-assessed PFS from the PAPILLON trial to the log-logistic TTNT extrapolation

Abbreviations: ATT: average effect of the treated; CP: carboplatin with pemetrexed; IO: immuno-oncology; KM: Kaplan-Meier; TTNT: time to next treatment

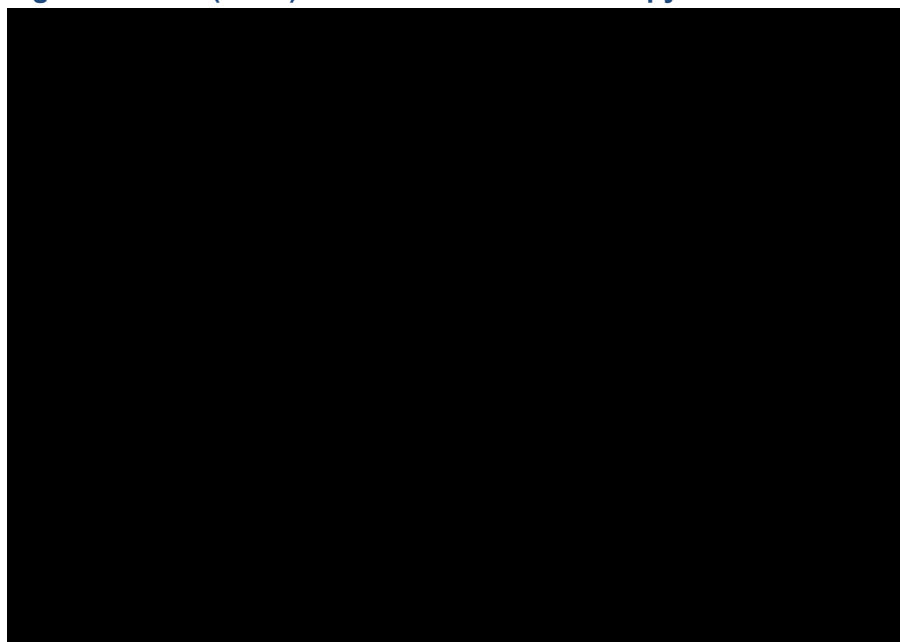
This is clinically plausible given it is expected that there would be a gap between progression and the initiation of the next line of therapy in clinical practice. Further, predicting a shorter PFS compared to TTNT for pembrolizumab with chemotherapy is aligned to the data observed for amivantamab with chemotherapy and chemotherapy in the PAPILLON study, as illustrated in Figure 9 and Figure 10 below.

Figure 9: PFS (BICR) and TTNT for amivantamab with chemotherapy in PAPILLON



Abbreviations: ACP: amivantamab in combination with carboplatin and pemetrexed; BICR: blinded independent central review; PFS: progression-free survival; TTNT: time to next treatment.

Figure 10: PFS (BICR) and TTNT for chemotherapy in PAPILLON



Abbreviations: BICR: blinded independent central review; CP: carboplatin and pemetrexed; PFS: progression-free survival; TTNT: time to next treatment.

Therefore, Johnson & Johnson consider the approach of deriving the PFS of pembrolizumab with chemotherapy from per cycle hazard ratios to be more clinically plausible compared with assuming that TTNT is a proxy for PFS.

g) Please clarify how the uncertainty related to this approach is reflected in the economic analyses.

Parameters for the parametric models for amivantamab-chemotherapy PFS (as assessed by BICR) and for pembrolizumab with chemotherapy TTNT were varied as part of the one-way sensitivity analysis and PSA. Furthermore, Johnson & Johnson have provided a scenario analysis using TTNT as a proxy for PFS across the comparators. These scenario analysis results have been updated from the CS in line with the changes to the reference costs and are presented in Table 14 in part d above.

h) Please provide scenario analyses that explore the impact of potential misestimations of the PFS (through the abovementioned approximation approach) on the ICER.

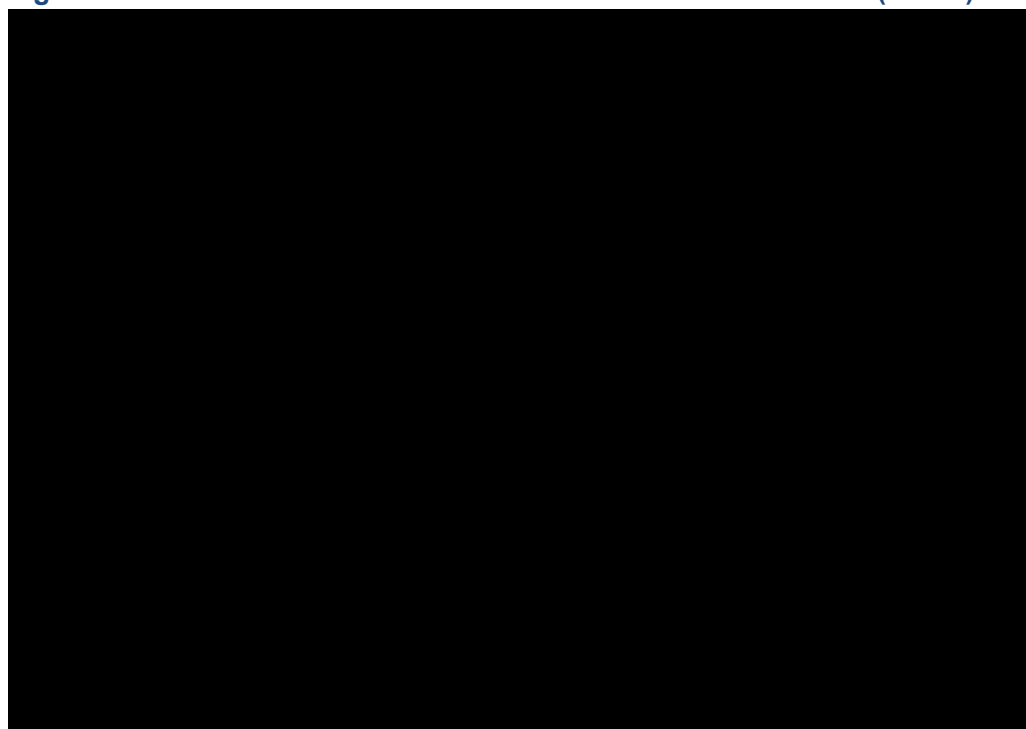
Johnson & Johnson have presented two scenarios that test alternative approaches to estimating pembrolizumab with chemotherapy PFS by applying the per cycle hazard ratio of amivantamab with chemotherapy TTNT versus BICR-assessed PFS to the selected TTNT extrapolation for pembrolizumab with chemotherapy.

The first scenario (scenario A) used the same approach as in the base case but altered this such that the per cycle hazards of TTNT versus PFS (assessed by BICR) for chemotherapy (instead of amivantamab with chemotherapy) were used.

The second scenario (scenario B) utilised PFS data that were available from the NECTAR study. However, both PFS and TTNT were only available from the ESME (France) database (full details

on this are provided within the full NECTAR study report, included within the reference pack of the CS).⁹ As only 11 patients in the ESME database received pembrolizumab-chemotherapy, the whole cohort (n=91) was utilised when estimating a single HR of PFS (INV) versus TTNT. The resulting HR of 0.6 (95% CI: 0.44, 0.81) was applied to the TTNT of pembrolizumab with chemotherapy to estimate PFS (Figure 11).

Figure 11: PFS INV vs. TTNT of real-world treatments in NECTAR (ESME)



Abbreviations: ESME: Épidémiologie Stratégie Médico-Economique; INV: investigator; PFS: progression-free survival; TTNT: time to next treatment.

The results of the two scenario analyses are presented in Table 15. Overall, the results show that there is little variation in the ICER when the approach to estimating the PFS of pembrolizumab with chemotherapy is changed. Further, the approach taken by Johnson & Johnson in the base case is not the most optimistic approach, resulting in an ICER between the two scenarios.

Table 15: Scenario analysis results (incorporating different pembrolizumab chemotherapy PFS estimations)

	With amivantamab PAS		
	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Base case (per cycle HR of ACP PFS vs. TTNT)	■	■	24,839
Scenario A (per cycle HR of CP PFS vs. TTNT)	■	■	25,032
Scenario B (OS = HR of RW TTNT vs. PFS INV)	■	■	24,092

Abbreviations: HR: hazard ratio; ICER: incremental cost-effectiveness ratio; Inc.: Incremental; INV: investigator; OS: overall survival; PAS: patient access scheme; PFS: progression-free survival; QALY: quality adjusted life year, RW: real-world; TTNT: time to next treatment.

- i) Please elaborate on the pros and cons of alternative approaches to approximate PFS for pembrolizumab-chemotherapy.

Please see response to part h).

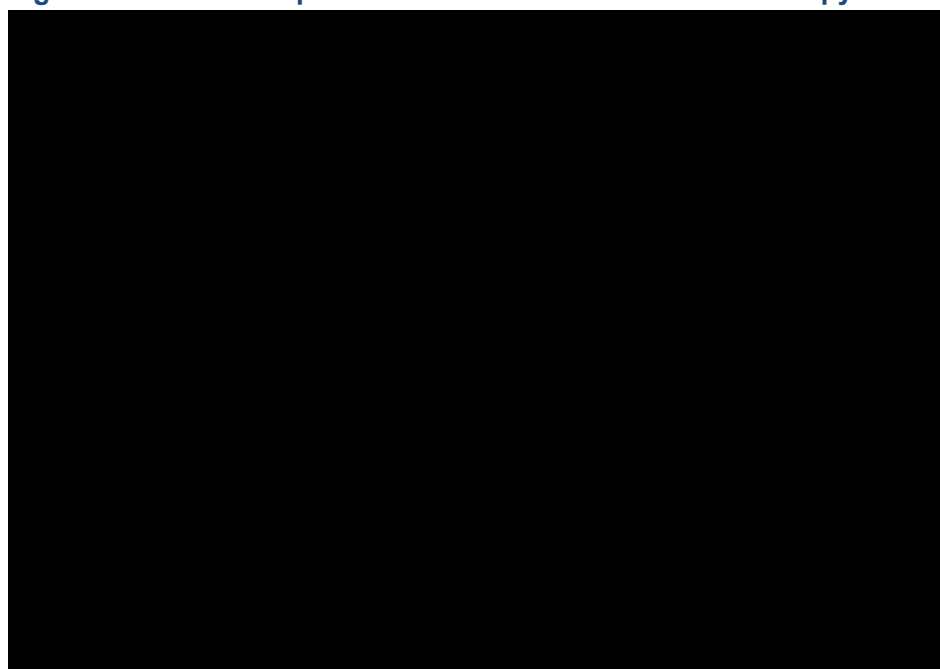
- j) Please clarify and justify how the parametric survival model distributions were selected for scenario 10 (CS Tables 87 and 88), using TTNT to model PFS for all treatments considered.

In scenario 10 presented within the CS (using TTNT as a proxy to model PFS), parametric curve selections for amivantamab with chemotherapy and for chemotherapy were not varied from the base case (i.e., the gamma distribution was selected for amivantamab with chemotherapy), as detailed further below. The parametric distribution selected for TTNT of pembrolizumab with chemotherapy was already based on the assessment of TTNT (CS, Section B.3.3.2.5).

Amivantamab-chemotherapy TTNT

All seven parametric distributions introduced above were independently fitted to the TTNT KM data from the PAPILLON trial for amivantamab-chemotherapy, and these curves are presented in Figure 12. A summary of all the AIC and BIC values for the extrapolations is further presented in Table 16. Among the seven models, Weibull had the best statistical fit to the data.

Figure 12: TTNT extrapolations for amivantamab-chemotherapy



Abbreviations: CP: carboplatin and pemetrexed; KM: Kaplan-Meier; TTNT: time to next treatment

Table 16: AIC and BIC values for amivantamab-chemotherapy TTNT extrapolations

Distributions	AIC	BIC	Sum of AIC / BIC
Exponential	516.46	519.49	1035.95
Weibull	509.17	515.24	1024.41
Lognormal	515.08	521.14	1036.22
Log-logistic	509.53	515.59	1025.12

Gompertz	511.6	517.66	1029.26
Gamma			
Generalised gamma	511.17	520.27	1031.44

Lowest (i.e. best fitting) AIC and BIC scores for each distribution are in **bold** text.

Abbreviations: AIC: Akaike's Information Criterion; BIC: Bayesian Information Criterion; TTNT: time to next treatment.

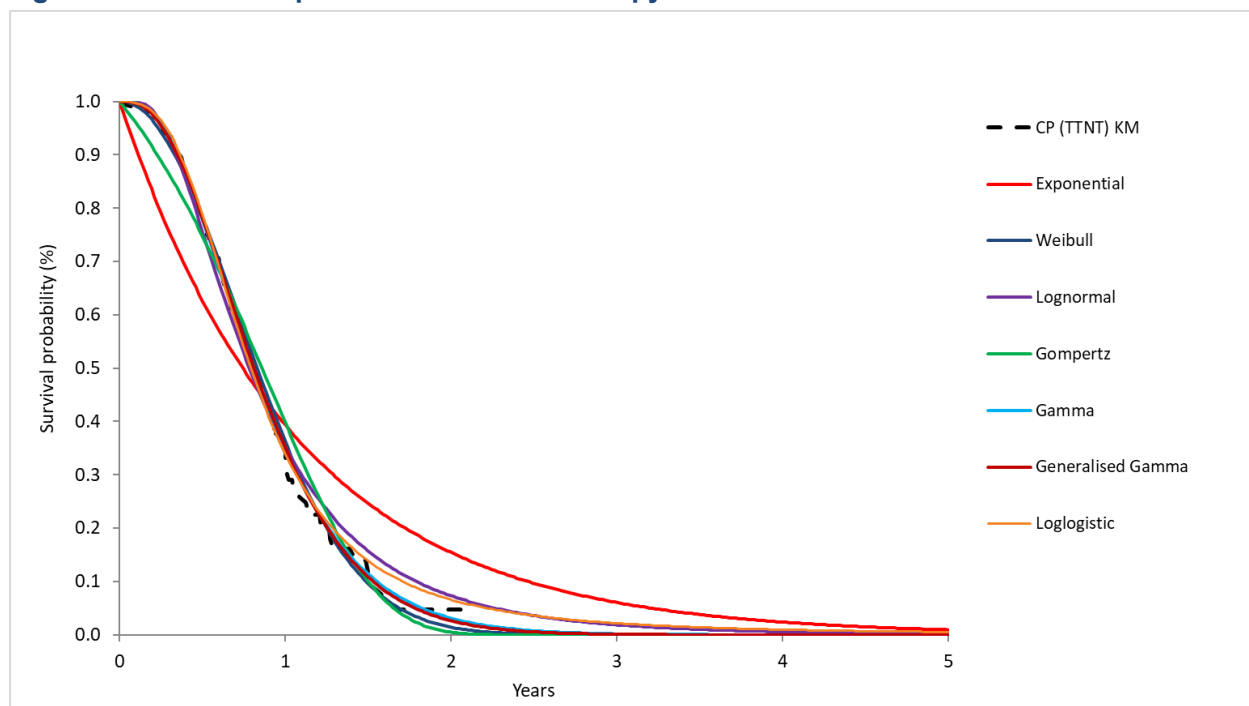
The TTNT data in the model were relatively mature, given that median TTNT had been reached in the PAPILLON study for the amivantamab with chemotherapy treatment arm. All extrapolations featured similar statistical fits and similar long-term survival outcomes. TTNT curve selection for amivantamab with chemotherapy was therefore driven by considerations of statistical fit, based on the sum of the AIC and BIC scores. Although the Weibull extrapolation had the best statistical fit, the gamma distribution had the second best fit and it was selected as a base case to align with the extrapolation curve for amivantamab-chemotherapy PFS (as assessed by BICR).

Chemotherapy TTNT

As per amivantamab with chemotherapy, the seven parametric distributions listed above were independently fitted to the TTNT data. The extrapolations applied to PFS data for the chemotherapy arm are presented in Figure 13.

A summary of all the AIC and BIC values for the extrapolations is further presented Table 17.

Figure 13: TTNT extrapolations for chemotherapy



Abbreviations: CP: carboplatin and pemetrexed; KM: Kaplan-Meier; TTNT: time to next treatment.

Table 17: AIC and BIC values for chemotherapy TTNT extrapolations

Distributions	AIC	BIC	Sum AIC / BIC
Exponential	776.54	779.58	1556.12
Weibull	712.62	718.71	1431.33

Distributions	AIC	BIC	Sum AIC / BIC
Lognormal	719.83	725.92	1445.75
Log-logistic	710.82	716.91	1427.73
Gompertz	732.71	738.8	1471.51
Gamma	712.33	721.46	1433.79
Generalised gamma			

Lowest (i.e. best fitting) AIC and BIC scores for each distribution are in **bold** text.

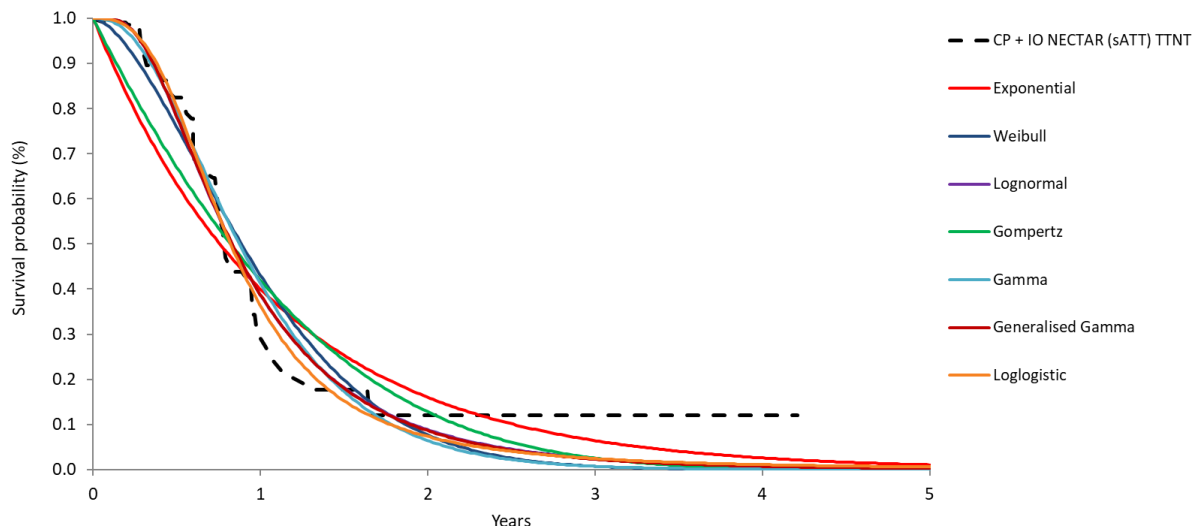
Abbreviations: AIC: Akaike's Information Criterion; BIC: Bayesian Information Criterion; DCO: data cut-off; TTNT: time to next treatment.

The TTNT data in the model are relatively mature, given that median TTNT had been reached in the PAPILLON study. Most extrapolations had similar statistical fits plus long-term survival outcomes, except for the exponential curve which provides a poor fit for chemotherapy. The curve selection was therefore driven by statistical fit and, based on the sum of AIC and BIC, the gamma distribution had the best statistical fit and was selected in the base-case. The gamma distribution is also in line with the choice of extrapolation for chemotherapy PFS (as assessed by BICR).

Pembrolizumab with chemotherapy TTNT

All seven parametric distributions were independently fitted to the TTNT KM data for pembrolizumab with chemotherapy (from the pooled RWE from the NECTAR study). The KM data, and the associated extrapolation curves are presented in Figure 14. A summary of all the AIC and BIC values for the TTNT extrapolations is also presented in Table 17. Among the seven models, the Log-logistic distribution had the best statistical fit to the data.

Figure 14: TTNT extrapolations for pembrolizumab-chemotherapy (ATT-weighted)



Note: Due to small patient numbers, the ITC pooled data from individual chemotherapy-IO regimens to conduct a comparison to 'platinum chemotherapy-IO treatment class'. This is assumed to be representative of pembrolizumab-chemotherapy.

Abbreviations: ATT: average treatment effect on the treated; CP: platinum-based chemotherapy; IO: immunology; KM: Kaplan Meier; TTNT: time to next treatment

Table 18: AIC and BIC values for pembrolizumab with chemotherapy TTNT (ATT-weighted) extrapolations

Distributions	AIC	BIC	Sum of AIC and BIC

Exponential	329.89	331.88	661.77
Weibull	317.2	321.18	638.38
Lognormal	307.28	311.26	618.54
Log-logistic	■	■	■
Gompertz	329.63	333.61	663.24
Gamma	311.03	315.01	626.04
Generalised gamma	309.26	315.23	624.49

Note: Lowest (i.e. best fitting) AIC and BIC scores for each distribution are in **bold** text.

Abbreviations: AIC: Akaike's Information Criterion; ATT: average treatment effect on the treated; BIC: Bayesian Information Criterion; TTNT: time to next treatment.

The TTNT data from the NECTAR study are relatively mature, given that median TTNT had been reached in this dataset. Furthermore, most extrapolations had similar statistical fits and long-term survival outcomes. Therefore, curve selection was driven by statistical fit and assessment of hazard functions. Based on the sum of the AIC and BIC values, the log-logistic extrapolation had the best statistical fit. Therefore, the log-logistic distribution was selected for pembrolizumab with chemotherapy TTNT in the base-case.

B 7. Priority question. Time to treatment discontinuation or death (TTDD)

data were used to accurately model the first-line treatment costs.

However, TTDD data were not available for pembrolizumab-chemotherapy. To approximate TTDD for pembrolizumab-chemotherapy: “the per cycle HR of TTDD for the amivantamab component of amivantamab-chemotherapy versus the PFS of amivantamab-chemotherapy was applied to the PFS curve derived for pembrolizumab-chemotherapy” (the approximation of the PFS curve is considered in the previous clarification question). Providing a detailed explanation is essential to ensure that the assumptions made in the economic model can be replicated and validated independently.

a) Please clarify the approach to estimate TTDD for pembrolizumab-chemotherapy in detail by providing step-by-step instructions.

Step-by-step instructions detailing the approach used to estimate TTDD for pembrolizumab-chemotherapy are detailed in the Excel provided as part of the response in B6.b.

b) Please explicitly state what assumptions are made by adopting this approach.

The approach assumes that the *ratio* of the per cycle probability of treatment discontinuation or dying before the treatment discontinuation *versus* per cycle probability of pre-progression death or progression observed in the amivantamab with chemotherapy arm holds for the pembrolizumab-chemotherapy arm.

- c) Please elaborate on the implications of this approach, i.e. whether it likely to result in over- or underestimation of TTDD for pembrolizumab-chemotherapy and why, similarly for the estimated ICER.**

This approach estimates that TTDD for pembrolizumab-chemotherapy arm is lower than the observed TTNT from NECTAR, which results in lower treatment costs compared to a theoretical scenario where patients are treated with pembrolizumab-chemotherapy till the initiation of the next line of therapy. Based on PAPILLON study we know that TTNT is longer than TTDD for both the amivantamab with chemotherapy and chemotherapy arms, which indicates that there is a gap between the discontinuation of an earlier treatment and the initiation of the next treatment. Therefore, Johnson and Johnson consider that the approach taken provides a conservative estimation on the treatment duration and costs of pembrolizumab-chemotherapy given the lack of available data of TTDD of pembrolizumab-chemotherapy.

- d) Please justify that the described approach provides a valid approximation of TTDD for pembrolizumab-chemotherapy.**

Please see response to part c.

- e) Please clarify how the uncertainty related to this approach is reflected in the economic analyses.**

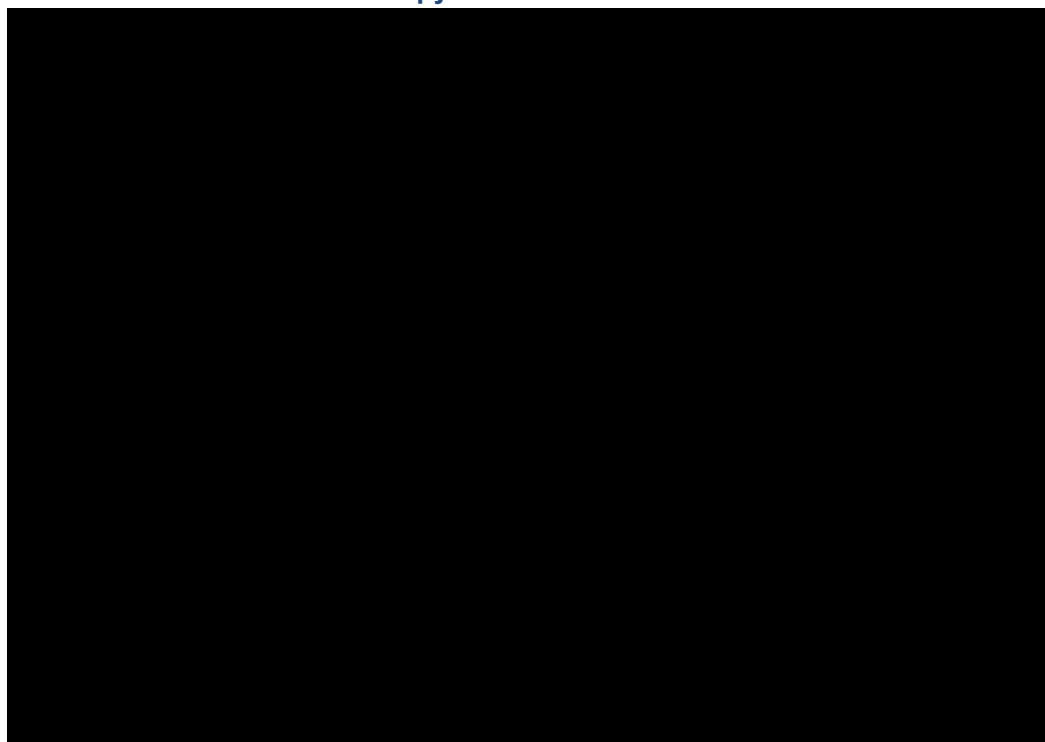
Parameters for the parametric models of amivantamab-chemotherapy PFS BICR, amivantamab alone TTDD, and pembrolizumab-chemotherapy TTNT are varied as part of the OWSA and PSA (CS, Section B.3.11.3).

- f) Please provide analyses, as well as an updated economic model, adopting an identical approach to estimate TTDD for all comparators (similar to scenario 10 in CS Tables 87 and 88, using TTNT to model PFS for all treatments considered).**

The PAPILLON study provides TTDD data for amivantamab with chemotherapy and chemotherapy. As illustrated in Figure 15 and Figure 16 below, the observed TTNT is substantially longer than the observed TTDD for both regimens. The median TTNT for amivantamab with chemotherapy is 17.7 months whereas the median TTDD is 13.2 months (difference of 4.5 months). Similarly, the median TTNT for chemotherapy is 9.9 months whereas the median TTDD is 7.5 months (difference of 2.4 months).

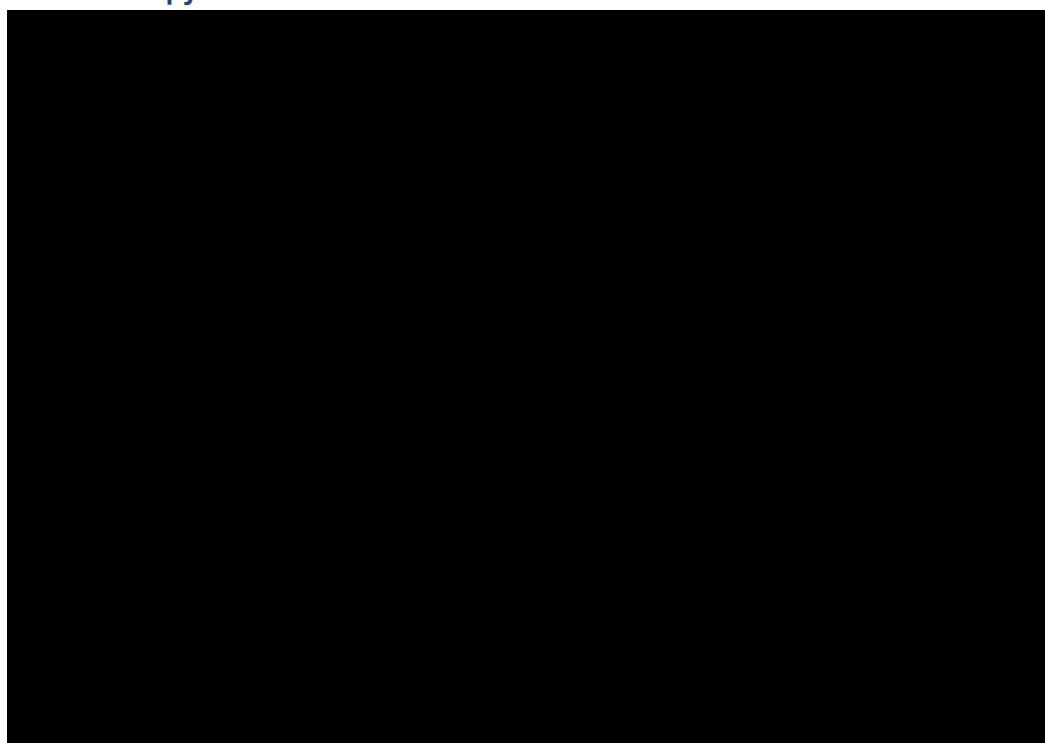
Therefore, assuming that patients in the amivantamab with chemotherapy and chemotherapy groups are treated until the start of the next line of (active) therapy would overestimate the treatment costs associated with these regimens. Thus, Johnson & Johnson consider that this scenario (i.e., assuming TTNT is a proxy for TTDD) would not provide sensible results.

Figure 15: Time to treatment discontinuation or death and time-to-next treatment for amivantamab with chemotherapy observed within the PAPILLON trial



Abbreviations: ACP: Amivantamab with carboplatin and pemetrexed; TTDD: time to treatment discontinuation of death; TTNT: time to next treatment.

Figure 16: Time to treatment discontinuation or death and time-to-next treatment for chemotherapy observed within the PAPILLON trial



Abbreviations: CP: carboplatin with pemetrexed; TTDD: time to treatment discontinuation of death; TTNT: time to next treatment.

B 8. Priority question. In CS Section B.3, it is described, for pembrolizumab with chemotherapy, that the: “data were ATT-weighted to have similar baseline characteristics to the amivantamab-chemotherapy treatment arm in the PAPILLON trial”.

a) Please elaborate on the implications of this approach, i.e. is it likely to result in over- or underestimation of OS, PFS and TTDD for pembrolizumab-chemotherapy and why, similarly for the estimated ICER.

Propensity score (PS) methods are used to mimic the effect of randomisation by creating a balance between two treatment groups with respect to important baseline covariates. These PS scores represent a summary of all characteristics included in the model for each patient. The ATT approach attempts to generate a comparative arm reflecting the population of the treated arm (PAPILLON ACP) by reweighting the pembrolizumab-chemotherapy real-world cohort to match the ACP patients of PAPILLON.

b) Please clarify how the uncertainty related to this approach in reflected in the economic analyses.

Please see response to part a.

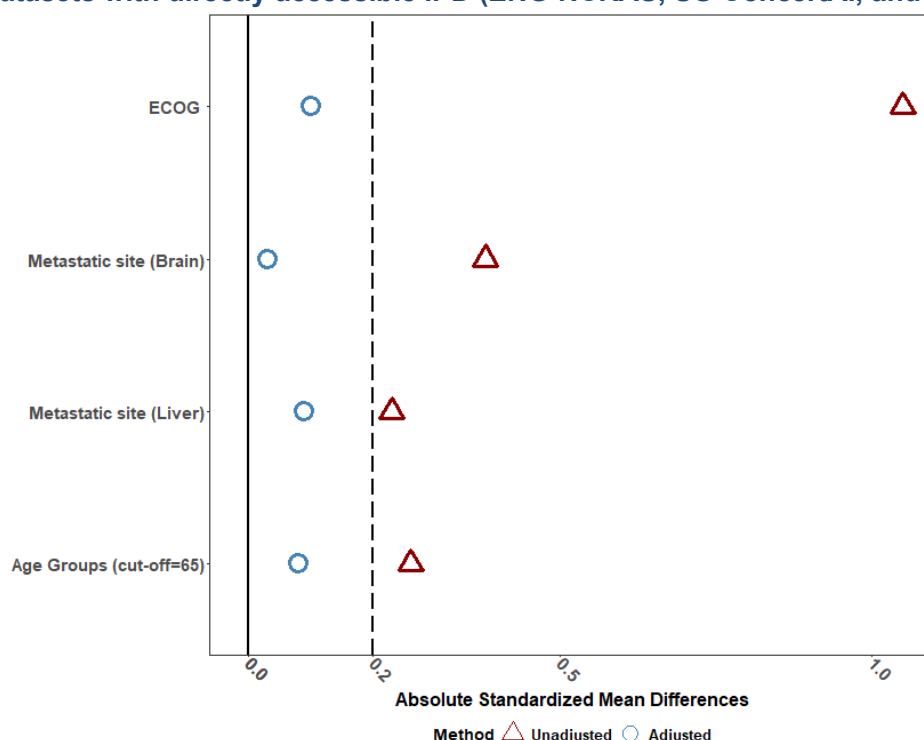
c) Please provide analyses, as well as an updated economic model, without the ATT-adjustment for pembrolizumab with chemotherapy.

Johnson & Johnson do not believe that a naïve comparison between pembrolizumab with chemotherapy and amivantamab with chemotherapy, without ATT-adjustment for confounders, is appropriate.

Weighting has been applied to the pooled RWE data from the NECTAR study, using IPW ATT methods, in order to account for potential confounders and to provide a similar distribution of confounders as the amivantamab-chemotherapy arm of the PAPILLON study. The use of IPW using the PSs has been well-reported within the literature as a method to obtain unbiased estimates of average treatment effects.²⁷ Additionally, population adjustment for effect modifiers using propensity score weighting is a recommended method to reduce systematic error in indirect comparisons within NICE TSD 18.²⁸

The impact that ATT-weighting has on reducing the differences between baseline characteristics of each population is illustrated in Figure 17 (Appendix 4.3, Figure 79, of the NECTAR study report).

Figure 17: Standardised mean differences plot of unadjusted and ATT-adjusted patient baseline characteristics for ACP versus RWD Platinum+IO: PAPILLON ACP arm and RWD datasets with directly accessible IPD (ENG-NCRAS, US-ConcertAI, and US-COTA)



Footnotes: This figure presents the differences in baseline characteristics for datasets where IPD is readily available, which comprise UK and US sources; data from the ESME database are not included.

Abbreviations: ACP: amivantamab in combination with carboplatin plus pemetrexed (PAPILLON active arm); ATT: average treatment effect in the treated; ECOG: Eastern Cooperative Oncology Group performance status; ENG: England; IO: immunotherapy; IPD: individual patient-level data; NCRAS: National Cancer Registration and Analysis Service; RWD: real-world data; US: United States.

Given that patients in both cohorts may not be comparable and/or exchangeable due to lack of randomisation, imbalances in prognostic baseline characteristics between both treatment cohorts need to be adjusted for, in this case using ATT-weighting, to avoid confounding bias. Consequently, relying on biased unadjusted results in the economic model is not justified.

d) Please provide analyses, as well as an updated economic model, using the results of all sensitivity analyses provided in response to clarification question A10.

As described in response to Question A10, the requested scenario analyses were deemed either not possible or not appropriate to perform, and therefore updated analyses are not provided here.

Effectiveness - parametric survival models

B 9. Priority question. Overall survival (OS) data were used to inform time to death using parametric survival models.

a) To examine the diagnostics of the parametric survival models (using the observed data), please provide the following Figures (separately per treatment):

- i. Plot the cumulative hazard versus time
- ii. Plot the log smoothed hazard versus time
- iii. Plot the standard normal quartiles versus log time
- iv. Plot the log survival odds versus log time

i) *Cumulative hazard versus time plots*

Figure 18: Cumulative hazard plot – amivantamab-chemotherapy OS

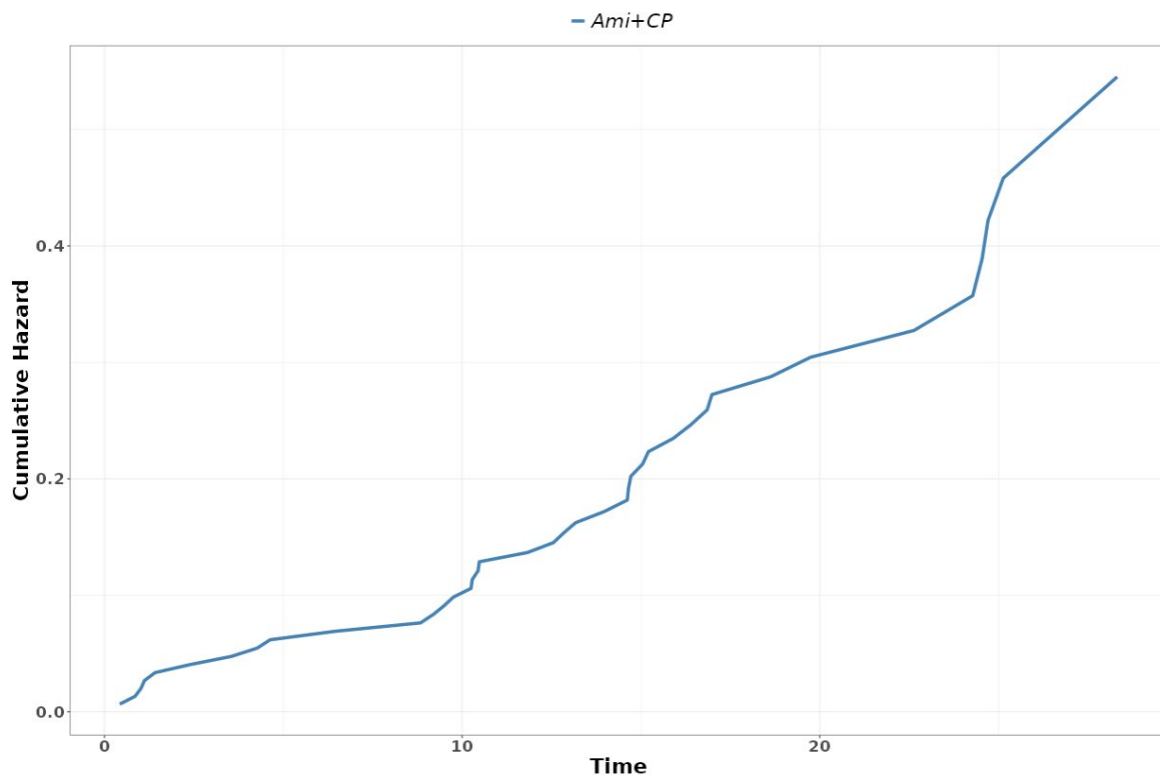


Figure 19: Cumulative hazard plot – CP (IPCW adjusted) OS

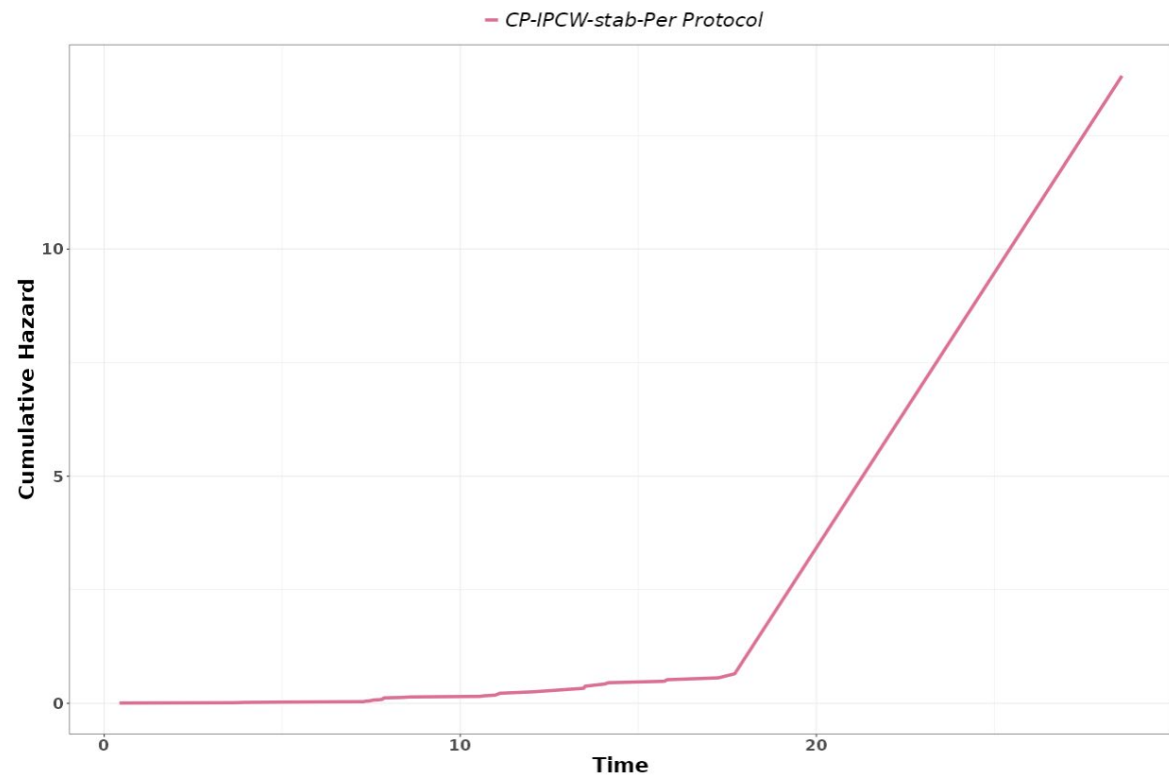
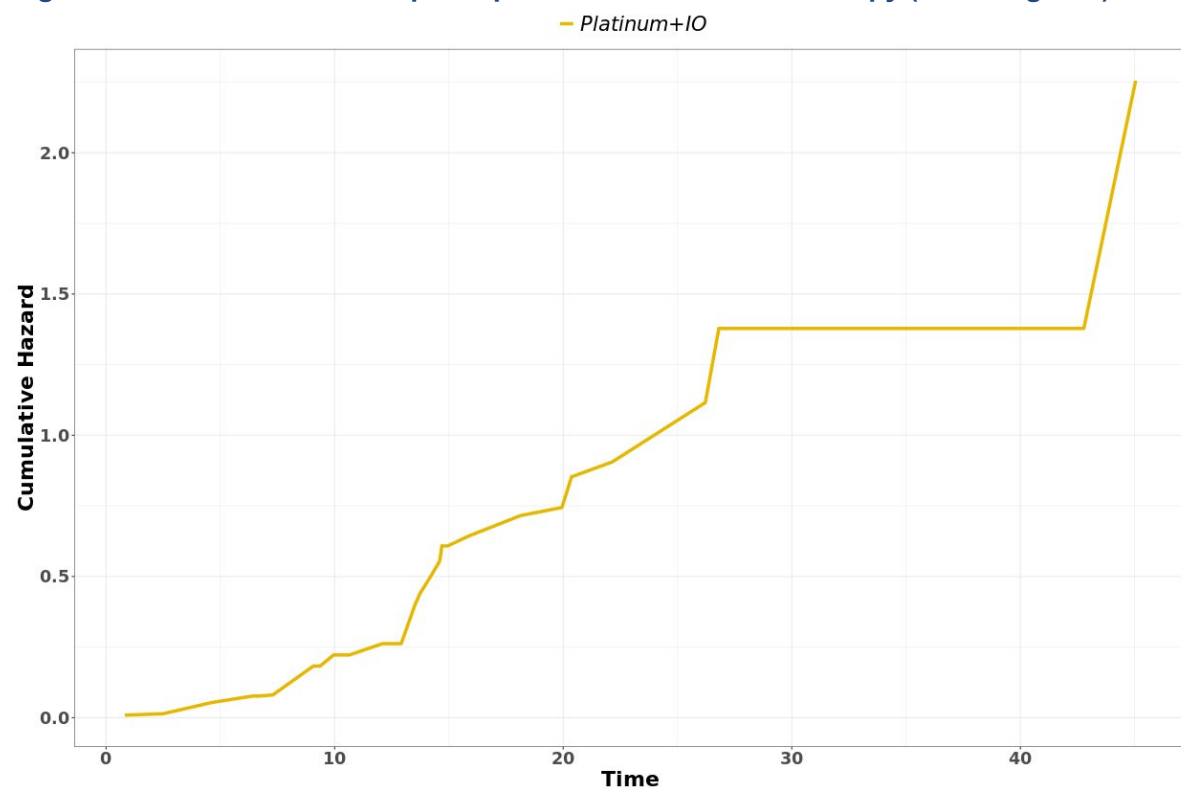


Figure 20: Cumulative hazard plot – pembrolizumab-chemotherapy (ATT weighted) OS



ii) *Log smoothed hazard versus time plots*

Figure 21: Log smoothed hazard plot – ACP OS

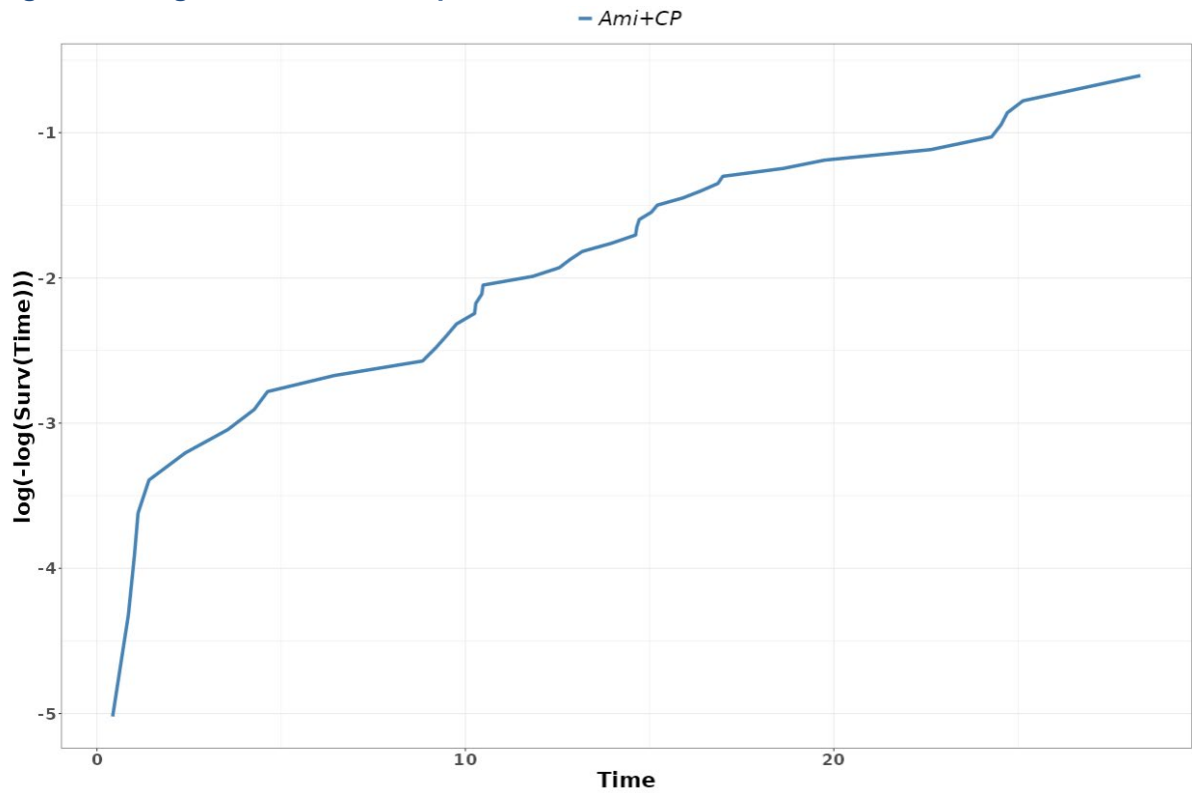


Figure 22: Log smoothed hazard plot – CP (IPCW adjusted) OS

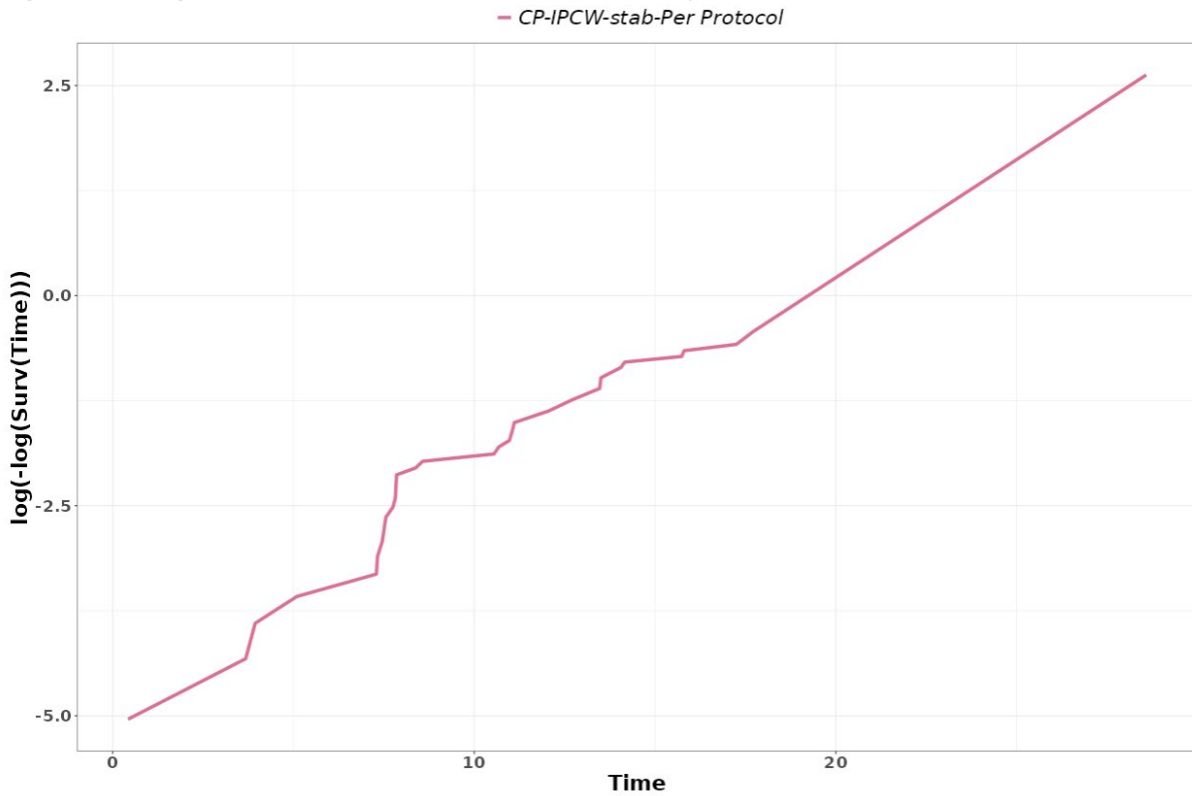
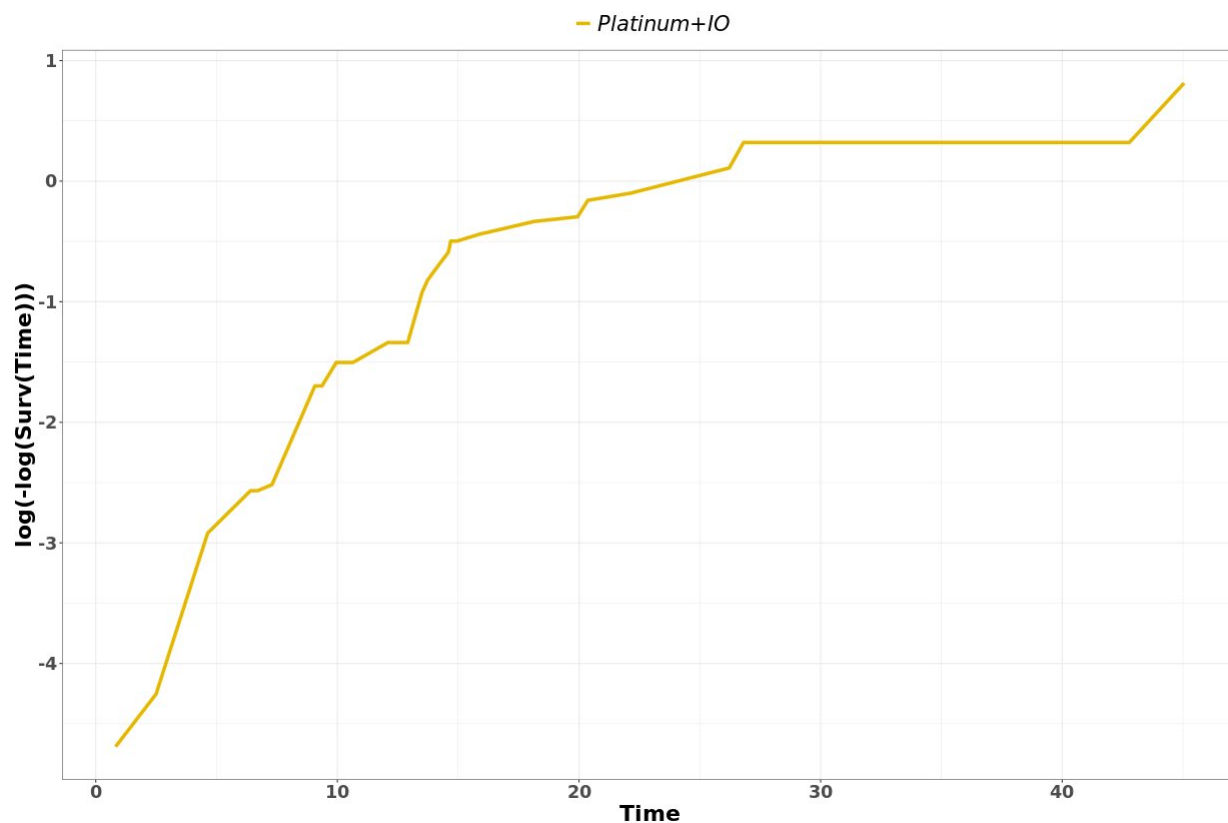


Figure 23: Log smoothed hazard plot – Pembrolizumab-chemotherapy (ATT weighted) OS



iii) Standard normal quantiles versus log time plots

Figure 24: standard normal quantiles vs. log time plot – ACP OS

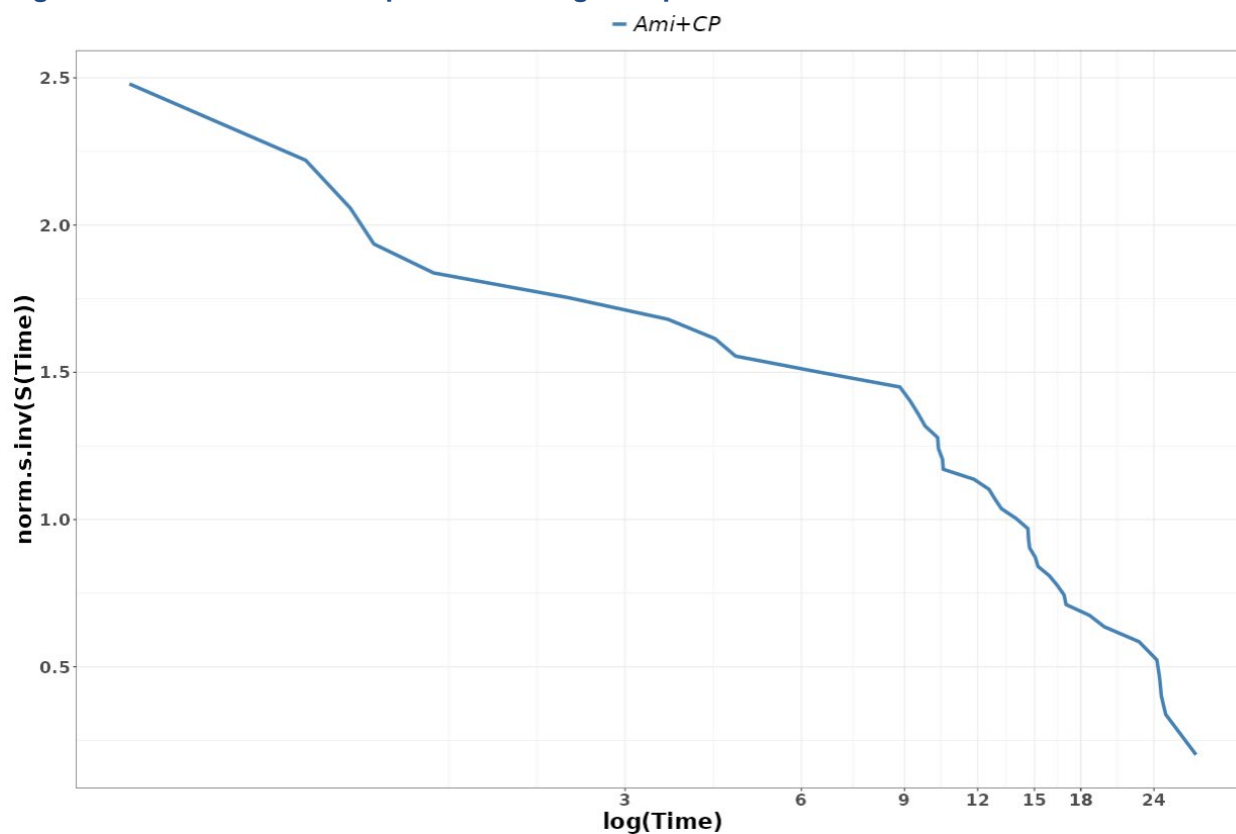


Figure 25: standard normal quartiles vs. log time plot – CP (IPCW adjusted) OS

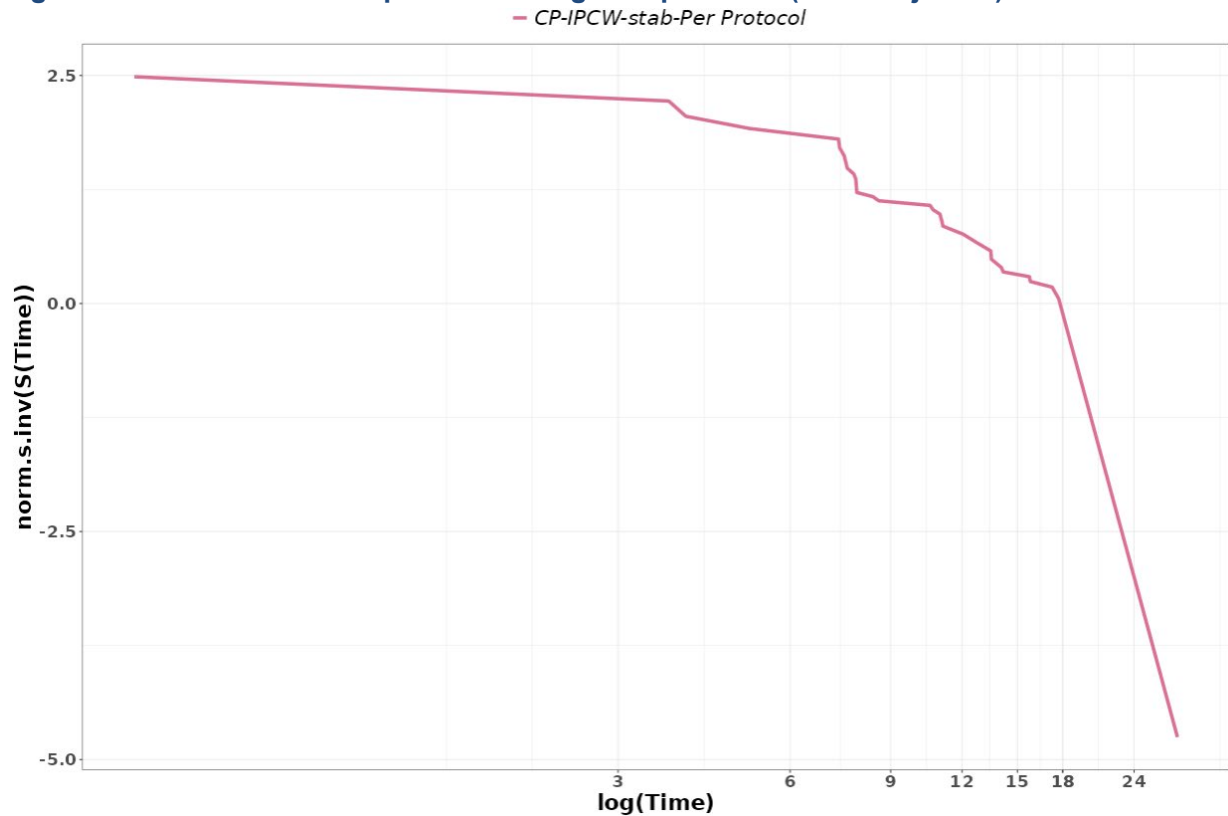
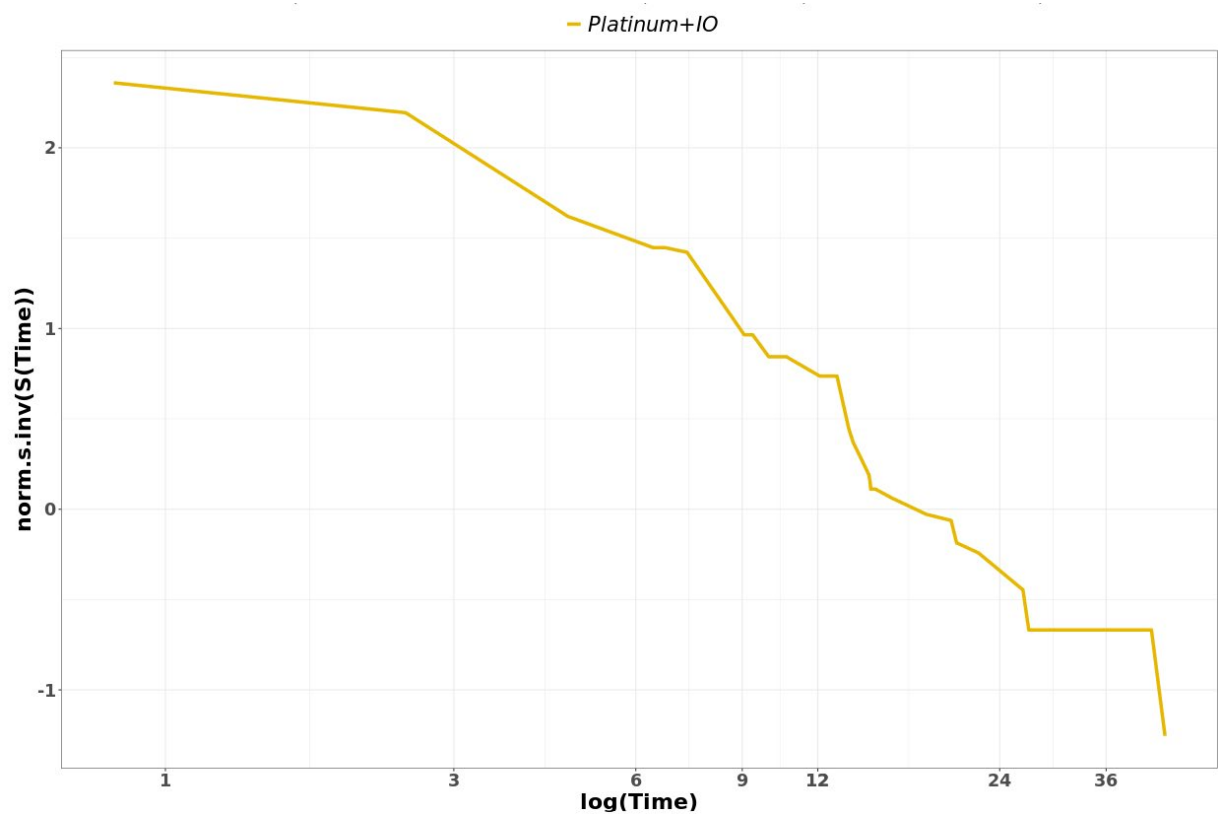


Figure 26: Standard normal quartiles vs. log time plot – Pembrolizumab-chemotherapy (ATT weighted) OS



iv) *Log survival odds versus log time*

Figure 27: Log survival odds vs. log time plot – ACP OS

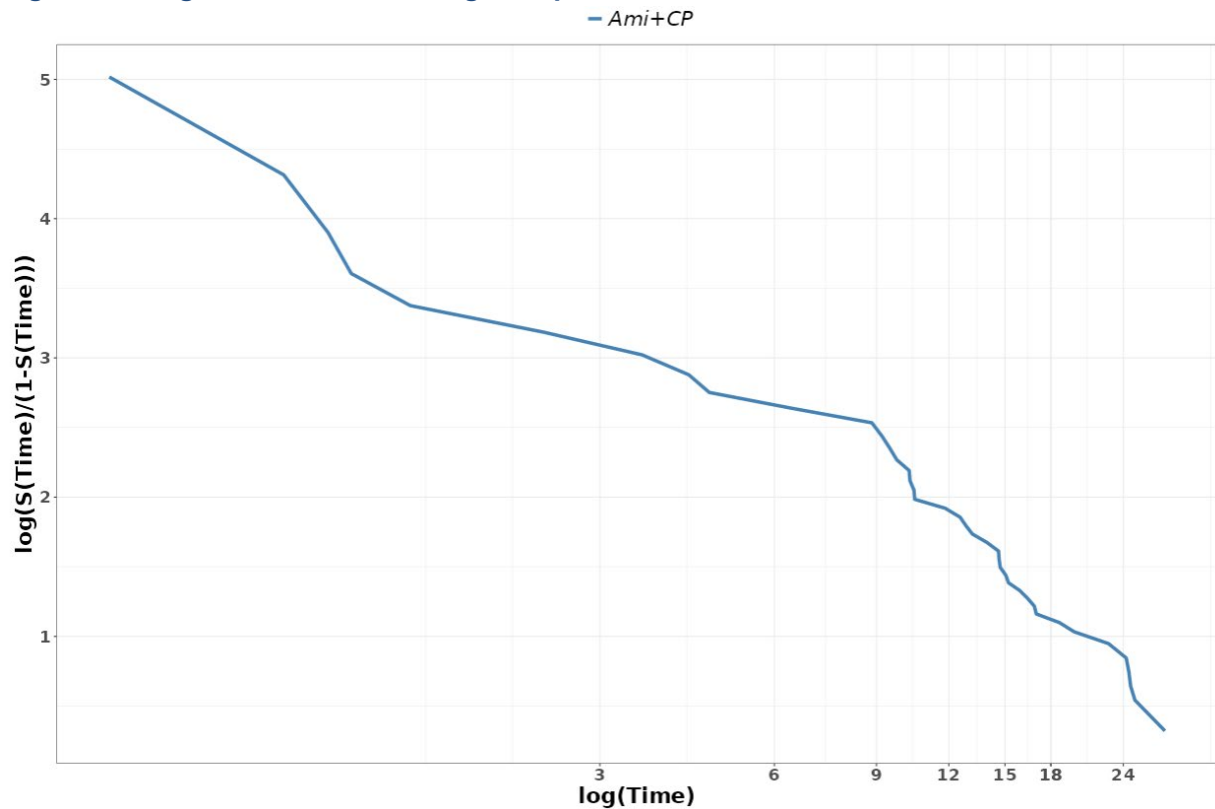
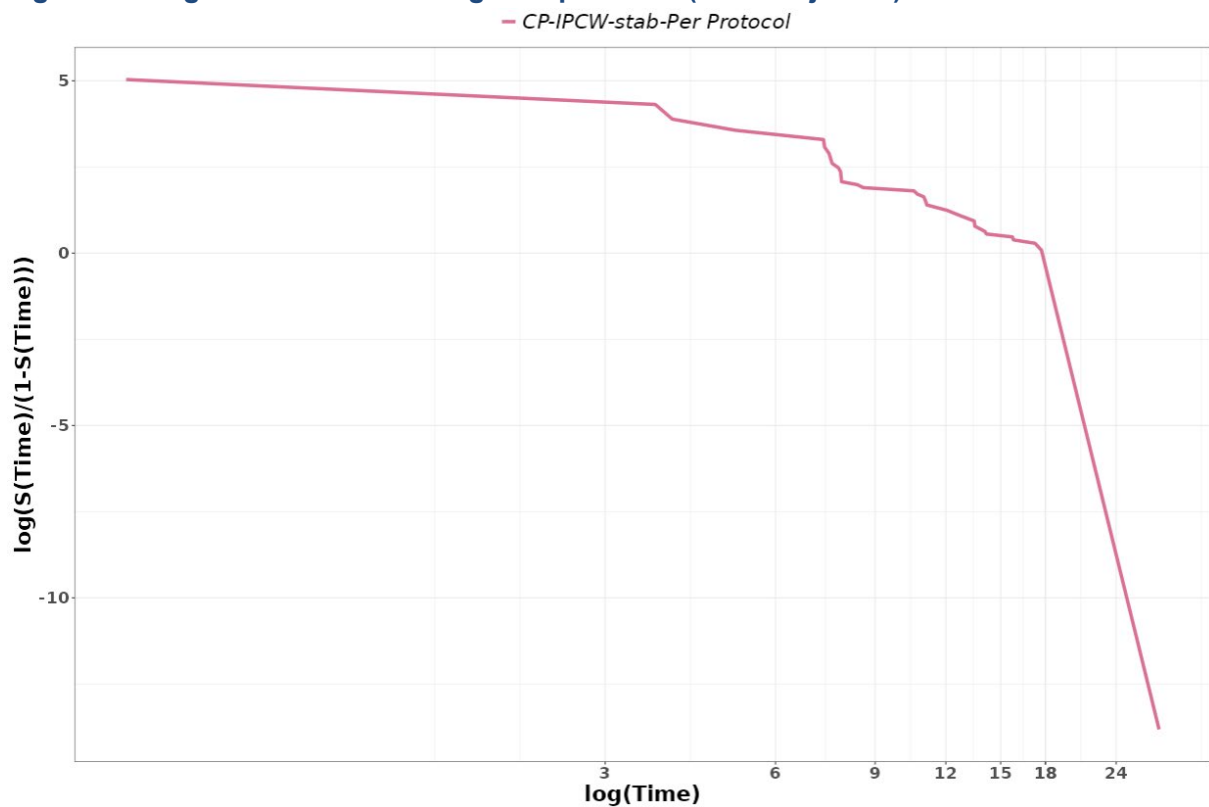


Figure 28: Log survival odds vs. log time plot – CP (IPCW adjusted) OS



The graph shows a decreasing trend for the Platinum+IO configuration. The y-axis represents $\log(S(\text{Time})/(1-S(\text{Time})))$ and the x-axis represents $\log(\text{Time})$. The curve starts at a high value of approximately 4.5 at $\log(\text{Time}) \approx 0.5$ and decreases steadily, reaching approximately -1.5 at $\log(\text{Time}) \approx 40$.

- To validate the choice of survival extrapolations, clinical expert opinion was sought during the August 2024 advisory board. The full meeting report is included within the reference pack of the CS.⁸ As per the report, this advisory board comprised two clinical experts:

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report. Advisor selection was conducted according to Johnson & Johnson standard operating procedure, which specifies advisors must be experts in their areas and each participant should be chosen according to their expertise, such that they will be able to contribute meaningfully to the purpose and expected outcomes of the meeting.

In order to validate survival extrapolations, OS estimates at distinct timepoints (3, 5, and 10 years) were elicited from both advisors individually. This was done for amivantamab-chemotherapy and chemotherapy (considering patients within the PAPILLON trial and within clinical practice) as well as pembrolizumab monotherapy, pembrolizumab with chemotherapy, and a basket of UK SoCs based on the NCRAS data (considering patients in clinical practice).

The individual point estimates were obtained via a pre-meeting survey and were then discussed during the advisory board meeting, in order to arrive at a discussion-based group consensus. This approach of eliciting point estimates from individual advisors followed by discussion to arrive at a group consensus is aligned to the SHELF methodology²⁹ which has been recommended as a structured protocol for expert elicitation to inform HTA dossiers within the 2022 NICE technology appraisal manual.³⁰

The pre-meeting survey shared with advisors is attached in the reference pack to the list of responses.³¹ The questions pertaining to the elicitation of OS estimates at 3-, 5-, and 10-years are detailed on slide 11.

A screen-shot of slide 11 is provided in Figure 30 below.

Figure 30: Slide 11 from the pre-meeting survey of the August 2024 advisory board, detailing what questions were asked regarding OS estimates for amivantamab with chemotherapy and chemotherapy at 3, 5, and 10 years

PAPILLON Trial Setting: OS (2/2)

- In this exercise, you are asked to consider the **patient population enrolled in the PAPILLON trial** (please see the Appendix for patient characteristics):
- Specifically, please consider estimates assuming that patients who receive CP cannot switch to amivantamab monotherapy after progressing (reflective of clinical practice in the UK)

For the first step of this exercise, please provide the proportion of patients you would expect to remain alive at 3, 5 and 10 years after initiation of first-line treatment, for the following two patient populations:

1) Patients with advanced EGFR Exon20 insertion mutation-positive advanced NSCLC enrolled into the PAPILLON trial who are **treated with ACP**

2) Patients with advanced EGFR Exon20 insertion mutation-positive advanced NSCLC enrolled into the PAPILLON trial who are **treated with CP**

Please complete the table below with your estimates:

Treatment	Survival at 3 years (%)	Survival at 5 years (%)	Survival at 10 years (%)
ACP			
CP			

J&J

Abbreviations: ACP: amivantamab in combination with carboplatin plus pemetrexed; CP: carboplatin plus pemetrexed; EGFR: epidermal growth factor receptor; NSCLC: non-small cell lung cancer; | Oncology
OS: overall survival

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The aggregated responses (average across the individual elicitations) are provided in Table 19 below.

Clarification questions

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Table 19: Aggregated OS estimates for amivantamab with chemotherapy and chemotherapy at 3, 5, and 10 years, considering patients in the PAPILLON trial, provided by clinical experts in the pre-meeting survey of the August 2024 advisory board

Treatment	Patients remaining alive at 3 years (%)	Patients remaining alive at 5 years (%)	Patients remaining on alive at 10 years (%)
ACP	50	27.5	7.5
CP	35	10	1

Abbreviations: ACP: amivantamab in combination with carboplatin and pemetrexed; CP: carboplatin and pemetrexed; OS: overall survival.

It should be noted that the SHELF methodology relies on a group consensus obtained through discussion of the elicited point estimates rather than relying solely on the point estimates themselves. Therefore, survival curve choice was driven by the consensus arrived at after discussing the above elicitations.

During the advisory board meeting, as per SHELF methodology, the advisors discussed the point estimates for the survival of amivantamab with chemotherapy and for chemotherapy at 3, 5, and 10 years and agreed that they were in line with their expectations. The consensus over the point estimates was then compared to the survival rates at the respective landmarks that were derived from the extrapolations (based on the seven parametric distributions).

Amivantamab with chemotherapy OS extrapolation

From the discussion of the elicited point estimates, the clinical experts agreed that the Weibull and gamma curves were the most plausible extrapolations for amivantamab with chemotherapy OS and agreed that the Gompertz and generalised gamma extrapolations were overly pessimistic and should not be considered.

Chemotherapy OS extrapolation

From the discussion, the clinical experts were in agreement that the Weibull curve presented the most realistic survival extrapolation for chemotherapy OS, after the data had been adjusted for via the two-stage estimation (company base-case at the time).

It should be noted that following advice from health economic experts during the August 2024 advisory board, Johnson & Johnson changed the base-case from the two-stage estimation to the IPCW approach for treatment switching. The Weibull extrapolation for two-stage-adjusted chemotherapy OS data predicted survival rates of 22%, 2%, and 0% at 3-, 5-, and 10-years respectively, which were most aligned to the survival estimates for the gamma extrapolation of IPCW-adjusted chemotherapy OS data.

c) Please clarify that the statement “During the August 2024 advisory board, UK clinical experts aligned on a consensus that around 27.5% of patients receiving amivantamab-chemotherapy were expected to be alive after 5-years and 7.5% were expected to be alive after 10-years” is in line with the response to sub-question b.

Yes. This statement pertains to the consensus for the survival estimates of amivantamab with chemotherapy following the methodology outlined in part b.

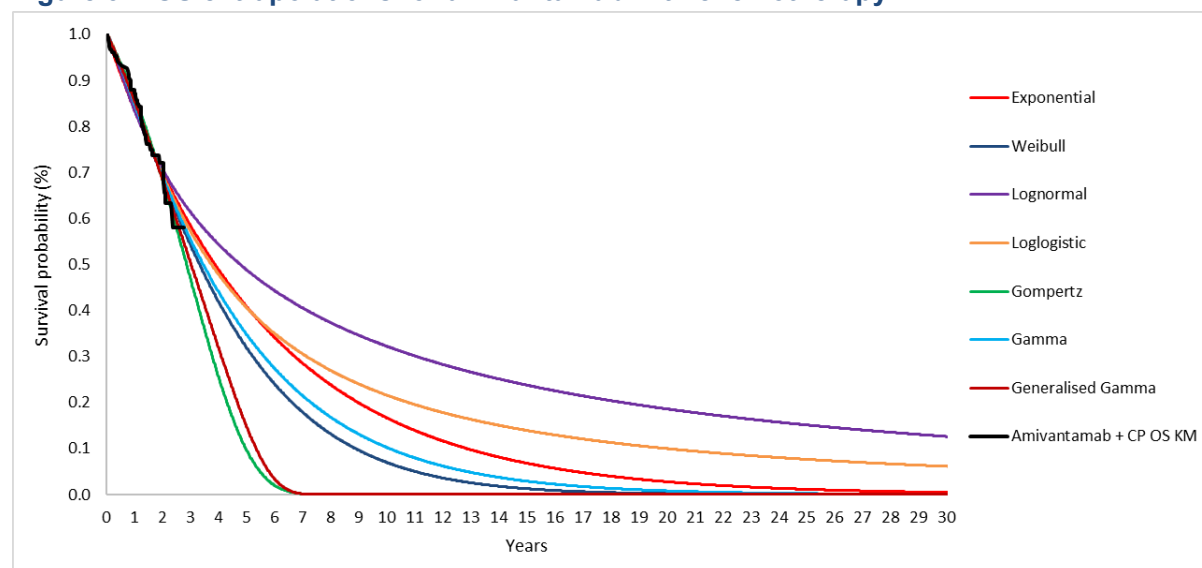
During the August advisory board, advisors discussed the point estimates for the survival of amivantamab with chemotherapy elicited from the pre-meeting survey. The advisors agreed that 27.5% of patients receiving amivantamab-chemotherapy were expected to be alive after 5 years and 7.5% were expected to be alive after 10 years. These estimates were used to inform the extrapolation chosen in the base case given they closely align with the proportions of patients alive at those landmarks in the Weibull extrapolation (32% and 7% respectively).

d) Please justify this quote from the CS: "However, visual inspection of the curves show that these distributions do not fit the KM OS data for amivantamab-chemotherapy well as they represent a highly optimistic estimate (exponential) and the most pessimistic (Gompertz) predictions of OS". Specifically, why the most pessimistic, i.e. Gompertz is not considered plausible (being the most pessimistic estimation does not automatically prohibit an option).

Visual inspection shows that the KM curve for amivantamab with chemotherapy sits in between the Gompertz and exponential extrapolations rather than closely aligning to either extrapolation, as illustrated in Figure 31.

It should be noted that the survival data are relatively immature and so other factors (statistical fit, alignment with hazards plots, and expert validation) have been used to justify the OS curve selection.

Figure 31: OS extrapolations for amivantamab with chemotherapy



Abbreviations: CP: carboplatin and pemetrexed (chemotherapy); DCO; data cut-off; OS: overall survival.

Although the Gompertz extrapolation for amivantamab with chemotherapy OS represents the best statistical fit, visual inspection shows that it sits below the KM curve.

During the August 2024 advisory board, the clinical experts agreed that the Gompertz and generalised gamma extrapolations were overly pessimistic and would underestimate the OS of

amivantamab with chemotherapy. As such, advisors agreed that these distributions could be discounted. These curves were perceived as underestimating OS given they do not include a tail as the survival from these extrapolations reaches 0% after 10 years. A tail to the survival was perceived as plausible for amivantamab given its immune modulating mechanism, with one advisor noting that there is evidence for a proportion of patients achieving long-term disease control with single-agent amivantamab in the second- and third-line setting in clinical practice.

The plausibility of a tail associated with the survival of amivantamab with chemotherapy can also be supported by the long-term survival benefit observed for amivantamab monotherapy in the CHRYSALIS trial where, after a median follow-up of 19.2 months, the median OS of patients receiving amivantamab monotherapy in the second line setting after progressing on chemotherapy was 23 months (95% CI, 18.5–29.5).³²

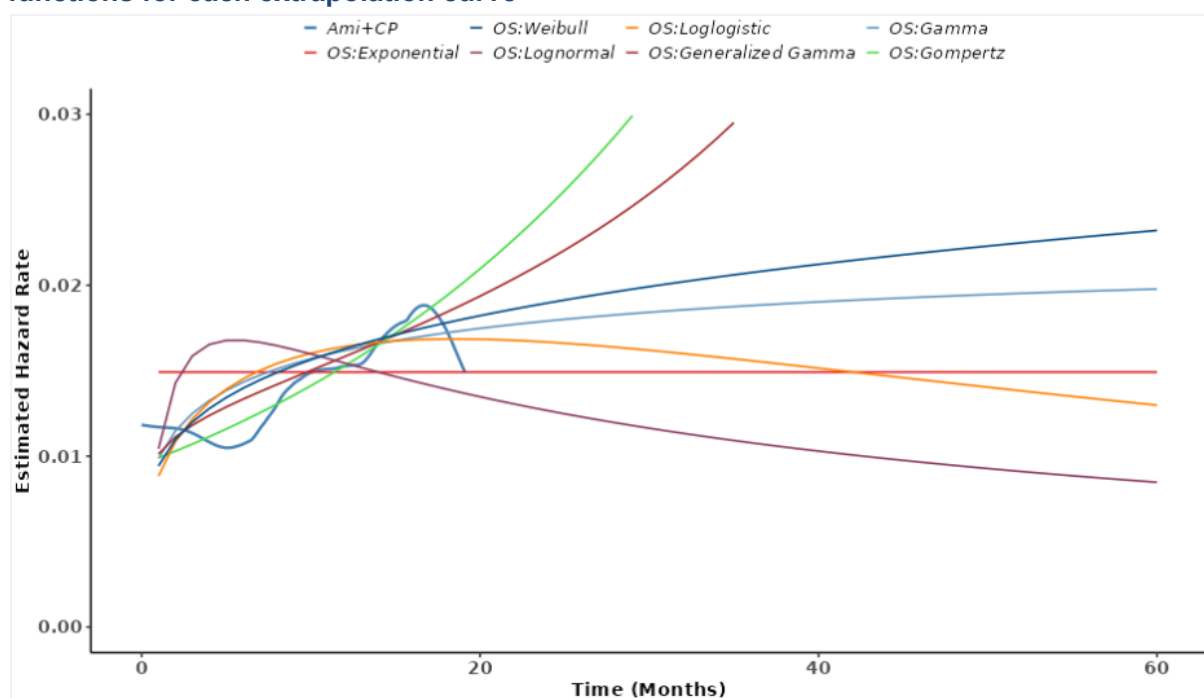
Therefore, based on clinical expert opinion, and expected efficacy profile of amivantamab with chemotherapy, the Gompertz and generalised gamma distributions were not seen as plausible.

e) Based on CS Figure 36, there seems to be an increasing hazard overall for amivantamab-chemotherapy (especially when considering that the tail is likely based on few events). The Gompertz and generalised Gamma distributions seem to fit reasonably early and is consistent with the observed trend of increasing hazard and might thus be a plausible alternative worthy to explore (supported by CS Table 51 and CS Figure 37). Please explain why these distributions were not included in the CS base case or scenario analyses, as considering them could provide valuable insights. Please provide scenario analyses using these distributions to estimate OS for amivantamab-chemotherapy.

As described above, the Gompertz and generalised gamma distributions do not include a tail to the survival of amivantamab with chemotherapy and were not seen as plausible by clinical experts. As such, these distributions are not relevant to consider in the base-case or scenarios.

Figure 36 of the CS is replicated below in Figure 32 and shows that the Gompertz and generalised gamma hazard plots do not align with that of amivantamab-chemotherapy. The KM data for amivantamab with chemotherapy indicates a slightly increasing hazard function over time whereas the hazard plots for the Gompertz and generalised gamma distributions show rapidly increasing hazard functions over time, particularly the Gompertz plot. As such, both functions may be expected to underestimate the true value for OS for amivantamab with chemotherapy over time. Therefore, scenario analysis results have therefore not been provided. The base case OS curve selection for the ACP arm, Weibull distribution, has the most rapidly increasing hazards after Gompertz and generalised gamma.

Figure 32: Comparison of the KM OS data for amivantamab-chemotherapy with the hazard functions for each extrapolation curve



The KM data for amivantamab-chemotherapy have been cut-off when the number of patients at risk of death dropped below 10.

Abbreviations: OS: overall survival.

f) Please clarify that the statement: “Clinical expert opinion from the August 2024 advisory board, informed through a discussion-based consensus, confirmed that the Weibull extrapolation was the most clinically plausible for the OS of patients receiving chemotherapy” is in line with the response to sub-question b.

Johnson & Johnson can confirm that this statement pertains to the consensus for the survival estimates of chemotherapy following the methodology outlined in part b.

During the August 2024 advisory board, advisors discussed the point estimates for the survival of chemotherapy at 3, 5, and 10 years and, through discussion, agreed upon a group consensus that the Weibull curve presented the most realistic survival extrapolation for chemotherapy OS, after the data had been adjusted for via the two-stage estimation (company base-case at the time).

As detailed in part b, following advice from health economic experts during the August 2024 advisory board, Johnson & Johnson changed the base-case from the two-stage estimation to the IPCW approach for treatment switching. The Weibull extrapolation for two-stage-adjusted chemotherapy OS data predicted survival rates of 22%, 2%, and 0% at 3-, 5-, and 10-years respectively, which were most aligned to the survival estimates for the gamma extrapolation of IPCW-adjusted chemotherapy OS data which was used in the base case.

g) Based on CS Figures 38 and 39 as well as CS Table 53 for chemotherapy, the log-logistic and generalised Gamma distributions

fit the observed data reasonably well and thus can be considered candidate distributions for estimating OS for chemotherapy. Please explain why these distributions were not included in the CS base case or scenario analyses, as considering them could provide valuable insights. Please provide scenario analyses using these distributions to estimate OS for chemotherapy.

The log-logistic distribution for chemotherapy OS provides the best statistical fit. However, the log-logistic extrapolation of chemotherapy OS (after adjustment via the IPCW methodology) predicts a 5-year survival rate of 7.70% which is not aligned to insight from the August 2024 advisory board where advisors agreed that an extremely low proportion of patients receiving chemotherapy would be alive after five years. Further, the hazard plot of the log-logistic extrapolation shows an increasing hazard rate up to around 20 months, after which, the hazard rate steadily decreases over time. This is different to the shape of the hazard function of the chemotherapy KM data, which show an increasing hazard function over time, with no signal that this decreases after around 20 months. In contrast, the gamma distribution (extrapolation selected in the base-case) provides a closer hazard function over time to the chemotherapy KM data.

In summary, the log-logistic distribution is regarded as clinically implausible due to predicting an unrealistically high 5-year survival and its hazard function not aligning to the hazard function of the observed chemotherapy KM data. Therefore, this fit is not considered a reliable representation and is not considered a relevant selection for the base case or a scenario. The gamma distribution (extrapolation selected in the base-case) provides a closer hazard function over time to the chemotherapy KM data.

The generalised gamma curve for chemotherapy OS is similar to the Gamma distribution chosen in the base-case (mOS = 21.16 months vs [REDACTED] months, respectively) with a slightly worse statistical fit. Given the similarity in curves, Johnson & Johnson have decided to use the best statistically fitting option but agree with the EAG that the generalised gamma could be a suitable distribution. Therefore, a scenario analysis using the generalised gamma distribution is presented in Table 20. Due to the similarity in extrapolations, changing the chemotherapy OS curve from gamma (base-case) to the generalised gamma (requested scenario) slightly reduces the ICER but with minimal effect.

Table 20: Scenario analysis results (chemotherapy OS: generalised gamma curve)

	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Base case	[REDACTED]	[REDACTED]	24,839
Chemotherapy OS: generalised gamma curve	[REDACTED]	[REDACTED]	24,390

Abbreviations: ICER: incremental cost-effectiveness ratio; Inc. incremental; PAS: patient access scheme; QALY: quality-adjusted life year.

h) Please clarify what advisor input was used to select the OS approach for pembrolizumab-chemotherapy and justify that this is in line with the response to sub-question b.

The same approach used for amivantamab with chemotherapy and chemotherapy, described above, was employed to inform the OS extrapolation for pembrolizumab with chemotherapy.

At the August 2024 advisory board, clinical experts were asked to consider individual estimates for the survival of pembrolizumab with chemotherapy at 3, 5, and 10 years. These estimates were elicited from the pre-meeting survey. Advisors were asked to consider the survival of patients with untreated EGFR Exon20 insertion mutation-positive advanced NSCLC in current clinical practice. The specific questions used to elicit the point estimates can be found on slide 15 of the pre-meeting survey, included within the reference pack of the responses.³¹ A screenshot of slide 15 is provided in Figure 33 below.

Figure 33: Slide 15 from the pre-meeting survey of the August 2024 advisory board, detailing what questions were asked regarding OS estimates for pembrolizumab with chemotherapy and chemotherapy at 3, 5, and 10 years

Real-world setting: OS (for IO, IO + CP, and UK SoC)



- In this exercise, you are asked to consider a patient population in the 'real-world' (i.e., based on your understanding of patients in clinical practice). Please see the Appendix for a summary of patient characteristics and OS curves for IO and IO + chemotherapy (from the NECTAR study) and for a basket of treatments reflecting UK SoC (collected from the NCRAS dataset)
- You will be asked to elicit estimates for patients receiving two IO therapy regimens (pembrolizumab and pembrolizumab with carboplatin and pemetrexed) and for patients receiving a basket of treatments reflecting UK SoC

In the following table, please estimate the proportion of patients with EGFR Exon20 insertion mutation-positive advanced NSCLC that you would expect to remain alive at each of the timepoints listed in the table below

Treatment	Patients remaining alive at 3 years (%)	Patients remaining alive at 5 years (%)	Patients remaining alive at 10 years (%)
Pembrolizumab ^a			
Pembrolizumab in combination with chemotherapy ^a			
UK SoC (NCRAS dataset) ^b			

a. IO therapy regimens have not been studied in randomised controlled trials within patients with EGFR Exon20 insertion mutation-positive advanced NSCLC. Therefore, comparative data for these has been derived from RWE (NECTAR study)

b. The basket of treatments within 'UK SoC' includes platinum-based chemotherapy, immunotherapy (with and without chemotherapy), EGR TKIs, and platinum-based chemotherapy

Abbreviations: CP: carboplatin and pemetrexed; IO: immuno-oncology drugs; NCRAS: National Cancer Registration and Analysis Service; OS: overall survival; RWE: real-world evidence; SoC: standard of care; TKI: tyrosine kinase inhibitor.

There were substantial ranges in the individual OS point estimates predicted by each expert for pembrolizumab with chemotherapy. Therefore, although the clinical expert opinion from the August advisory board was considered, the choice of extrapolation for pembrolizumab with chemotherapy was driven by statistical fit. This approach was taken given the survival data for pembrolizumab with chemotherapy were relatively mature and all extrapolations explored had similar statistical fits and long-term estimated survival outcomes, as illustrated in Table 21 and Figure 34 below.

Table 21: AIC and BIC values for pembrolizumab-chemotherapy OS extrapolations

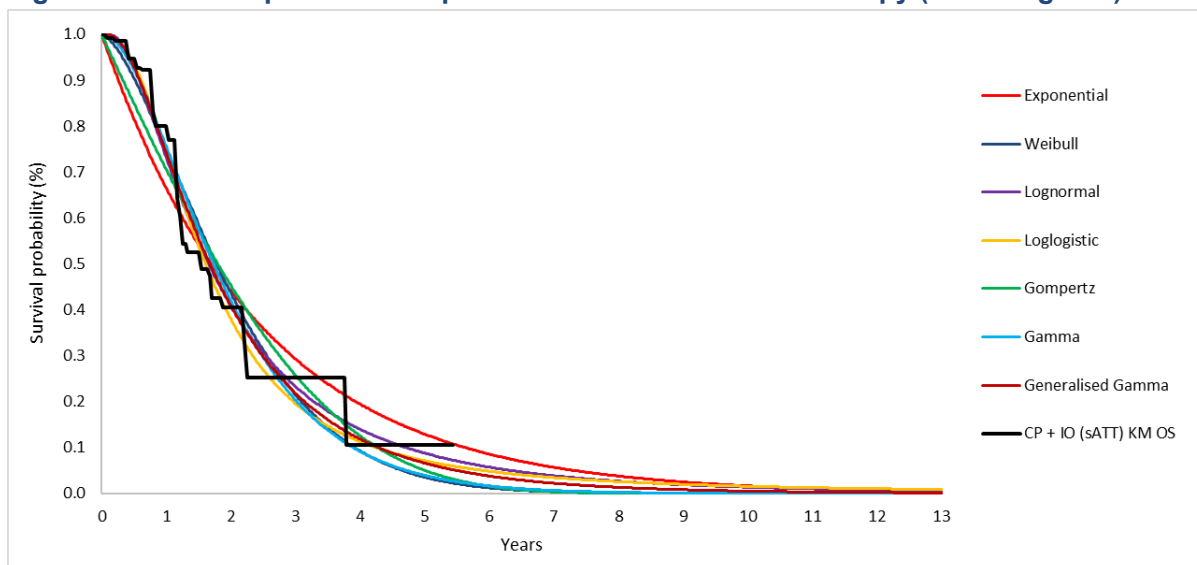
Distributions	AIC	BIC	Sum AIC / BIC
Exponential	304.15	306.15	610.30
Weibull	297.83	301.85	599.68
Lognormal	294.70	298.71	593.41
Log-logistic	████	████	████
Gamma	295.54	299.56	595.10
Gompertz	303.91	307.93	611.84

Distributions	AIC	BIC	Sum AIC / BIC
Generalised gamma	296.19	302.31	598.50

Lowest (i.e. best fitting) AIC and BIC scores for each distribution are in **bold** text.

Abbreviations: AIC: Akaike's Information Criterion; BIC: Bayesian Information Criterion; OS: overall survival.

Figure 34: OS extrapolations for pembrolizumab with chemotherapy (ATT-weighted)



Abbreviations: ATT: average treatment effect on the treated; IO: immuno-oncology; OS: overall survival.

i) Comparing CS Table 54 and Table 7 from the company's August 2024 advisory board indicates that in the CS base-case, long-term survival for chemotherapy is substantially underestimated. Please justify the approach used to estimate OS for chemotherapy, given this inconsistency.

Table 7 in the August advisory board report highlights that, for chemotherapy, the aggregated point estimates from the pre-meeting survey for the proportion of patients alive at 3, 5, and 10 years were 35%, 10%, and 1%.

However, the SHELF methodology for structured elicitation does not rely solely on point estimates provided by individuals to inform desired quantity of interest (in this case, survival).³³ The methodology involves discussion on the elicited point estimates to arrive at a group consensus.

The point estimates from individual advisors that were obtained from the pre-meeting survey, presented in Table 7 of the August 2024 advisory board report,⁸ were discussed during the advisory board. From this discussion, advisors arrived at a group consensus that the Weibull curve presented the most realistic survival extrapolation after the chemotherapy OS data had been adjusted for via the two-stage estimation (company base-case at the time). The Weibull curve for chemotherapy OS (after TSE adjustment) had lower survival rates at 3, 5, and 10 years (22%, 2%, and 0%, respectively) compared with the point estimates elicited from the pre-meeting survey (35%, 10%, 1%).

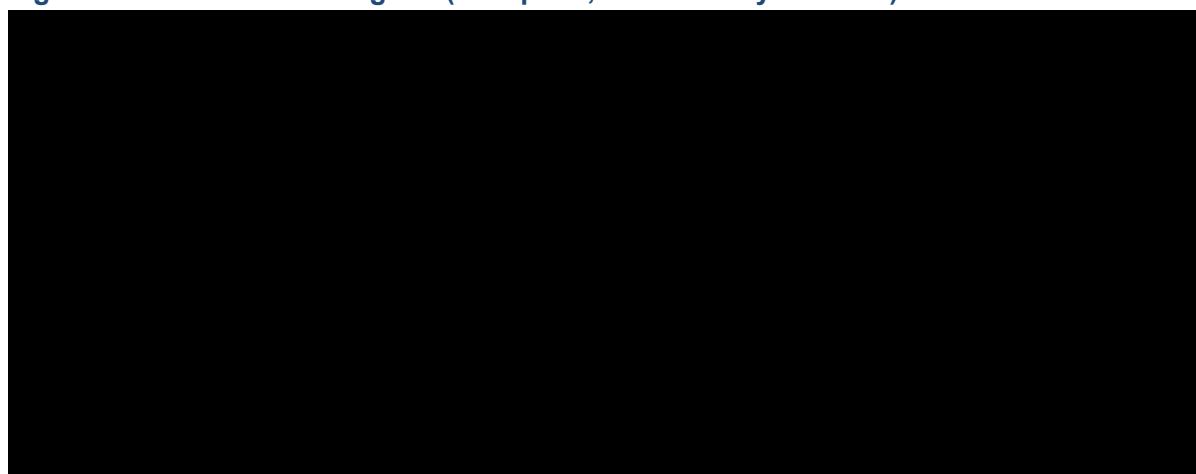
Following advice from health economic experts on the August advisory board,⁸ Johnson & Johnson changed the treatment switch methodology in the base-case to the IPCW approach. Johnson & Johnson then selected the extrapolation of IPCW-adjusted chemotherapy OS data that most closely matched the Weibull extrapolation of two-stage adjusted chemotherapy OS data.

Therefore, the discrepancy between the survival estimates provided in Table 7 of the August 2024 advisory board report and Table 54 of the CS arises from the point estimates (obtained from pre-meeting survey responses) being different from the group consensus (arrived at after discussion).

j) Based on CS Figures 40 and 41 as well as CS Table 55 for pembrolizumab-chemotherapy, the lognormal, Gamma and generalised Gamma distributions fit the observed data reasonably well and thus can be considered candidate distributions for estimating OS for pembrolizumab-chemotherapy. Please explain why these distributions were not included in the CS base case or scenario analyses, as considering them could provide valuable insights. Please provide scenario analyses using these distributions to estimate OS for pembrolizumab-chemotherapy.

As described above in part h, all extrapolations for pembrolizumab with chemotherapy had similar statistical fits and long-term estimated survival outcomes. Additionally, the choice of OS curve for pembrolizumab with chemotherapy did not have a large impact on the overall ICER, as detailed in the tornado diagram, Figure 35. Therefore, Johnson & Johnson did not view adding scenarios using different extrapolations for pembrolizumab with chemotherapy as appropriate within in the CS.

Figure 35: DSA tornado diagram (PAS price, 1.2x severity modifier)



Footnotes: 'p' represent parameters of the survival extrapolations.

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

However, Johnson & Johnson acknowledge that additional distributions to estimate OS for pembrolizumab-chemotherapy may be valuable to the EAG. As such, Johnson & Johnson have

provided the results for several scenarios in which the next best statistically fitting extrapolations after the log-logistic curve have been selected for pembrolizumab with chemotherapy OS. The results from these scenarios are detailed in Table 22 below.

Table 22: Scenario analysis results (incorporating different extrapolation curves for pembrolizumab with chemotherapy OS)

	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Base case (OS = log-logistic)	████	██	24,839
Scenario A (OS = log normal)	████	██	25,067
Scenario B (OS = gamma)	████	██	24,474
Scenario C (OS = generalised gamma)	████	██	24,734

Abbreviations: ICER: incremental cost-effectiveness ratio; Inc.: Incremental; OS: overall survival; PAS: patient access scheme; QALY: quality adjusted life year

The results in Table 22 demonstrate varying the choice of OS extrapolation for pembrolizumab-chemotherapy has very little effect on the ICER. This is due to the pembrolizumab-chemotherapy data being relatively mature, and the weighted comparator consisting of only 30% pembrolizumab-chemotherapy. This therefore confirms that varying the choice of extrapolation for pembrolizumab-chemotherapy OS has very little impact on the cost-effectiveness.

k) Comparing CS Table 56 and Table 8 from the company's August 2024 advisory board indicates that in the CS base-case, long-term survival for pembrolizumab-chemotherapy is substantially underestimated. Please justify the approach used to estimate OS for pembrolizumab-chemotherapy, given this inconsistency.

Table 8 in the August 2024 advisory board report highlights that, for pembrolizumab with chemotherapy, the aggregated point estimates from the pre-meeting survey for the proportion of patients alive after 3, 5, and 10 years were 20%, 13%, and 5%, respectively.⁸

However, there were substantial ranges across the survival estimates from individual advisors and the aggregated numbers cited above are driven by high proportions cited by one advisor.

The point estimates from individual advisors that were obtained from the pre-meeting survey, presented in Table 8 of the August 2024 advisory board report, were discussed during the advisory board. From this discussion, advisors agreed that patients typically respond poorly to pembrolizumab with chemotherapy. As such, the point estimates were seen as optimistic. Due to substantial ranges in the proportions of patients alive after 3, 5, and 10 years provided by the individual clinical experts, the survival data for pembrolizumab with chemotherapy being relatively mature (medians had been reached), and all extrapolations having similar statistical fits plus long-term estimated survival outcomes, the choice of OS curve for pembrolizumab with chemotherapy was mainly driven by statistical fit. As such the Log-logistic curve was chosen, which estimated lower survival rates at 3, 5, and 10 years (████%, █████%, and █████, respectively) compared with the proportions cited in Table 8 of the August 2024 advisory board (20%, 13%, and 5%, respectively). It should be noted that all extrapolations of pembrolizumab with chemotherapy are similar and varying the distribution has little effect on the overall ICER, as show in Table 22.

Therefore, the discrepancy between survival estimates provided in Table 8 of the August 2024 advisory board report and Table 56 of the CS arise from point estimates (obtained from pre-meeting survey responses) being different from the survival rates estimated from the selected extrapolation for OS (Log-logistic).

The justification for the choice of OS extrapolation for pembrolizumab with chemotherapy is provided in part h above.

I) To estimate OS, the CS base-case uses different distributions for different treatment options (i.e. Weibull for amivantamab-chemotherapy, Gamma for chemotherapy and loglogistic for pembrolizumab-chemotherapy). As suggested in NICE DSU TSD 14, please provide "*substantial justification*" in case different types of parametric models are used for different treatment options (i.e. further elaborate on the last paragraph of B.3.3.2).

NICE TSD 14 states that fitting different types of parametric model to different treatment arms requires substantial justification, as different models allow very different shaped distributions.³⁴ Johnson & Johnson believe that the shape of the survival distributions for each comparator (e.g., amivantamab with chemotherapy and chemotherapy) are very different and that the difference can be attributed to different mechanisms of action.

Given different mechanisms, the efficacy profiles of each comparator is expected to substantially differ and, as such, Johnson & Johnson believe that selecting different parametric models for each different comparator is appropriate.

During the August 2024 advisory board, the clinical and health economic experts agreed that there is justification for amivantamab with chemotherapy and chemotherapy survival to be modelled with separate distributions, given that the therapies have differing mechanisms of action.

Additionally, for both arms, switching the distribution of one treatment to the same distribution of the other only improves relative outcomes for amivantamab with chemotherapy. Switching the OS distribution of amivantamab with chemotherapy so that it reflects the base-case extrapolation of chemotherapy (gamma) only increases the life years associated with amivantamab with chemotherapy (given the gamma curve predicts a higher survival function). Similarly, switching the OS distribution of chemotherapy so that it reflects the base-case extrapolation of amivantamab with chemotherapy (Weibull) decreases the survival function of chemotherapy.

Therefore, due to different efficacy profiles between the intervention and comparators (driven by distinct mechanisms of action) and the fact that aligning models across treatment arms only serves to improve the relative outcomes for amivantamab with chemotherapy, different parametric models have been selected for comparators. It should be noted that even though the OS curve selection is different for amivantamab with chemotherapy and chemotherapy, both the Weibull (base-case for amivantamab with chemotherapy OS) and gamma (base-case for chemotherapy OS) model monotonically increasing hazards.

- m) Please justify the relevance of the CHRYSLIS trial for validating OS extrapolations, i) that the effectiveness estimates are generalisable and ii) that long-term OS are available (i.e. number of patients at risk at 3, 5, 8 and 10 year)**

The CHRYSLIS trial is a Phase I study which demonstrated the benefit of amivantamab monotherapy in patients with EGFR Exon20 insertion mutation-positive advanced NSCLC who had previously received platinum chemotherapy.³²

i) Whilst the CHRYSLIS study included patients who had received prior therapy in the advanced setting, and evaluated the efficacy and safety of amivantamab monotherapy only, the long-term data available otherwise support the long-term efficacy of amivantamab in patients with EGFR Exon20 insertion mutation-positive NSCLC, which can likely be attributed to the immune-modulating mechanism of action, as indicated by UK clinical experts.^{7, 8} This insight provides further support for the tail associated with the survival extrapolation of amivantamab-chemotherapy.

ii) The longest published follow-up for CHRYSLIS is as described on page 144 of the CS, at 19.2 months, where a median OS of 23 months (95% CI, 18.5–29.5) was observed.³² Johnson & Johnson acknowledge that the line of therapy and absence of chemotherapy in the amivantamab treatment regimen limits the direct comparison between CHRYSLIS and the model extrapolations for the first-line setting. However, the expectation is that patients in the first-line would similarly benefit substantially from the targeted, immune-modulating mechanism of action of amivantamab and experience a durable length of OS.

- n) In CS Section B.3.3.2.4 it is stated that: “To fit parametric distributions, the patient-level data needed to be simulated using the algorithm developed by Guyot et al. in 2012”. Please clarify in detail why it was required to reconstruct the patient-level data for the chemotherapy arm (informed by the PAPILLON trial) and justify (quoting NICE DSU TSD 16 where appropriate) that this is in line with good practices (when correcting for treatment switching using the IPWC).**

Using time-varying stabilized weights, IPCW-adjusted Kaplan-Meier (KM) curves were created based on the formula from Howe et al. (2011).³⁵ However, these adjusted KM data cannot be directly used for fitting parametric survival models. To address this, individual patient-level data (IPD) was simulated from the adjusted KM data using the methods recommended by Guyot et al. (2012). The simulated IPD from the IPCW-adjusted survival curves were then extrapolated using parametric methods, following the same approach as in the unadjusted case. This approach is in line with the recommendations from TSD16 (Page 26 and Figure 2).

- o) Please clarify that Figure 2 (Treatment switching analysis framework) from NICE DSU TSD 16 has been adhered to and provide the considerations per stage (1 to 6) of this flowchart.**

The information presented below outlines how the six considerations outlined within NICE TSD 16 have been adhered to for both the IPCW (base-case) and two-stage estimation (scenario) approach to treatment switch adjustment. Information on the RPSFTM methodology has not been included as this was not an appropriate adjustment methodology, based on feedback from health economists in the August 2024 advisory board.

Description of the data and unadjusted results

D1. Provide unadjusted results from an ITT analysis for comparison:

ITT results showing the unadjusted HR for OS vs chemotherapy are reported in Table 2 of the treatment switch technical report which is included within the reference pack to the responses.¹⁰ This is also included within the reference pack of the CS (table 2, page 13) and within the CSR (also included within the reference pack of the CS).

D2. Describe the treatment switching mechanism - who can switch and when.

The study design permitted patients in the chemotherapy arm with BICR-confirmed disease progression to switch to 2L amivantamab monotherapy. Patients who switched were allowed to initiate treatment with amivantamab monotherapy between [REDACTED] after their last dose of chemotherapy regardless of the time of progression.

D3. Detail the number of patients who switched, the number eligible to switch and when switching occurred.

Figure 2 (page 5) of the treatment switch technical report provides a graphical representation of the treatment switching. This includes the exposure times (in months) to first and subsequent-lines for amivantamab with chemotherapy and chemotherapy before death or administrative censoring.

D4. Give an overview of the data available for adjustment - what predictors were collected and how frequently were they measured.

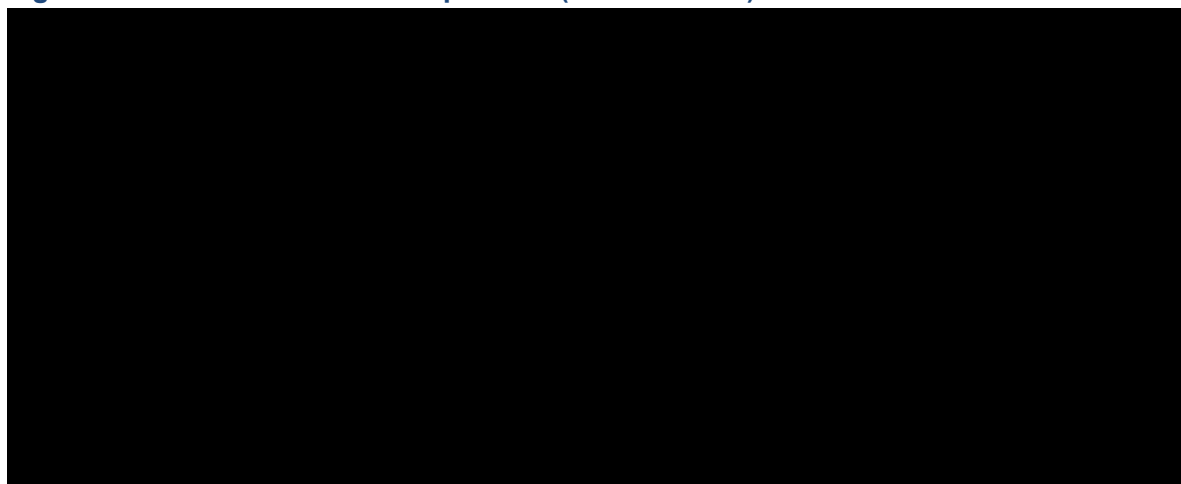
Section 5.2 in the treatment switch technical report provides an overview of all prognostic variables used in the statistical analyses for IPCW and two stage method (these covariates are not relevant for RPFSTM).

The prognostic variables were identified through a systematic literature review and clinical expert validation. The SLR and expert validation report for identifying these confounders was included within the reference pack of the company submission.

D5. Include a summary of subsequent treatments received in both/all arms of the trial, including which subsequent treatments were received, the number and proportion of patients that received subsequent treatments, and when subsequent treatments were received.

Figure 1 of the treatment switch technical report details the proportion of patients within the chemotherapy arm who received subsequent amivantamab monotherapy upon BICR-confirmed disease progression. This is detailed in Figure 36 below. The other subsequent therapies that patients within the chemotherapy and the amivantamab-chemotherapy arms received were balanced between the intervention and comparator arm and these have therefore not been adjusted for.

Figure 36: PAPILLON Patient Disposition (October 2023)



Source: Treatment switch adjustment technical report (figure 1, page 4)

D6. Describe which switches do not represent standard treatment pathways in the NHS in England and Wales

Amivantamab monotherapy is not recommended by NICE for the treatment of adult patients with advanced NSCLC with activating EGFR Exon20 insertion mutations, after failure of platinum-based therapy; as such, it is not available to patients in UK clinical practice via the NHS.¹¹

Given the large proportion of patients within the chemotherapy arm who switched to amivantamab monotherapy upon BICR-confirmed disease progression, as per Figure 36, these patients who switched treatment have been adjusted for.

D7. Describe and justify the type of switches that adjustments have been made for

All patients within the chemotherapy arm who switched to receive amivantamab monotherapy as a subsequent treatment as per protocol (i.e., after BICR-confirmed disease progression) were adjusted for. As described in D5, the other subsequent therapies received by patients in both the intervention and comparator arms, were relatively balanced between the arms. For these patients none of the applied treatment switch adjustment methods allow to adjust for switching to multiple treatments unless strong additional assumptions are made regarding the relative efficacy of these treatments. Therefore, no other adjustments to the other subsequent therapies have been made.

Method selection

M1. State whether the chosen adjustment approach, including all model fitting steps, was prespecified; if not, explain how the final method and model was selected

Both the IPCW and RPFSTM methods were included in the prespecified statistical analysis plan for the PAPILLON study (section 5.4.1.3 Analysis methods) which was included within the reference pack of the company submission. These were included as supplementary analyses to adjust for the impact of treatment crossover.

The section on the IPCW method prespecified the inclusion of baseline covariates and time-dependent covariates predictive of treatment crossover, such as disease burden and occurrence of serious adverse events.

The two- stage method was not included in the original SAP but was added in an additional SAP specific for the adjustment treatment switching, which specified further details on the implementation of all three methods, including the TSE, in line with the approaches recommended in DSU 16.

IPCW

IPCW1. Provide a statement around the plausibility of the no unmeasured confounders assumption (this can include a relevant DAG for selection of variables)

Covariates included in the statistical analyses were in line with the variables identified in a SLR, as described in of the company submission.

The following prognostic factors in advanced NSCLC were identified and ranked based on the SLR and expert validation (report included within the reference pack of the company submission): Functional ECOG score at baseline, presence of metastases (brain, liver, other) at advanced NSCLC diagnosis, age at baseline, people of Asian ethnicity, smoking history and sex. Further details on this are presented in sections B.2.9.1 (“Selection of evidence sources”) and B.2.9.4 “identification and adjustment of prognostic variables” in the company submission.

A copy of the SLR and validation report is attached within the reference pack to the responses.³⁶

IPCW2. Provide summary statistics for each variable included in the switching model by treatment arm and switch status to assess the plausibility of the positivity assumption

As PAPILLON is a randomised trial, (nearly) complete overlap is expected between both treatment arms at baseline.

As switching only occurred in the chemotherapy arm, overlap within the progressed patients, between patients who switched versus not switched to second-line amivantamab monotherapy, is of interest.

Table B1 (within the appendix of the treatment switch technical report) provides patient characteristics for patients who switched to second-line amivantamab versus patients who did not switch, illustrating that the overlap of distributions. The comparison of the baseline characteristics between switchers and non-switchers is also provided within Johnson & Johnson’s response to clarification question A7b

IPCW3. State whether unstabilised or stabilised weights were used

For the main analysis, stabilised weights were used, but non-stabilised weights were used as a sensitivity analysis.

IPCW4. Detail the statistical procedure used to calculate weights (e.g. pooled logistic regression, Cox model)

The time-dependent weights over time for progressed patients in the chemotherapy arm were estimated from the ratio of probabilities estimated from two repeated logistic regression models. The model for the denominator fitted to all chemotherapy patients included both baseline and time-dependent covariates. For stabilized weights, the model for the numerator only included baseline covariates. See section 7.1.2 of the treatment switch technical report for further details.

IPCW5. State the portion of data used in the switch model including time-varying predictors (e.g. post-progression data only)

The repeated logistic regression model to estimate the probabilities of switching over time was fitted to progressed chemotherapy patients only, where OS for amivantamab switchers was censored at time of switch (see section 7.1.2 in the treatment switch technical report).

IPCW6. Describe the extent of, and the method used to address, missing data on predictors in the switch model(s)

None of the baseline covariates had any missingness, except race, for which four patients with race unknown were assigned to the non-Asian category (see table 1 of the treatment switch technical report).

ECOG and EQ5D utilities, captured in the trial every 3 and 6 weeks respectively, were used as time-dependent covariates, with values for timepoints between two measurements imputed using last observation carried forward.

The AE based time-varying covariates could be defined on a daily basis without any missingness, as dates for adverse events were systematically captured in the trial.

IPCW7. Present parameter estimates and associated measures of precision from the switch model(s)

The parameter estimates for all covariates included in the repeated logistic regression models are presented in table 3 (model including all baseline and time-varying covariates) and table 4 (model only including baseline covariates) of the treatment switch technical report.

IPCW8. Summarise the distribution of weights and state whether values were truncated

The distribution of both stabilised as unstabilised weights over time are presented in figures A1 and A2 (Appendix A), respectively, of the treatment switch technical report. As no extreme weights were observed, no truncation was implemented.

IPCW9. Detail the final outcomes model (i.e. the model fitted to the weighted dataset to estimate the treatment effect, or to model survival), including the estimation method (e.g. robust variance estimation) and the baseline variables adjusted for

The hazard ratio was estimated using a weighted cox model including time dependent weights. The robust variance (“sandwich”) estimator was used to properly reflect the inclusion of time dependent weights in the confidence intervals for the hazard ratio. Prognostic variables included for the IPCW are reported in section 5.2 of the treatment switch technical report.

Baseline variables were age, gender, race, history of brain metastasis, history of liver metastasis, history of smoking and prior major surgery. ECOG performance status, EQ5D utility score, occurrence of treatment emergent serious adverse events were used as time-varying covariates.

IPCW10. Report on sensitivity analyses showing the robustness of treatment effect estimates and survival extrapolations to violations of key assumptions. Estimated treatment effects and survival extrapolations, AIC, BIC and maximum and minimum switch weights should be compared for versions of the models with different numbers of cubic splines, functional forms, and alternative definitions of categorical variables derived

from continuous variables. If weights were truncated, there must be some sensitivity analysis around the truncation percentiles, including a comparison with no truncation.

All measures of fit for the survival extrapolations, including AIC, BIC and diagnostic plots were included in the submission document.

As no extreme weights were observed, no truncation was implemented (see IPCW8)

Two-stage estimation (simple version)

TSEs1. State the disease-related secondary baseline used

The date of progressive disease was used as the secondary baseline.

TSEs2. State the parametric model used and consider its appropriateness

A multivariable Weibull model was used to estimate the shrinkage factor. The fit of the model was assessed based on AIC/BIC (compared to alternative parametric models) and diagnostic plots. Section B in the technical report provides further details.

TSEs3. Provide a statement around the plausibility of the no unmeasured confounding assumption. This can include a relevant DAG for selection of variables

See response provided to IPCW1

TSEs4. Provide a statement around the plausibility of the assumption of no time-dependent confounding between secondary baseline and time of switch. This should include a graph illustrating the time from secondary baseline to switch across all switching patients

Figure B1 within the treatment switch technical report provides a graphical representation of the distribution of the time between date of progression and time of switch to second-line amivantamab monotherapy, with the time from progression to treatment switch ranging between ■ to ■ days.

As acknowledged in the company submission, as informed by health economic expert opinion during the August 2024 advisory board, this may reflect a key limitation regarding the core assumption of the TSE approach regarding absence of time-dependent confounding.

TSEs5. Describe the extent of, and the method used to address, missing data on predictors used in the analysis

See response provided to IPCW6

TSEs6. Present the estimated time ratio (or acceleration factor) and its confidence interval

Table 5 in the treatment switch technical report provides the estimates for all variables in the multivariate Weibull AFT model, including the estimate of the acceleration factor, which represents the PPS benefit of switching to second-line amivantamab monotherapy versus no switching.

TSEs7. Detail the model fitted to the adjusted dataset, including the method used to calculate confidence intervals around the estimated treatment effect and/or survival extrapolation (e.g. bootstrapping) and baseline variables adjusted for

The relative efficacy of ACP vs. CP on adjusted/counterfactual OS was then estimated by fitting a Cox proportional hazards model with randomised treatment as a covariate.

The conventional estimators of standard error (SE) and 95% confidence intervals (CIs) in the Cox model do not account for the uncertainty around the estimated acceleration factor (or shrinkage parameter) from the preceding TSE analysis. This additional source of uncertainty was properly propagated in subsequent analyses by bootstrapping the entire two-step procedure as follows: by first conducting a TSE analysis and then fitting a Cox regression model to the counterfactual OS to estimate the relative effect of ACP compared with CP (see section 7.2 in the treatment switch technical report).

TSEs8. Present results with and without re-censoring

While the result without recensoring was presented as the base case TSE analysis, results for the analyses with re-censoring were included as well in section 8.1.2 of the treatment switch technical report.

TSEs9. Report on sensitivity analyses showing the robustness of treatment effect estimates and survival extrapolations to violations of key assumptions. Estimated treatment effects, survival extrapolations, AIC and BIC should be compared for versions of the models with different parametric distributions and covariates included

It should be noted that the estimated HRs representing a summary measure for the estimated treatment effect based on the three different adjustment methods are not used as input for the CE-model and as such do not impact the estimation of the ICER. OS extrapolations for the CP-arm used as inputs for the CE-model are based on the counterfactual outcomes estimated from the three approaches.

Two-stage estimation (g-estimation version)

TSE using g-estimation was explored using available software (ref) were explored, but available software finally did not allow to generate stable results, due to lack of convergence.

p) Please add a supplementary document following the reporting recommendations specified in NICE DSU TSD 24 (recommendation 8).

Detailed reporting of all the recommended steps towards treatment switching, as outlined in NICE DSU TSD 16 and 24, have been provided in part o above.

q) Please provide the results of a scenario analysis without the treatment switching adjustment (i.e. based on the ITT).

Johnson & Johnson do not believe that a scenario analysis with unadjusted chemotherapy OS data (without any adjustment for treatment switching) is appropriate given it would be modelling a population who received subsequent therapies that are not available in UK clinical practice.

Amivantamab monotherapy after progression on platinum-based chemotherapy is not recommended by NICE (as per guidance in TA850) and so patients within the chemotherapy arm who received amivantamab monotherapy after progression do not reflect UK clinical practice.¹¹ Therefore, the chemotherapy OS data were adjusted to account for this treatment switching. This was done to reflect the survival of patients receiving chemotherapy, had they followed UK clinical practice after progression. This form of adjustment is used to mitigate potential confounding from the subsequent therapy that is not received by patients in the UK, ensuring that efficacy data are as reflective of clinical practice as possible.

Adjusting for treatment switching has been recommended by NICE DSU TSDs 16 and 24.^{37, 38}

As an analysis of unadjusted chemotherapy OS data would not reflect patients in UK clinical practice and is not aligned to recommendations within NICE DSU TSDs, Johnson & Johnson have not conducted this scenario analysis.

B 10. Priority question. TTDD data were used to inform time on treatment and hence inform acquisition costs of treatment using parametric survival models.

- a) To examine the diagnostics of the parametric survival models (using the observed data), please provide the following Figures (separately per treatment):**
- i. Plot the cumulative hazard versus time**
 - ii. Plot the log smoothed hazard versus time**
 - iii. Plot the standard normal quartiles versus log time**
 - iv. Plot the log survival odds versus log time**

i) *Cumulative hazard versus time plots*

Figure 37: Cumulative hazard plot – Amivantamab alone - ACP TTDD

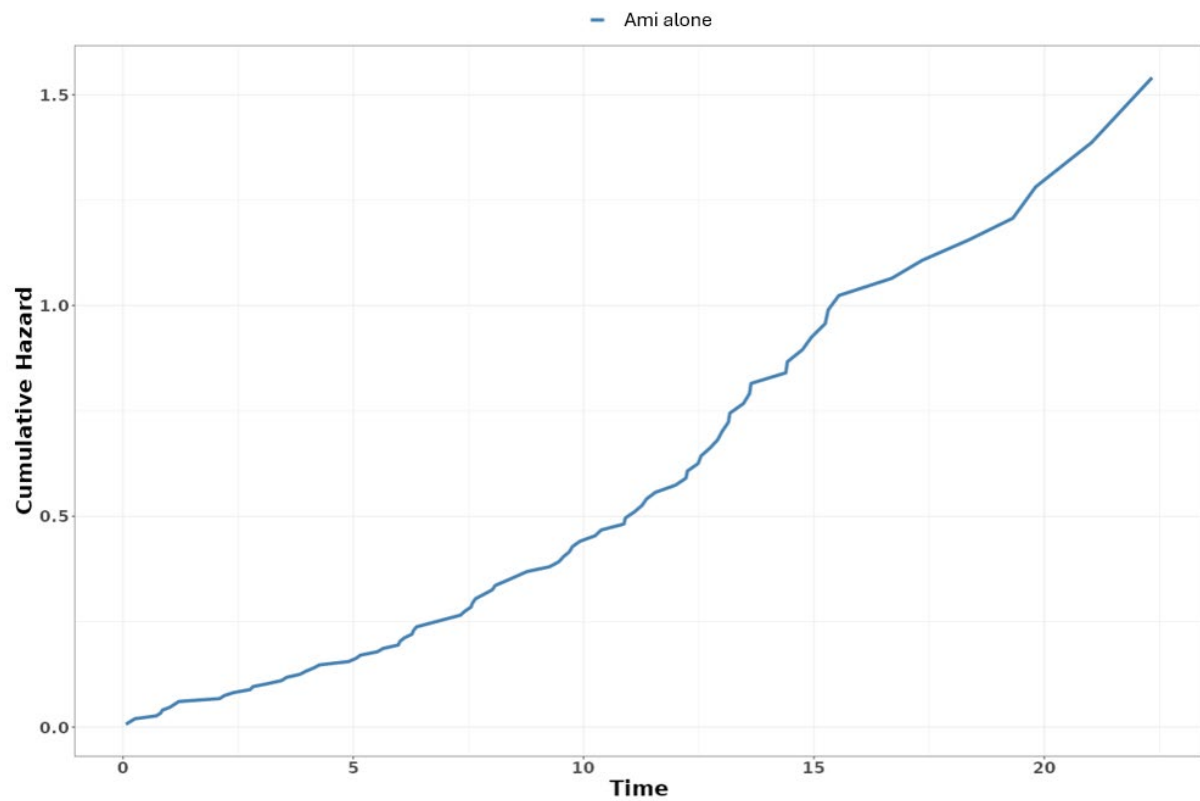


Figure 38: Cumulative hazard plot – CP alone - ACP TTDD

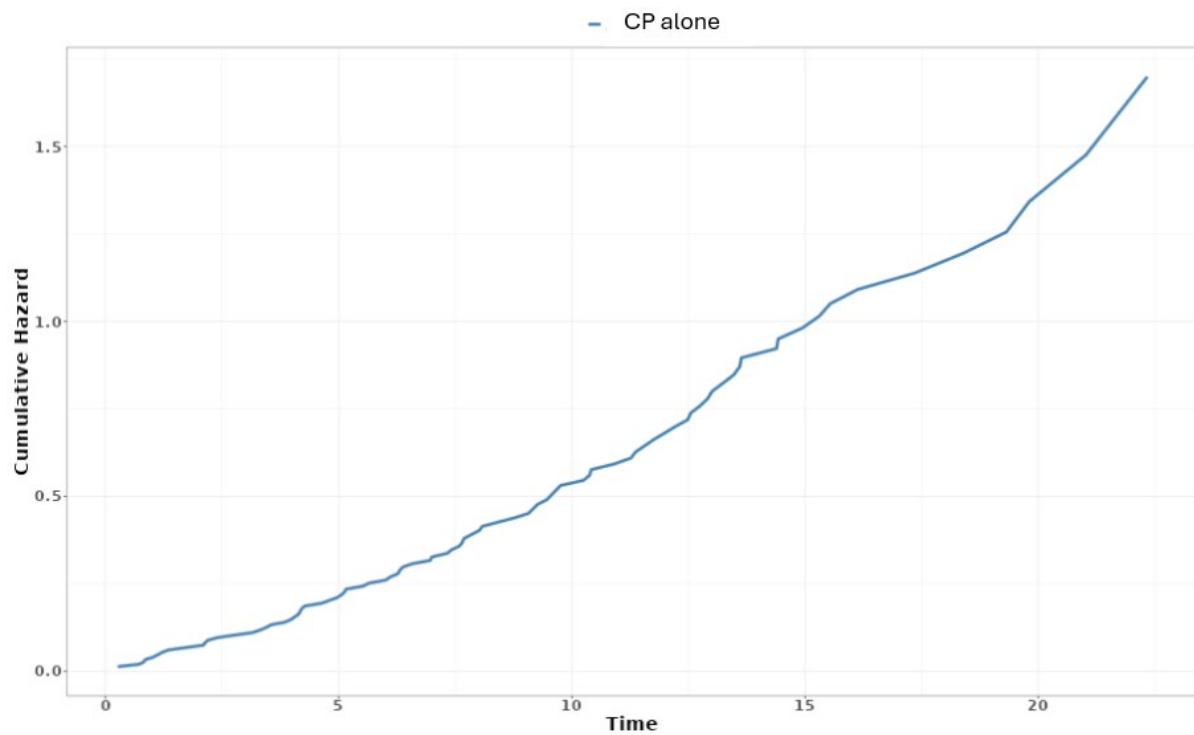
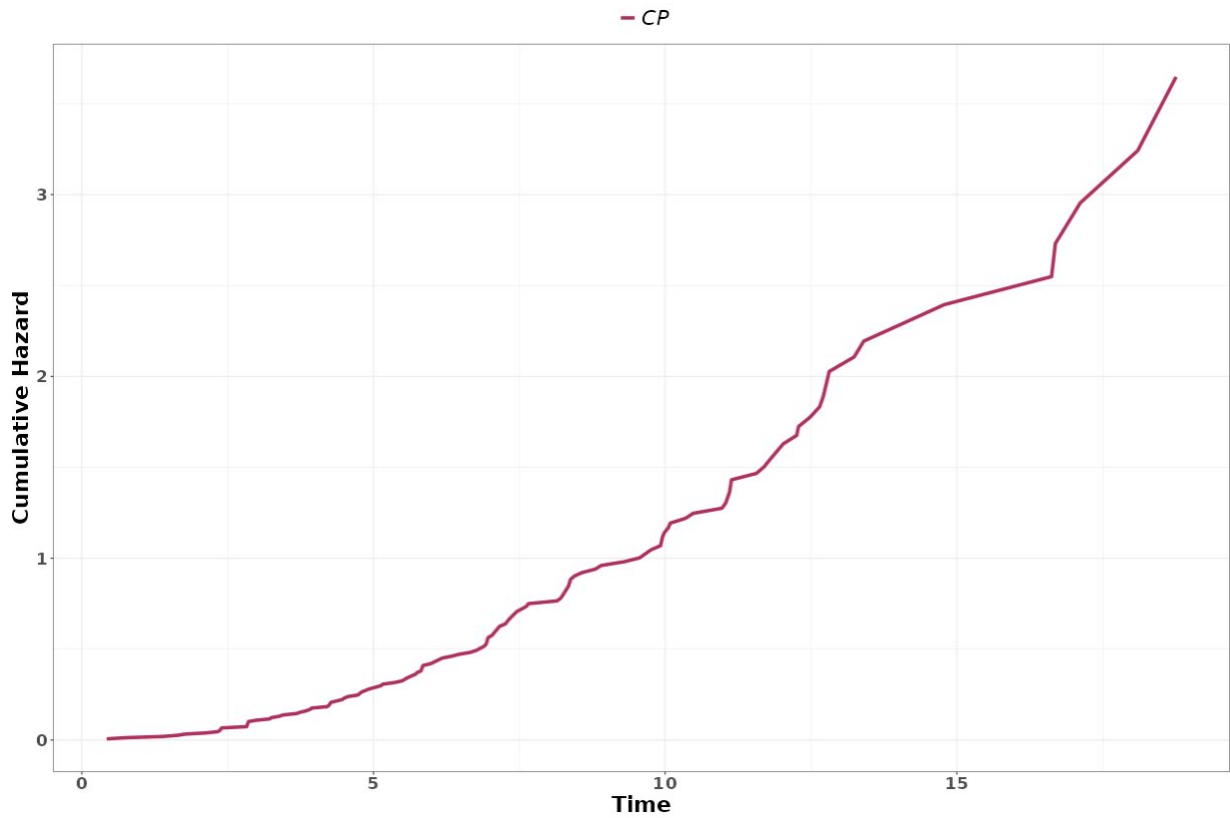


Figure 39: Cumulative hazard plot – CP TTDD



ii) Log smoothed hazard versus time plots

Figure 40: Log smoothed hazard plot – Amivantamab alone - ACP TTDD

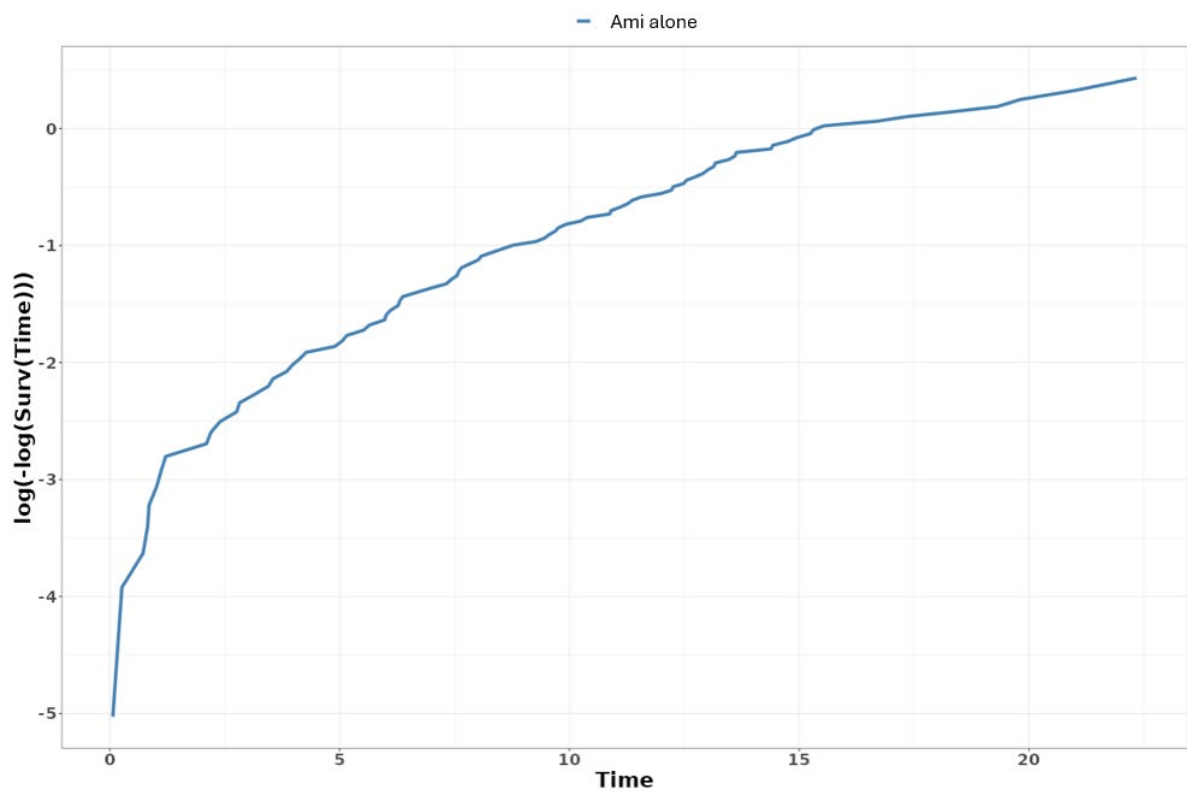


Figure 41: Log smoothed hazard plot – CP alone - ACP TTDD

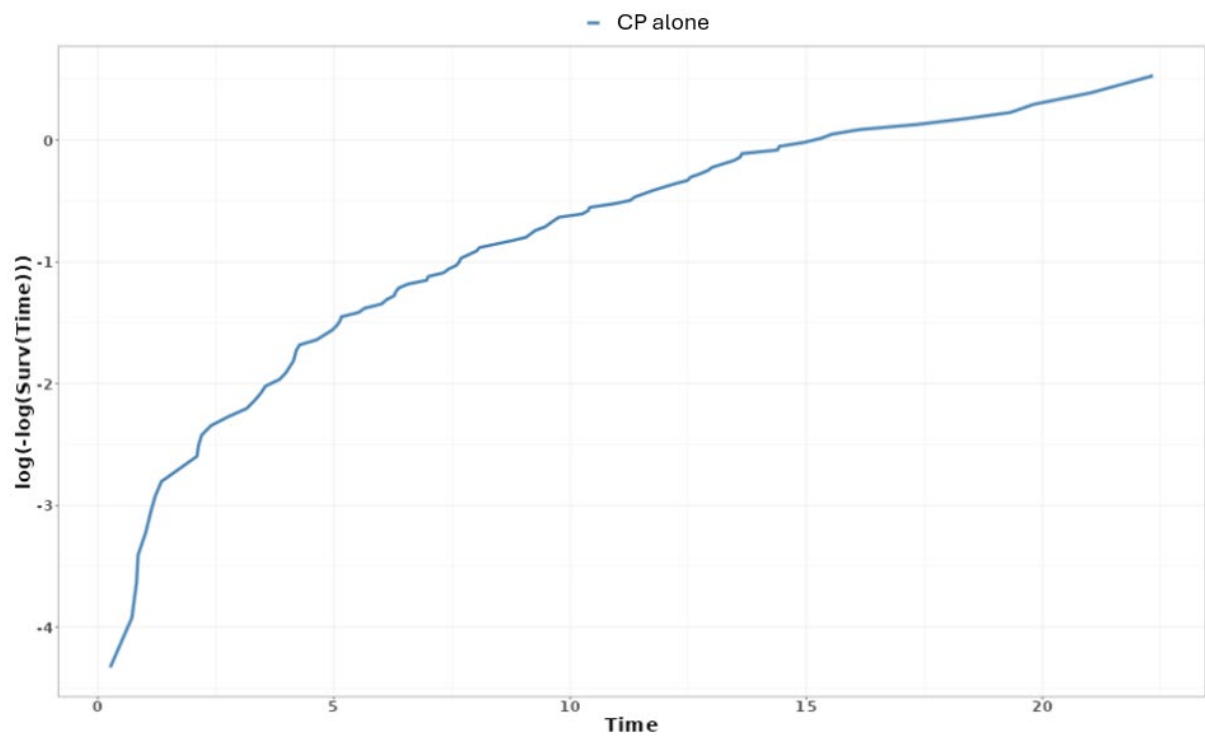
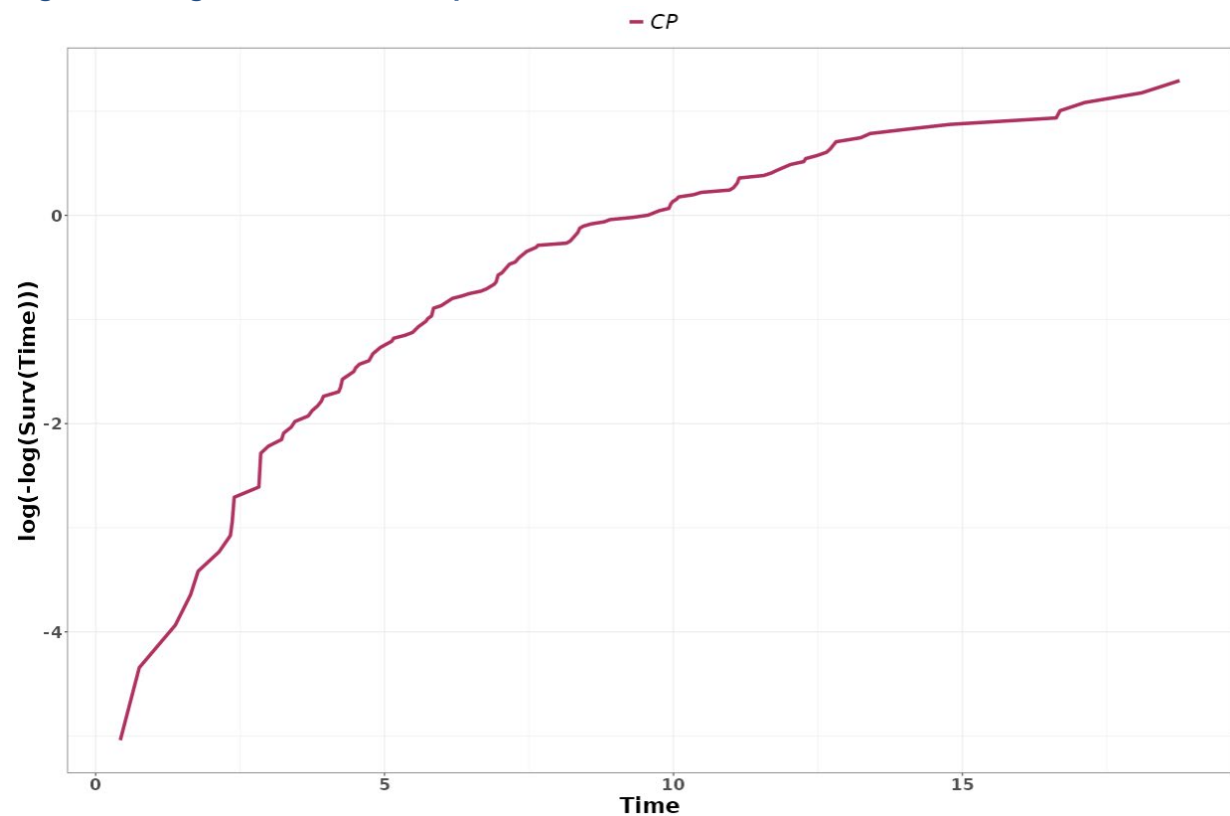


Figure 42: Log smoothed hazard plot – CP TTDD



iii) *Standard normal quantiles versus log time plots*

Figure 43: Standard normal quantiles vs. log time plot – Amivantamab alone - ACP TTDD

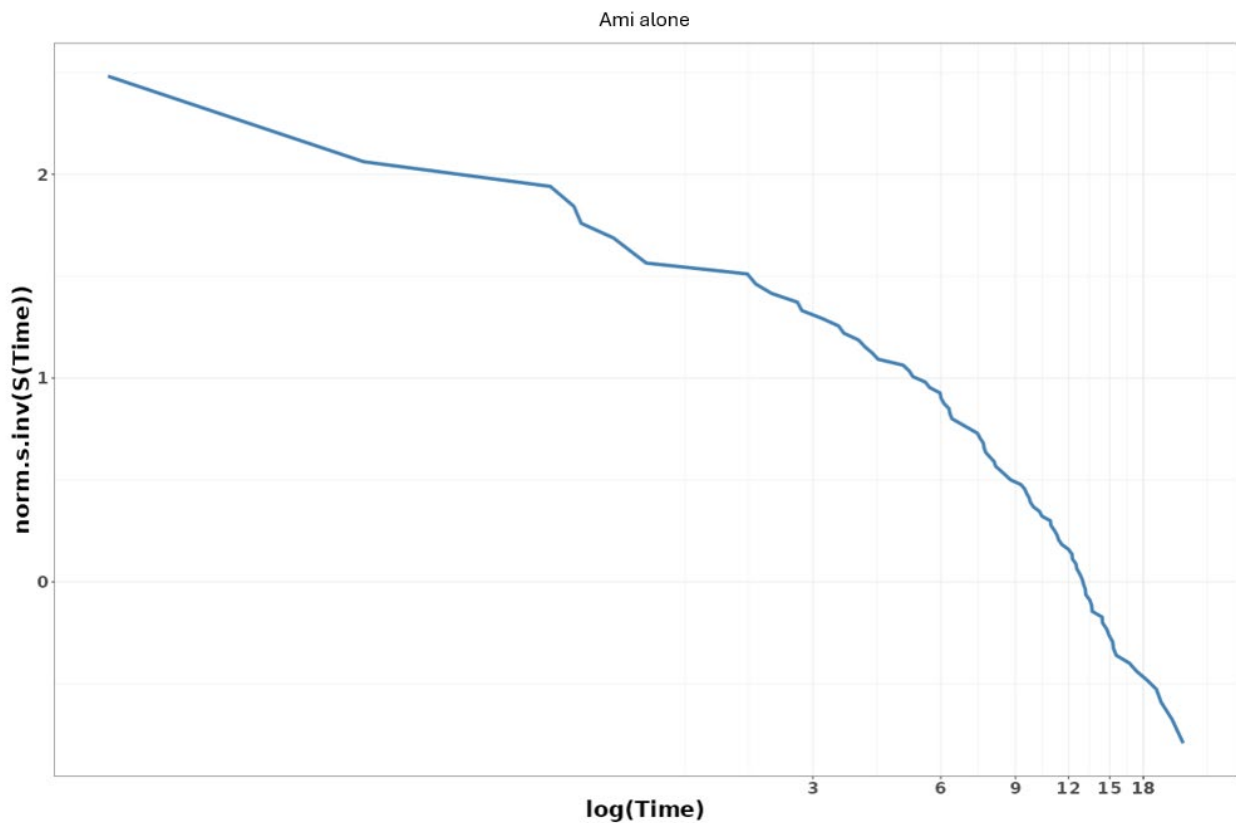


Figure 44: Standard normal quantiles vs. log time plot – CP alone - ACP TTDD

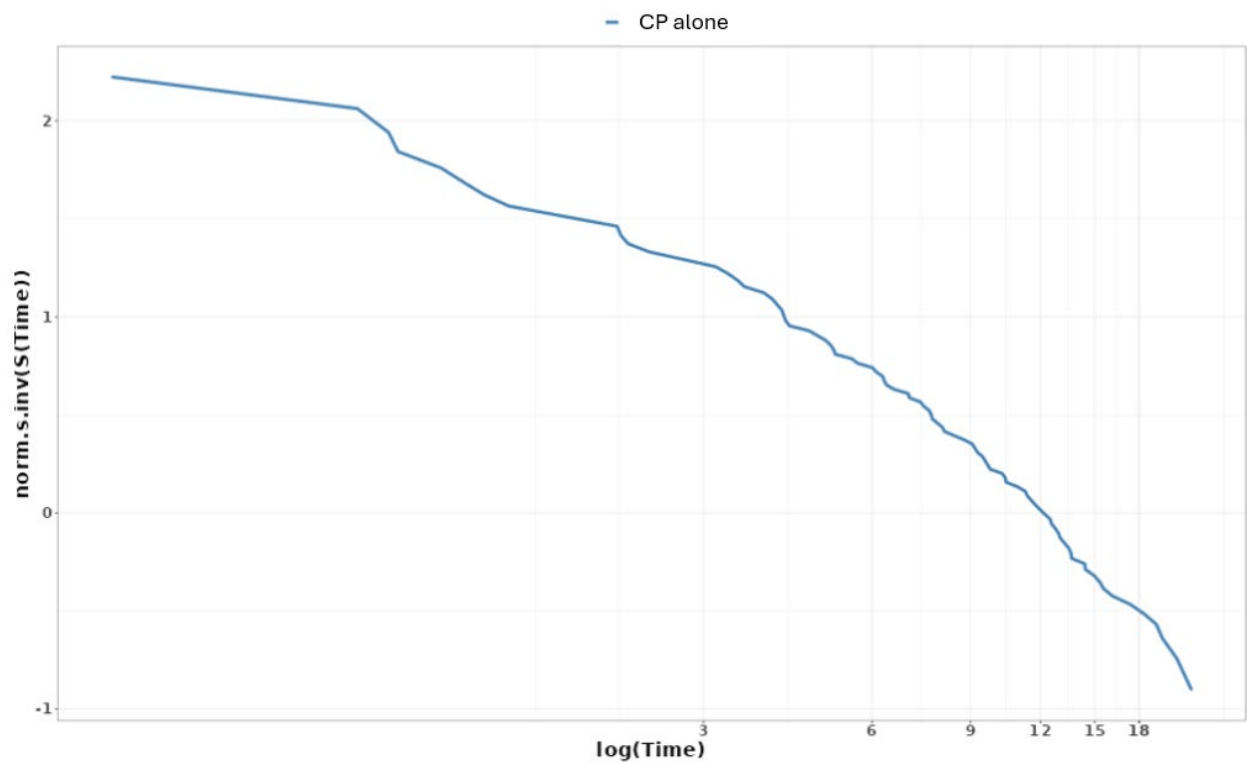
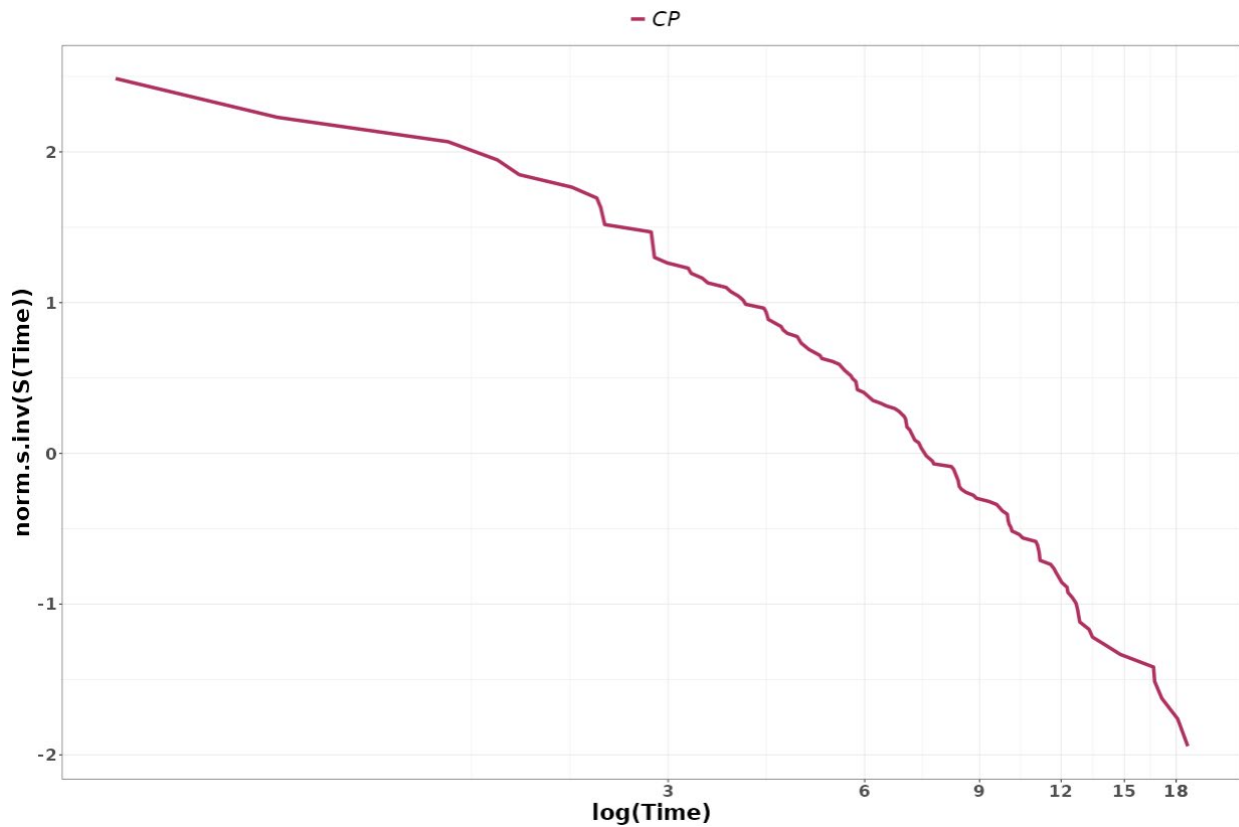


Figure 45: Standard normal quantiles vs. log time plot – CP TTDD



iv) *Plot the log survival odds versus log time*

Figure 46: Log survival odds vs. log time plot – Amivantamab alone - ACP TTDD

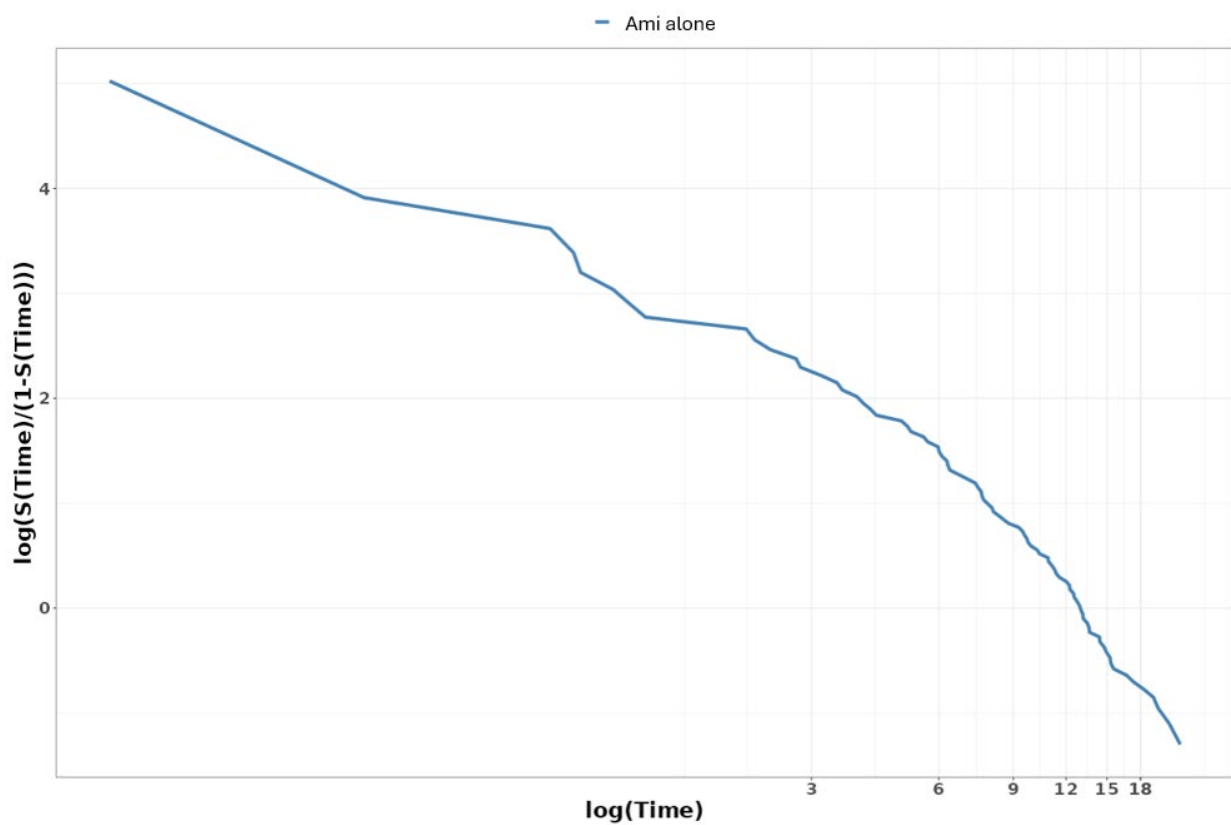


Figure 47: Log survival odds vs. log time plot – CP alone - ACP TTDD

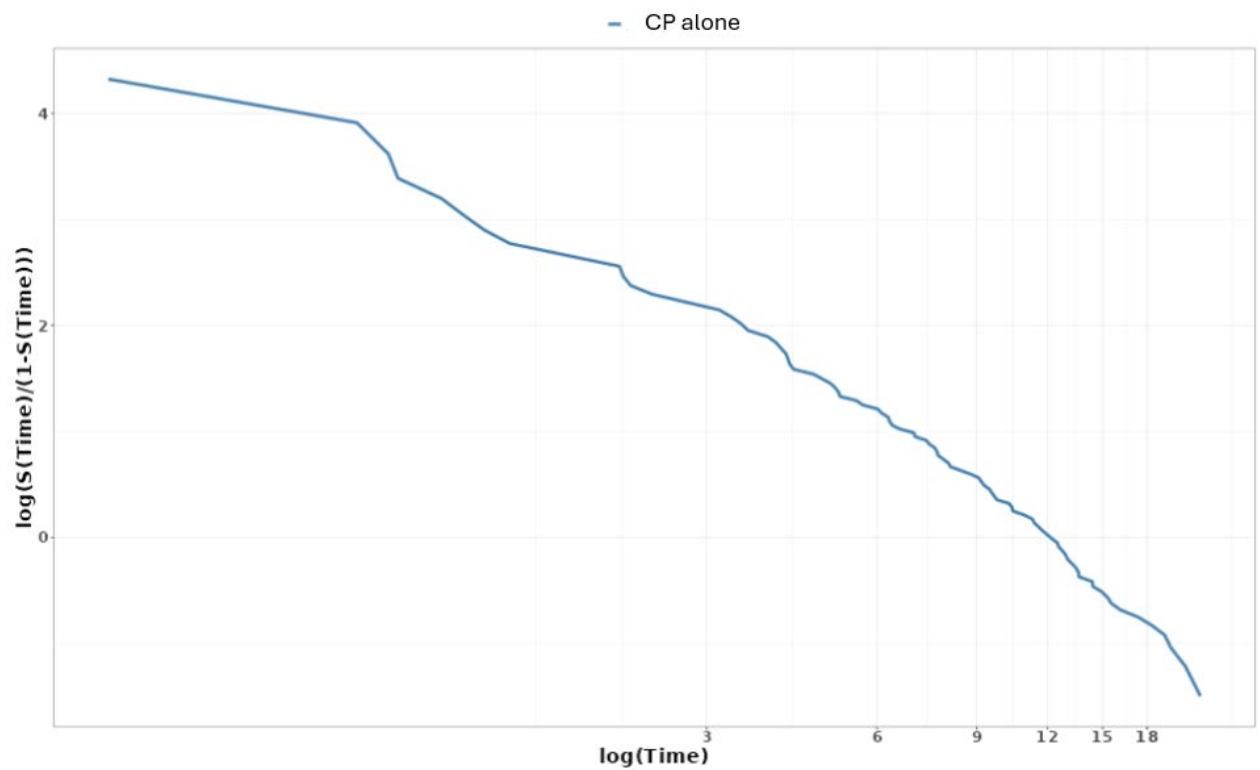
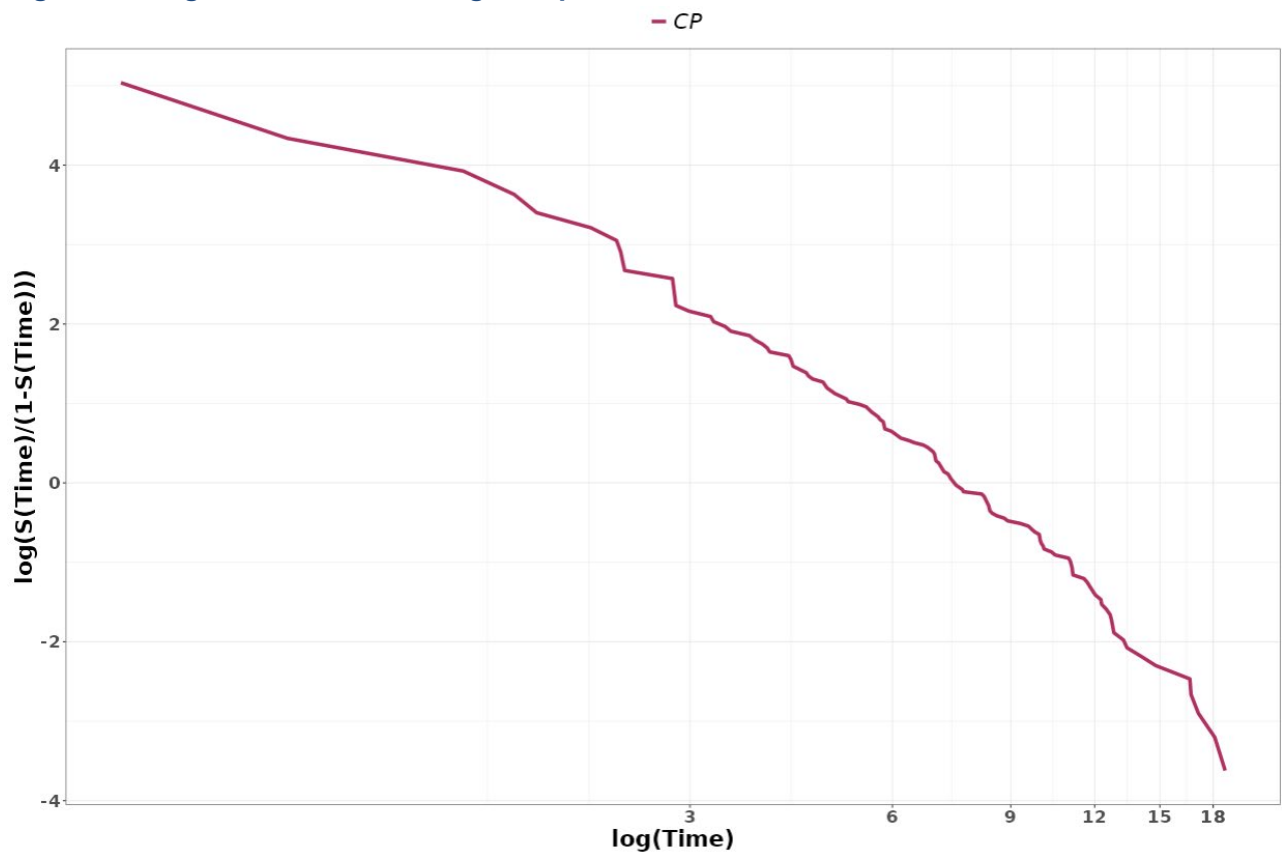


Figure 48: Log survival odds vs. log time plot – CP TTDD



b) Please clarify in detail how the clinical expert opinion was derived to inform the selection of the parametric survival model approach for TTDD. This should include (but not limited to), per advisor:

- i. what advisor was consulted,**
- ii. why this advisor qualified as expert for this topic,**
- iii. what information was provided to the advisor,**
- iv. what questions were asked,**
- v. exact statements as well as point estimates (%) and/or ranges provided by the advisor (separately per treatment).**

To validate the choice of TTDD extrapolations, clinical expert opinion was sought during the August 2024 advisory board. This advisory board comprised two clinical experts:

████████████████████ and
██

Johnson & Johnson cannot compliantly share personal data related to individual advisors, including qualifying criteria for attendance, beyond what was presented within the advisory board report. However, advisor selection was conducted according to Johnson & Johnson standard operating procedure, which specifies that advisors must be experts in their areas and each participant should be chosen according to their expertise, such that they will be able to contribute meaningfully to the purpose and expected outcomes of the meeting.

In order to validate the choice of TTDD extrapolation curve, individual estimates for TTDD at distinct timepoints (3, 4, and 5 years) were elicited from both advisors. This was done for amivantamab with chemotherapy and chemotherapy (considering patients within the PAPILLON trial and within clinical practice) and for pembrolizumab monotherapy, pembrolizumab with chemotherapy, and a basket of UK SoCs based on the NCRAS data (considering patients in clinical practice).

The individual point estimates were obtained via a pre-meeting survey and were then discussed during the advisory board meeting, to arrive at a discussion-based group consensus. This approach of individual elicitation of point estimates followed by discussion to arrive at a group consensus is aligned to the SHELF methodology that has been described above in clarification question B10. The pre-meeting survey has been included within the reference pack of the responses.³¹ The specific questions pertaining to the elicitation of TTDD estimates at 3, 4, and 5 years are detailed on slides 8 and 15 of the pre-meeting survey. A screenshot of slide 8 is provided in Figure 49.

Figure 49: Slide 8 from the pre-meeting survey of the August 2024 advisory board, detailing what questions were asked regarding TTDD estimates for amivantamab with

chemotherapy and chemotherapy at 3, 4, and 5 years, considering patients within the PAPILLON study

PAPILLON Trial Setting: TTDD



- In this exercise, you are also asked to consider the **patient population enrolled into the PAPILLON trial** (please see the Appendix for patient characteristics):

Please provide the proportion of patients you would expect to be (alive) and remaining on first-line treatment at the specified timepoints for the following two patient populations:

1) Patients with untreated EGFR Exon20 insertion mutation-positive advanced NSCLC enrolled into the PAPILLON trial who are **treated with ACP** (considering ami and CP separately if you think that the treatments have different treatment durations)

2) Patients with untreated EGFR Exon20 insertion mutation-positive advanced NSCLC enrolled into the PAPILLON trial who are **treated with CP**

1) Please complete the table below with your estimates:

Treatment		Proportion of patients remaining on treatment at 3 years (%)	Proportion of patients remaining on treatment at 4 years (%)	Proportion of patients remaining on treatment at 5 years (%)
ACP	Ami			
	CP			

2) Please complete the table below with your estimates:

Treatment	Proportion of patients remaining on treatment at 3 years (%)	Proportion of patients remaining on treatment at 4 years (%)	Proportion of patients remaining on treatment at 5 years (%)
CP			

J&J Abbreviations: ACP: amivantamab in combination with carboplatin plus pemetrexed; CP: carboplatin plus pemetrexed; EGFR: epidermal growth factor receptor; NSCLC: non-small cell lung cancer; | Oncology
TTDD: time to treatment discontinuation or death

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The individual advisor responses for TTDD estimates elicited from the pre-meeting survey, and associated ranges, are detailed within the full advisory board report which is included within the reference pack of the CS. It should be noted that the SHELF methodology relies on a group consensus obtained through discussion of the elicited point estimates rather than relying solely on the point estimates themselves. This is especially relevant for TTDD given the point estimates elicited from individual clinicians varied quite broadly and as such, were further discussed during the advisory board.

c) Please clarify that the advisor input (response to previous question) supports the CS base-case (i.e. supporting the selection of Weibull for amivantamab-chemotherapy, Gamma for chemotherapy and HR approach for pembrolizumab-chemotherapy).

Amivantamab with chemotherapy and chemotherapy:

After discussing the point estimates for TTDD at 3, 4, and 5 years, the advisors were able to provide a consensus over which extrapolations were most appropriate for amivantamab with chemotherapy (noting that the TTDD of each component was assessed separately) and chemotherapy.

From the discussion, when considering the amivantamab component of amivantamab with chemotherapy, the clinical experts agreed that the gamma and Weibull extrapolations of TTDD were the most accurate. The gamma and Weibull curves were also seen as the most accurate TTDD extrapolations when considering the chemotherapy component within amivantamab with chemotherapy.

When considering chemotherapy (comparator arm), all extrapolations of TTDD were seen as appropriate as they all predicted similar outcomes.

The advisor input and discussion-based consensus over the appropriate TTDD extrapolations of amivantamab with chemotherapy and chemotherapy align with the extrapolations chosen in the base-case of the submission.

Pembrolizumab with chemotherapy

The TTDD for pembrolizumab with chemotherapy was derived using the ratio between the per cycle hazard of TTDD for the amivantamab component of amivantamab-chemotherapy and TTNT for the amivantamab-chemotherapy treatment arm in the PAPILLON study, which was multiplied by the per cycle hazard of the selected TTNT extrapolation of pembrolizumab-chemotherapy.

Advisor input on the TTNT estimates of pembrolizumab with chemotherapy obtained from the August 2024 advisory board was used to inform the TTNT extrapolation. However, there were wide ranges in estimates provided by individual advisors and as such, the point estimates for TTDD obtained from the advisory board were uncertain. Therefore, curve selection was mainly driven by statistical fit and assessment of hazard function. This was done because the TTNT data from the NECTAR study were relatively mature (median had been reached) and most extrapolations had similar statistical fits plus long-term survival outcomes.⁹

d) According to the company's August 2024 advisory board report, considering of TTDD extrapolations for amivantamab in ACP treatment: *"Both clinical experts agreed that the gamma TTDD extrapolation was likely the most accurate for ACP"* and *"The clinical experts agreed that the gamma extrapolation was the most plausible curve for both the amivantamab and CP components of ACP, with AG noting the Weibull may be acceptable for the amivantamab component"*. Please justify why the Gamma distribution was not used to extrapolate TTDD for amivantamab.

For the amivantamab component of amivantamab with chemotherapy, the clinical experts at the August 2024 advisory board agreed that the gamma and Weibull extrapolations of TTDD were likely to be the most accurate.⁸ This was driven by the fact that both curves estimate a low proportion of patients remaining on treatment at the 5-year timepoint.

For the chemotherapy component within amivantamab with chemotherapy, the clinical experts agreed that the gamma and Weibull extrapolations of TTDD were seen as the most accurate.

For both the amivantamab component and the chemotherapy component, the Weibull distribution was chosen in the base-case because it had a better statistical fit compared with the gamma distribution, and both gamma and Weibull were seen as plausible by the clinical experts. However, to consider the other plausible extrapolation based on the August 2024 advisory board, the gamma distribution in the amivantamab and chemotherapy components of amivantamab with chemotherapy was provided in scenarios 5, 6 and 7 of the C.S. As discussed the model has been updated with the latest NHS reference costs and so an updated version of scenarios 5, 6 and 7 have been provided and are detailed in Table 23.

Table 23: Scenario analysis results (deterministic) when applying the gamma extrapolation to the TTDD of amivantamab and chemotherapy (components of amivantamab with chemotherapy)

Scenario	WITH PAS		
	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
TTDD parametric extrapolations			
Gamma extrapolation for amivantamab and chemotherapy as part of ACP	■	■	26,385
Gamma extrapolation for amivantamab; Weibull for chemotherapy as part of ACP	■	■	26,361
Weibull extrapolation for amivantamab; gamma for chemotherapy	■	■	24,876

Abbreviations: ACP: amivantamab with carboplatin and pemetrexed; BICR: blinded independent central review;; ICER: incremental cost-effectiveness ratio; PAS: Patient Access Scheme; QALY: quality-adjusted life year; TTDD: time to treatment discontinuation or death;.

- e) Similarly to previous question, according to the company's August 2024 advisory board report, considering of TTDD extrapolations for chemotherapy in ACP treatment: *"BC called out the gamma extrapolation as being the appropriate curve"*. Please justify why the Gamma distribution was not used to extrapolate TTDD for chemotherapy in ACP treatment.

Please see combined response in Part d.

- f) To estimate TTDD, the CS base-case uses different distributions for different treatment options (i.e. Weibull for amivantamab-chemotherapy, Gamma for chemotherapy and HR approach for pembrolizumab-chemotherapy). As suggested in NICE DSU TSD 14, please provide *"substantial justification"* in case different types of parametric models are used for different treatment options (i.e. further elaborate on the last paragraph of B.3.3.2). Please note that: *"experts validated this approach as appropriate, given amivantamab and chemotherapy would be expected to have different treatment durations in clinical practice"* is not considered a plausible justification given different treatment duration can be modelled using the same parametric distributions.

Similar to the explanation provided in question B9I, given different mechanisms, the efficacy profiles of each comparator is expected to substantially differ and, as such, Johnson & Johnson believe that selecting different parametric models for the TTDD each different comparator is appropriate.

g) Please clarify the appropriateness of combining time to treatment discontinuation and death, including why death was not already considered a discontinuation event.

Patients dying prior to treatment discontinuation should be considered as part of treatment discontinuation end-point to account for deaths prior to treatment discontinuation in partitioned survival modelling framework. This is an appropriate assumption as both death and treatment discontinuation represent the curtailment of treatment, and drug acquisition costs ceased to be incurred from that point.

B 11. Priority question. In the CS base-case no treatment waning was assumed, i.e. the PFS and OS were assumed to be different for amivantamab and the comparator for the whole duration of the time horizon.

a) Please justify the assumption of no treatment waning, i.e. that there is a lifetime difference in PFS and OS based on the initial treatment.

Johnson & Johnson maintain that treatment waning will not be incorporated into the model for the following reasons:

- Patients with EGFR Exon20 insertion mutation-positive advanced NSCLC have a poor prognosis. Although there is an improvement in survival following amivantamab with chemotherapy treatment, the period in which patients remain progression free is relatively short, given the severity of the disease. Specifically, from the data observed in the PAPILLON study, patients treated with amivantamab with chemotherapy had a median PFS by BICR of 11.4 months. This suggests that patients receiving amivantamab with chemotherapy are unlikely to experience treatment effect waning within their lifespan. Even if such waning were to occur, it would be highly unlikely to have a clinically meaningful impact considering the short time periods over which it could apply. This rationale has been deemed appropriate by the NICE committee, in previous appraisals such as TA850, and should be considered in this evaluation.¹¹
- Amivantamab is a continuous, treat to progression treatment. Amivantamab-chemotherapy is administered until patients experience a progression event, as opposed to being given the treatment for a predetermined period of time. Moreover, subsequent lines of therapy are incorporated into the model, ensuring that patients are continuously receiving treatment throughout the model's time horizon. Consequently, the inclusion of treatment waning is not considered to be necessary. Therefore, Johnson & Johnson maintain that the current modelling approach, which does not explicitly account for treatment effect waning for amivantamab, is both appropriate and accurately reflects clinical practice. As such, an updated economic model has not been provided.
- Treatment waning effects would be implicitly captured in the selected curves, should it be expected in clinical practice: As described in Section B.3.3.2 of the CS, UK clinicians consulted by Johnson & Johnson validated the long-term clinical plausibility of the selected amivantamab OS curve extrapolations. For example, UK clinical experts aligned on a consensus that around 27.5% of patients receiving amivantamab-chemotherapy

were expected to be alive after 5 years and 7.5% were expected to be alive after 10 years. Based on this feedback and statistical fit data, the Weibull extrapolation was selected for use in the base case, since it has Year 5 and 10 survival probabilities of 32% and 7%, respectively. Given that the long-term outcomes implemented within the model were validated by UK clinicians as clinically plausible, Johnson & Johnson consider that should any treatment effect waning be observed, it would be captured implicitly in the selected curves. As such, explicit application of treatment effect waning for amivantamab is not appropriate.

- In TA850, which evaluated amivantamab for treating EGFR Exon20 insertion mutation-positive advanced NSCLC after platinum-based chemotherapy, treatment waning was discussed. Although TA850 focuses on a different line of therapy and assesses amivantamab monotherapy, its conclusions are relevant to the current appraisal given both indications are associated with a poor prognosis and short life expectancy. In the appraisal guidance for TA850, the committee noted *“waning has typically been applied in previous appraisals for immunotherapies when stopping rules have been applied. Amivantamab has no stopping rule and so a waning effect is not considered appropriate.”*¹¹

b) Please provide an updated economic model and scenario analyses while assuming treatment waning (at different time points).

For the reasons described in the response to part a; Johnson & Johnson uphold that the current approach to not incorporate treatment effect waning into the model is appropriate and accurately reflects clinical reality. Therefore, treatment waning has not been included in the model.

B 12. Progression free survival (PFS) data were used to inform time on progression or death using parametric survival models.

a) To examine the diagnostics of the parametric survival models (using the observed data), please provide the following Figures (separately per treatment):

- i. Plot the cumulative hazard versus time
- ii. Plot the log smoothed hazard versus time
- iii. Plot the standard normal quartiles versus log time
- iv. Plot the log survival odds versus log time

i) Cumulative hazard versus time plots

Figure 50: Cumulative hazard plot – ACP PFS (BICR)

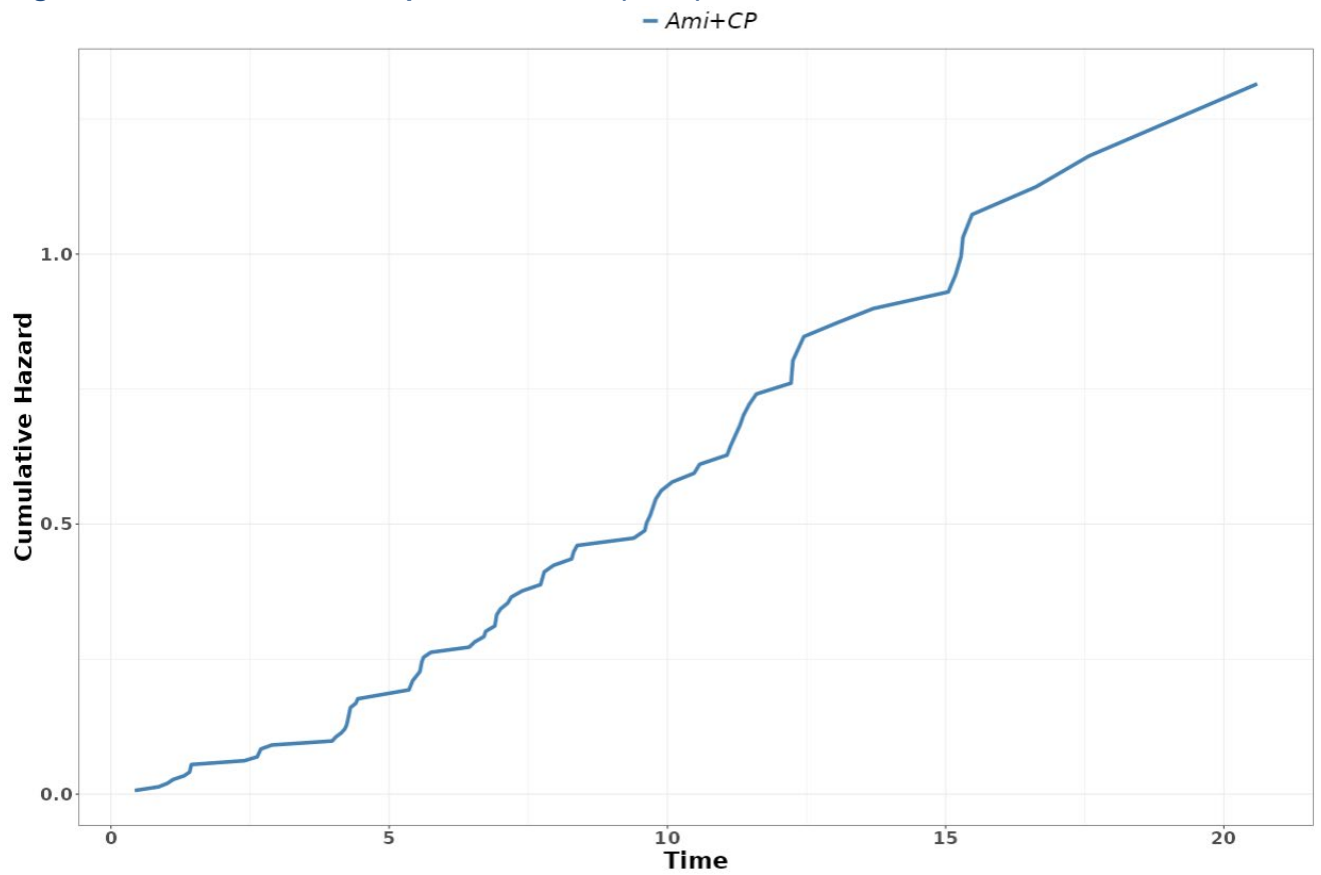


Figure 51: Cumulative hazard plot – CP PFS (BICR)

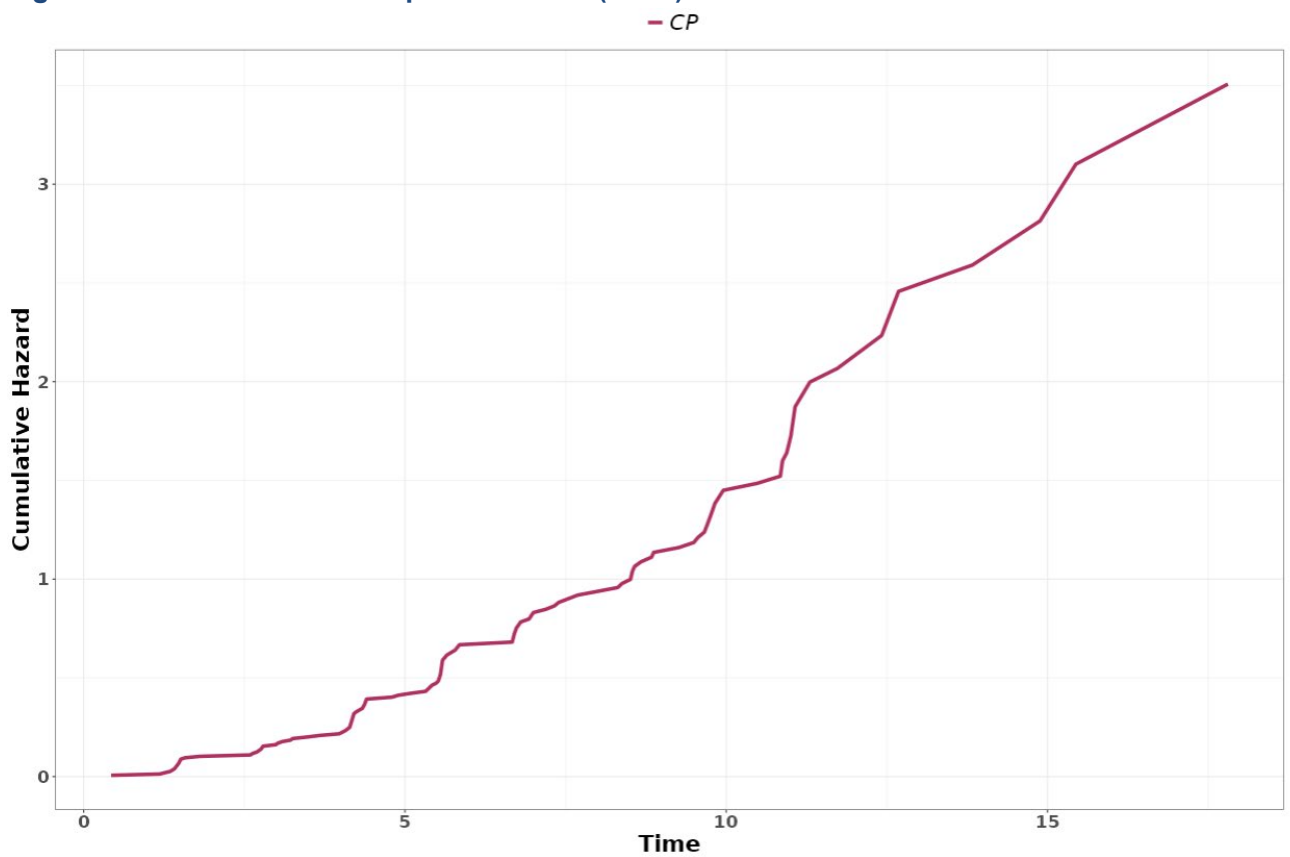
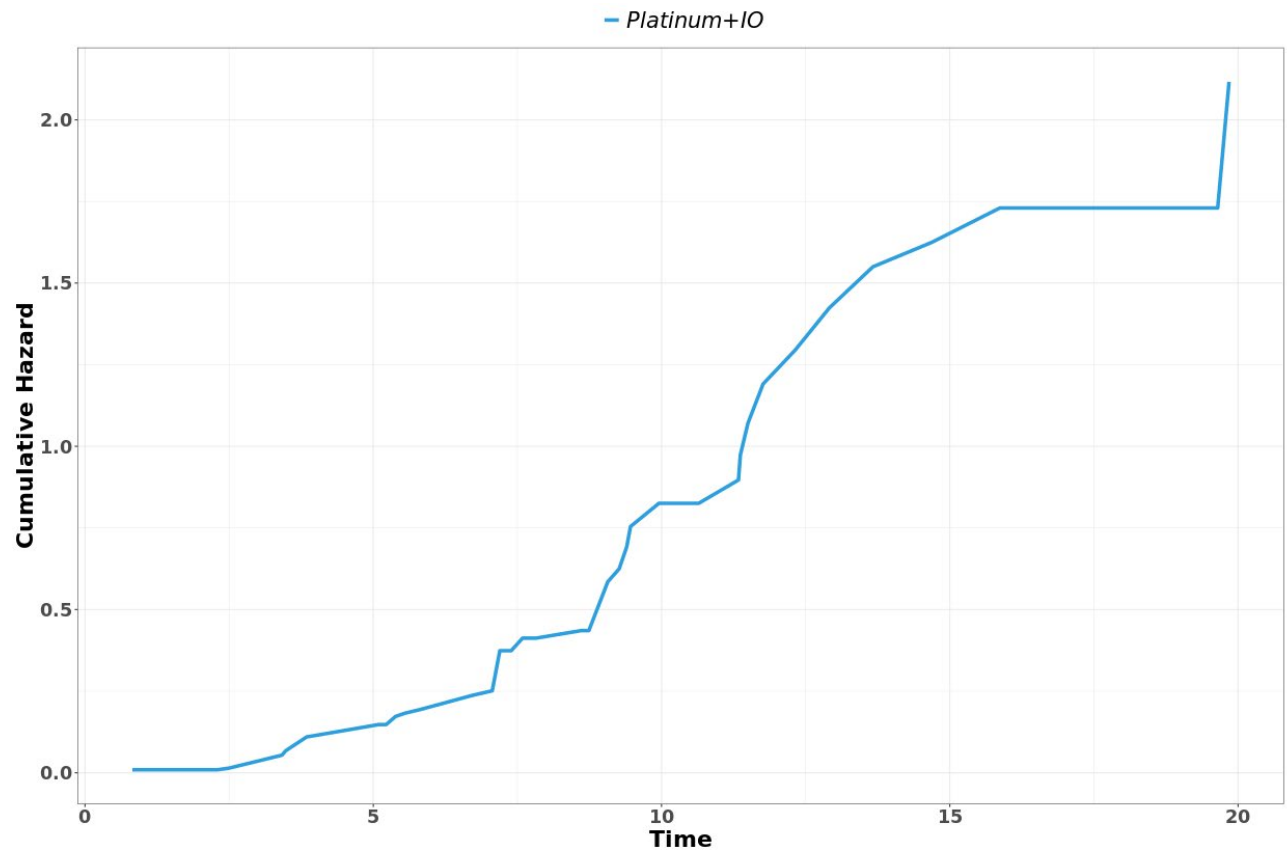


Figure 52: Cumulative hazard plot – Pembrolizumab-chemotherapy TTNT (ATT weighted)



ii) Log smoothed hazard versus time plots

Figure 53: Log smoothed hazard plot – ACP PFS (BICR)

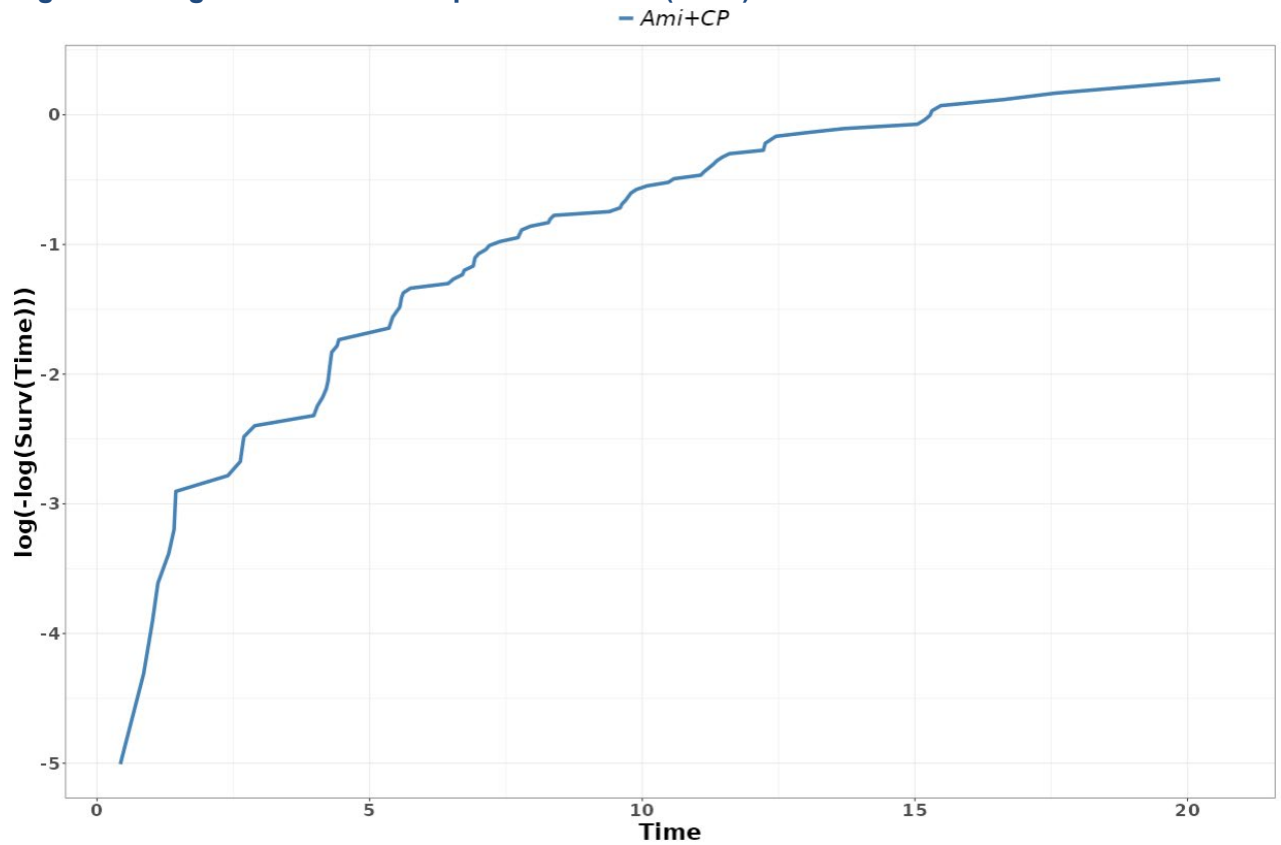


Figure 54: Log smoothed hazard plot – CP PFS (BICR)

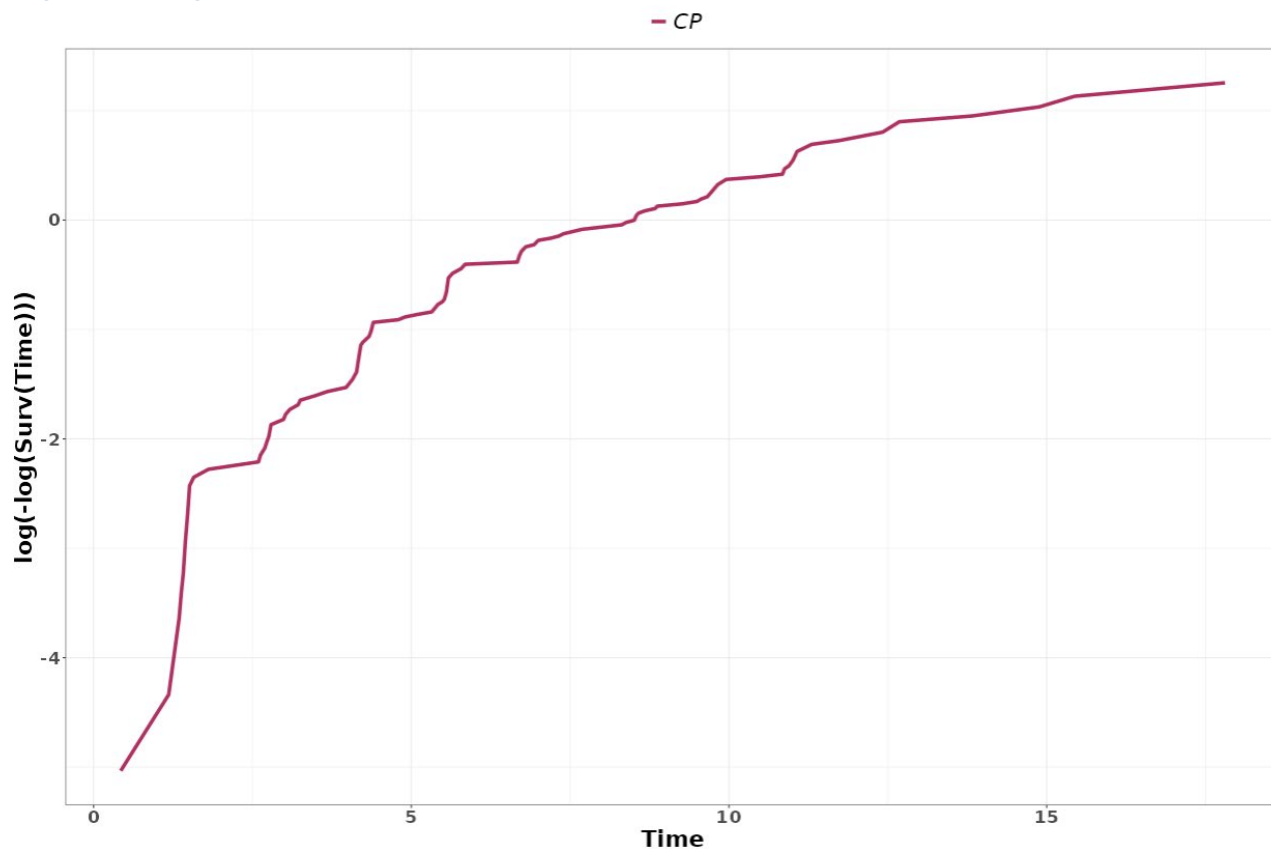
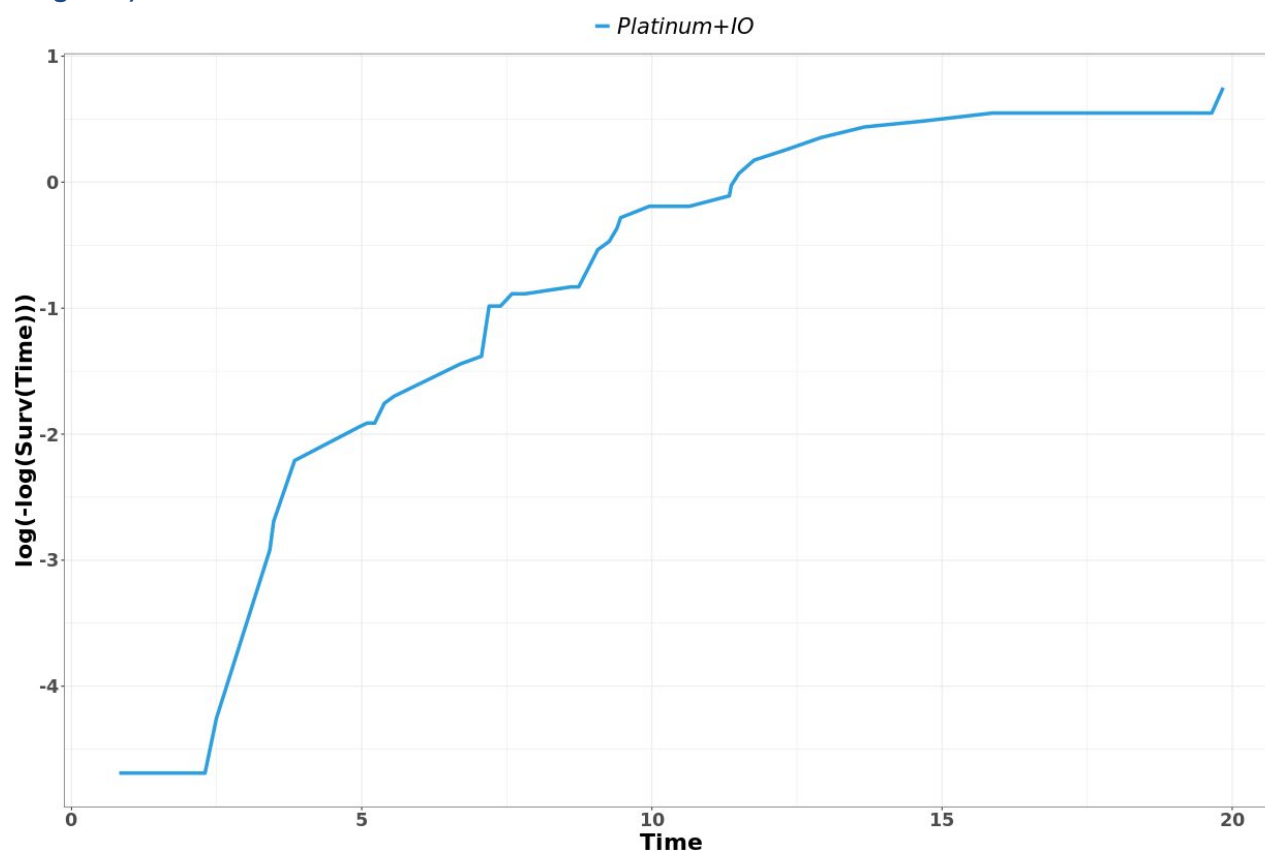


Figure 55: Log smoothed hazard plot – Pembrolizumab-chemotherapy TTNT (ATT weighted)



iii) *Standard normal quantiles versus log time plots*

Figure 56: standard normal quantiles vs. log time plot – ACP PFS (BICR)

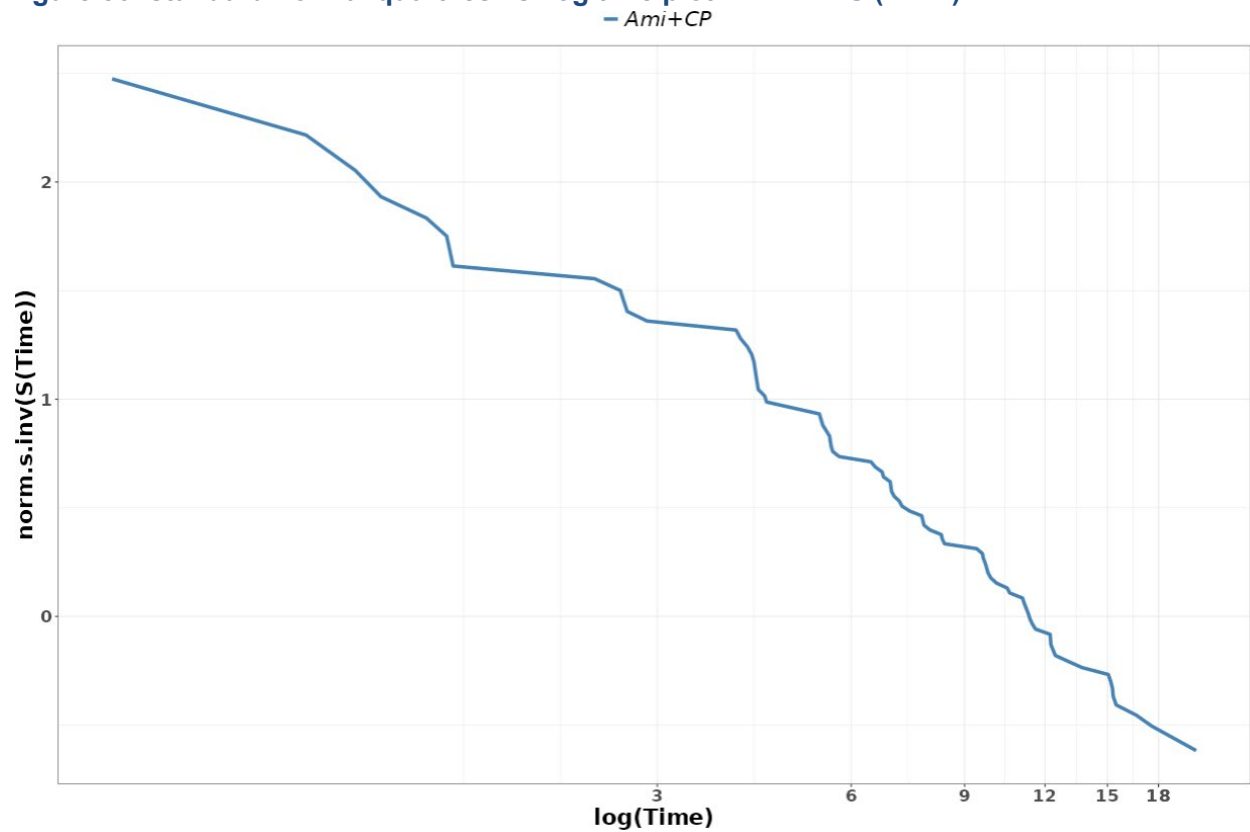


Figure 57: standard normal quantiles vs. log time plot – CP PFS (BICR)

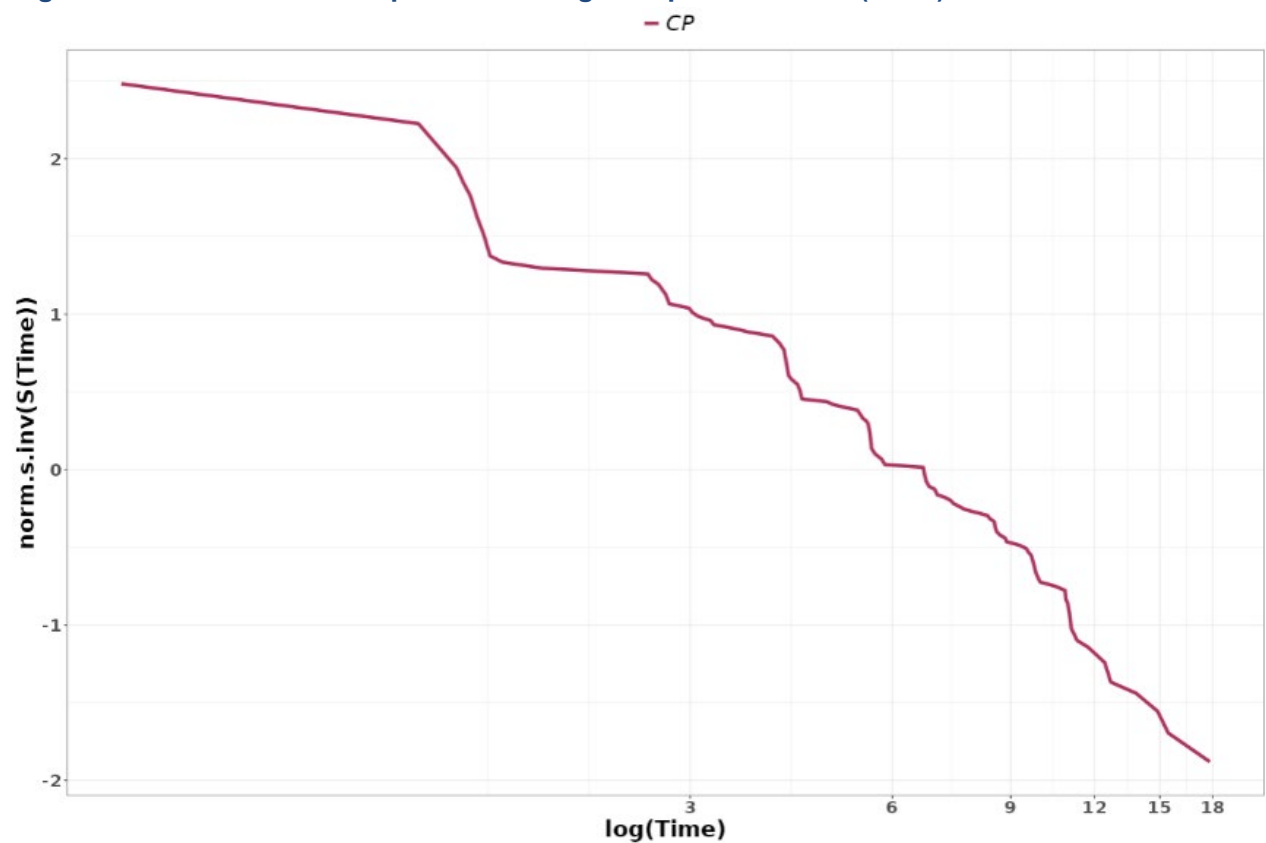
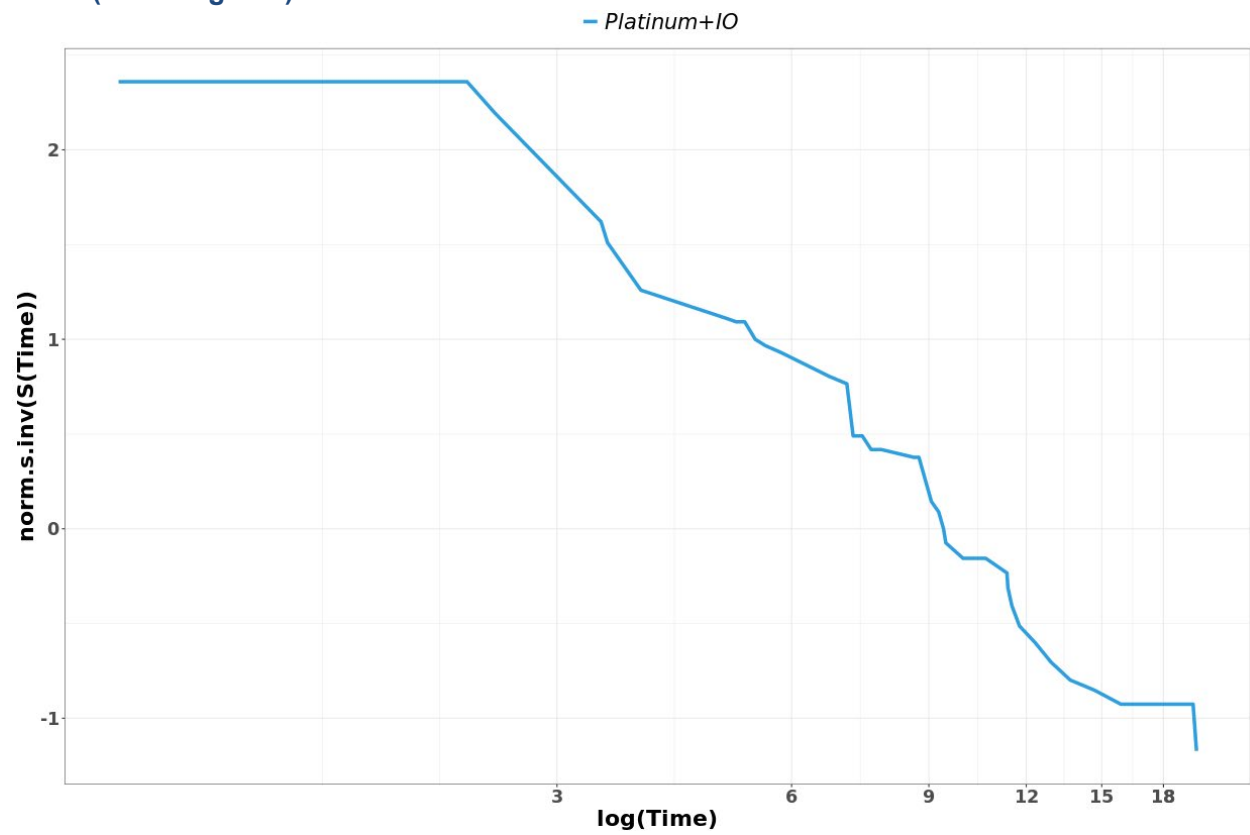


Figure 58: standard normal quantiles vs. log time plot – Pembrolizumab-chemotherapy
TTNT (ATT weighted)



iv) Plot the log survival odds versus log time

Figure 59: Log survival odds vs. log time plot – ACP PFS (BICR)

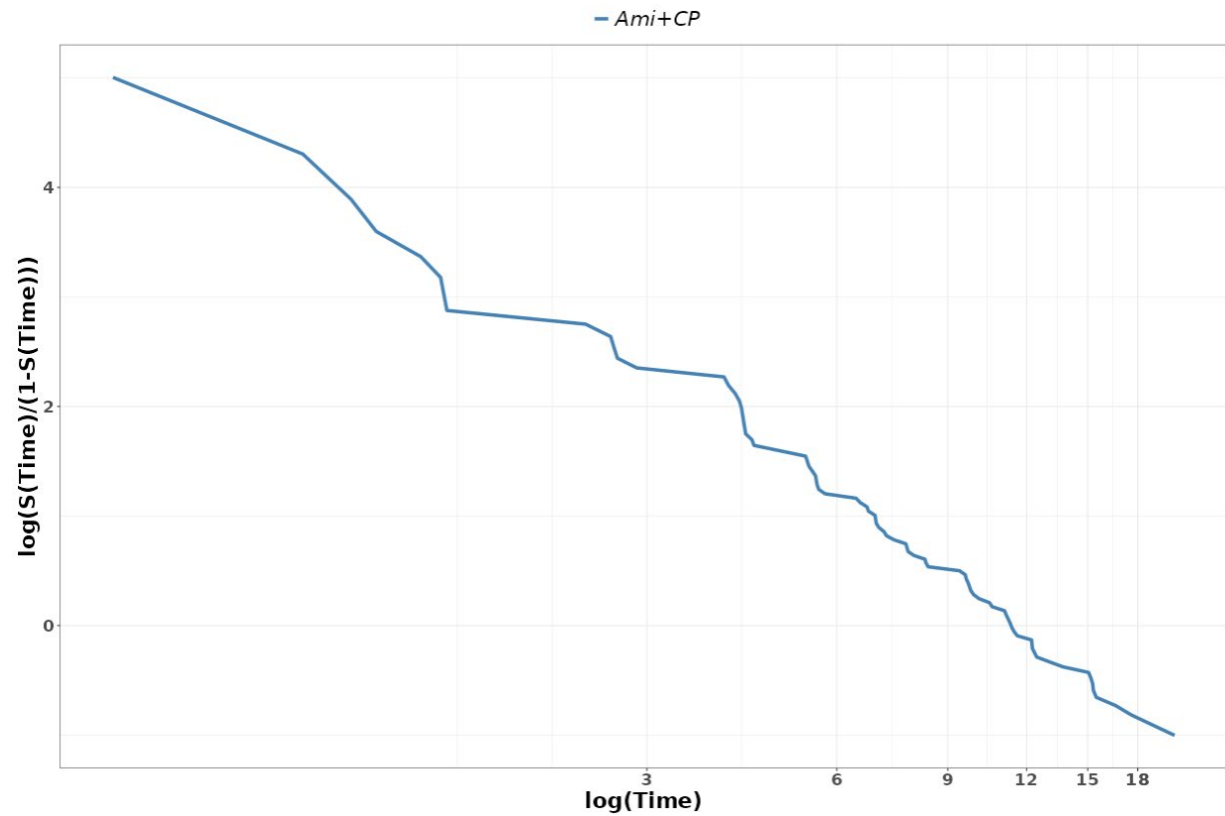


Figure 60: Log survival odds vs. log time plot – CP (IPCW adjusted) OS

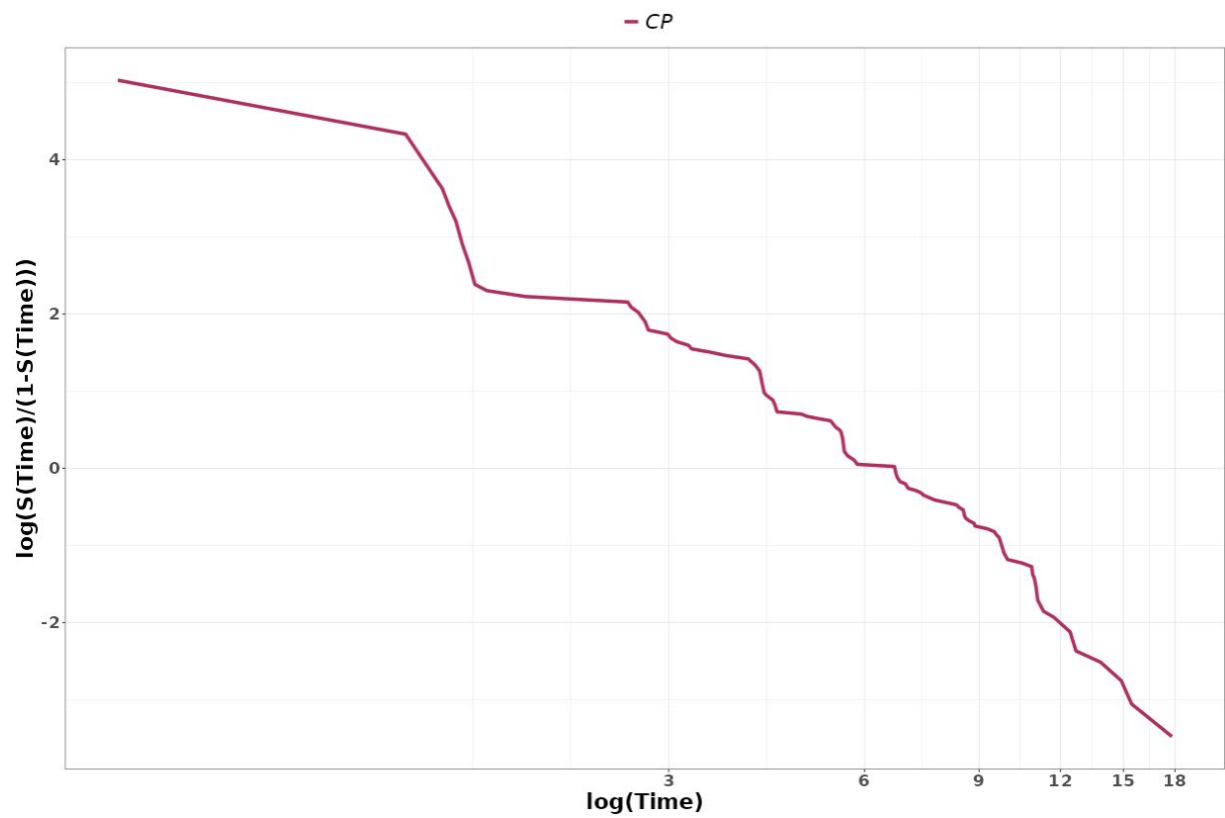
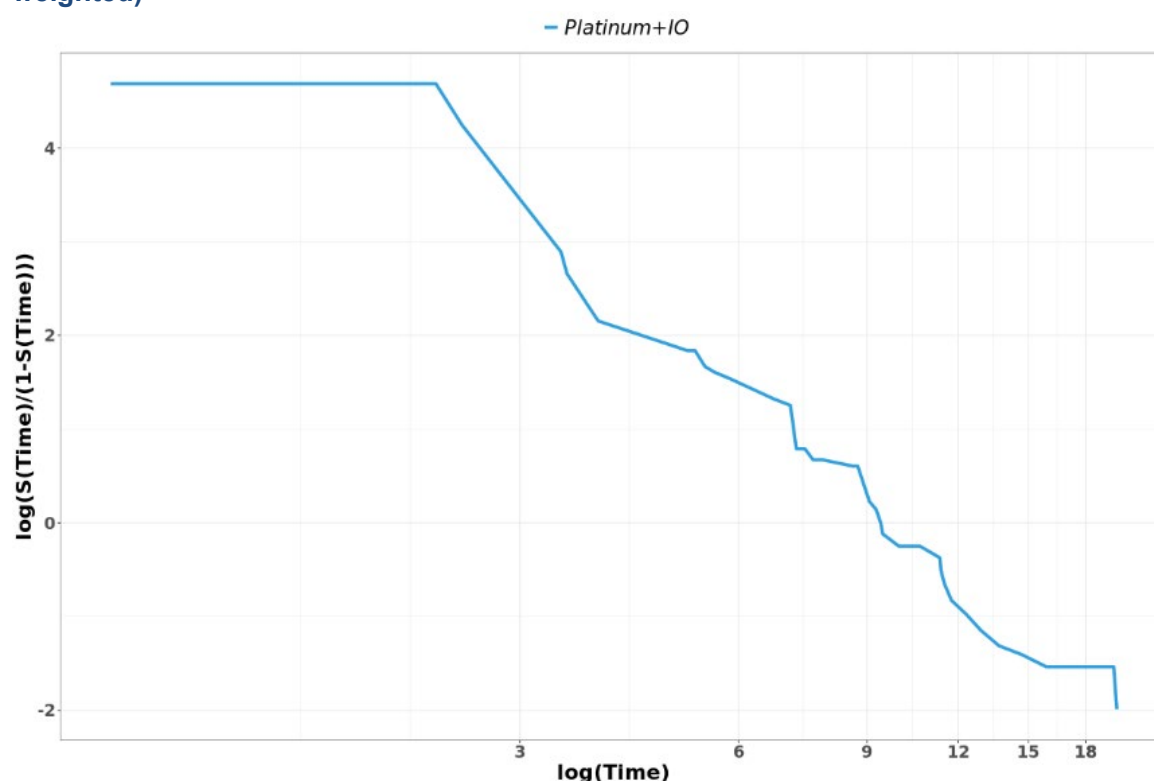


Figure 61: Log survival odds vs. log time plot – Pembrolizumab-chemotherapy TTNT (ATT weighted)



b) Please clarify in detail how the clinical expert opinion was derived to inform the selection of the parametric survival model approach for PFS. This should include (but not limited to), per advisor:

- i. what advisor was consulted,
- ii. why this advisor qualified as expert for this topic,
- iii. what information was provided to the advisor,
- iv. what questions were asked,
- v. exact statements as well as point estimates (%) and/or ranges provided by the advisor (separately per treatment).

Clinical expert estimates for PFS were not elicited as part of the advisory boards conducted by Johnson & Johnson. This was because the modelling approach that was being followed at the time of the advisory boards assumed TTNT was a proxy for PFS for amivantamab-chemotherapy and comparators. Therefore, clinical experts were asked to provide and discuss elicitations for TTNT rather than PFS.

However, during the August 2024 advisory board, clinical experts highlighted that assuming TTNT was a proxy for PFS was not appropriate given there is expected to be a gap between progression and initiation of a subsequent therapy.⁸ Additionally, some patients in the first-line setting would be expected to transition to receive palliative BSC in the second-line setting, and therefore modelling PFS based on time to next (active) treatment would not reflect clinical practice.

Following this insight, Johnson & Johnson adopted a different approach where PFS data from the PAPILLON study were incorporated into the model and PFS for pembrolizumab with chemotherapy was derived by applying the per cycle HR for amivantamab-chemotherapy TTNT versus BICR-assessed PFS from the PAPILLON study to the TTNT log-logistic extrapolation (selected due to best statistical fit).

- c) Please clarify that the advisor input (response to previous question) supports the CS base-case (i.e. supporting the selection of Gamma for amivantamab-chemotherapy, Gamma for chemotherapy and HR approach for pembrolizumab-chemotherapy).

Clinical expert opinion was not used to inform the PFS extrapolations given that a different modelling approach (assuming TTNT was a proxy for PFS) was used at the time of the August 2024 advisory board.⁸ Therefore, clinical experts were asked to provide and discuss elicitations for TTNT rather than PFS.

The PFS data in the model for amivantamab with chemotherapy and chemotherapy are relatively mature, given that median PFS had been reached in the PAPILLON study for both arms. All extrapolations of PFS featured similar statistical fits and similar long-term survival outcomes. Therefore, PFS curve selection was driven by statistical fit and alignment with the KM hazard function. The PFS for pembrolizumab with chemotherapy was derived using the TTNT extrapolation and applying the per cycle hazard ratio of amivantamab with chemotherapy TTNT vs BICR-assessed PFS (from the PAPILLON study) to this. The TTNT data for pembrolizumab with chemotherapy were relatively mature and most extrapolations had similar statistical fits and long-term outcomes. Therefore, TTNT curve selection was also driven by statistical fit.

- d) No scenario analyses are included in CS Tables 87 and 88 using alternative parametric survival models to estimate PFS. Please provide scenario analyses providing alternative plausible parametric survival models to estimate PFS.

Johnson & Johnson agree with the EAG that it is valuable to explore other PFS extrapolations. Therefore, the following scenarios have been conducted:

- Amivantamab with chemotherapy: Incorporating a scenario using the log-logistic extrapolation for PFS. The log-logistic extrapolation is the best statistically fitting PFS curve but was not selected within the base-case due to the tail being perceived as clinically implausible.
- Chemotherapy: Incorporating a Weibull extrapolation for PFS. This is the second-best fitting curve behind the gamma distribution which was selected in the base-case.

- Pembrolizumab with chemotherapy: Incorporating a log-normal extrapolation for TTNT. This is the second best-fitting curve behind the log-logistic distribution that was selected in the base-case.

The results from the scenarios are presented in Table 24 below.

Table 24: Deterministic cost-effectiveness results for amivantamab with chemotherapy versus the weighted comparator in the base-case and in scenarios for different PFS extrapolations

	With PAS		
	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Base-case (Amivantamab with chemotherapy PFS = gamma; Chemotherapy PFS = gamma; Pembrolizumab with chemotherapy PFS = log-logistic)	████	████	24,839
Scenario A (Amivantamab with chemotherapy PFS = log-logistic)	████	████	24,116
Scenario B (Chemotherapy PFS = Weibull)	████	████	24,831
Scenario C (Pembrolizumab with chemotherapy PFS = Lognormal)	████	████	24,712

Abbreviations: ICER: incremental cost-effectiveness ratio; Inc.: Incremental; PFS: progression-free survival; PAS: patient access scheme; QALY: quality adjusted life year

In all scenarios, choosing the best or second best-fitting curve for the intervention and both components of the weighted comparator has a minimal impact on the ICER and in all scenarios the ICER is lower versus the company base case, demonstrating the base-case is more conservative in choice of PFS extrapolation. This is due to the PFS being relatively mature in both the PAPILLON trial and NECTAR study.

Adverse events

B 13. AEs considered in the model were limited to treatment-emergent grade 3 or 4 events that had occurred in at least 5% of patients in either treatment arm of PAPILLON or the pembrolizumab-chemotherapy arm of KEYNOTE-189

- a) Please provide justification regarding the applicability of the KEYNOTE-189 trial to inform the incidence of AE in the economic model. Please also comment on why KEYNOTE-189 was deemed more suitable than other KEYNOTE trials in NSCLC.

The KEYNOTE-189 trial specifically assessed adverse events in adult patients with previously untreated, advanced NSCLC with no sensitising EGFR mutations who were receiving carboplatin and pemetrexed with or without pembrolizumab.³⁹ Although the trial did not include patients with EGFR mutations, it is a pivotal trial providing AE data for the treatment of interest, pembrolizumab in combination with carboplatin and pemetrexed, within patients with untreated advanced NSCLC; as such it is considered the most relevant KEYNOTE trial. There are no other trials investigating pembrolizumab-chemotherapy in patients with EGFR mutations, and as advised by clinical experts that this treatment is used within the patient population of interest, the KEYNOTE-189 study was deemed the most relevant study to source the needed data.

KEYNOTE-024 and KEYNOTE-042 investigated pembrolizumab monotherapy in locally advanced or metastatic NSCLC rather than in combination with chemotherapy and therefore are less appropriate than KEYNOTE-189, which specifically investigated pembrolizumab plus chemotherapy (the relevant comparator to this decision problem).

- b) Please compare the incidence, duration, disutilities, and associated costs of the AEs from other relevant TAs (e.g., TA850, TA855, TA428).

Table 25 displays the incidence, duration and disutilities of the AEs reported in relevant TAs.^{11, 24, 40, 41} TA653 (osimertinib for treating EGFR T790M mutation-positive advanced non-small-cell lung cancer) has been used in place of TA855 as it has been utilised as a source for AE disutilities. TA850 (amivantamab for treating EGFR exon 20 insertion mutation-positive advanced non-small-cell lung cancer after platinum-based chemotherapy) and TA428 (pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy) have been included as suggested. Associated costs have also not been included as costs have been defined from NHS reference costs, which differ year to year, as recommended by NICE reference case. The approach to AE costs is detailed further in response to Question 20. Most of the disutility values have been calculated using Nafees 2008 reflecting the similar disutilities across TAs. Duration of AE events was not consistently reported in the TAs throughout.

Table 25: Incidence, duration and disutility of AEs reported in TAs

AE		Current Evaluation ^b	TA850 ^c	TA653 ^d	TA428 ^e	TA855 ^f
Anaemia	Incidence (%)	10.6/12.26	11.8/3.8	0/3.8	0.9/1.6	6.14/0.88
	Duration (days)	19.88	NR	NR	NR	9.42
	Disutilities	-0.073	-0.073	0.073	-0.07	-0.0735
Paronychia ^a	Incidence (%)	6.62/0.00	NR	NR	NR	0
	Duration (days)	38.78	NR	NR	NR	NR
	Disutilities	-0.032*	NR	NR	NR	NR
Hypo-kalaemia	Incidence (%)	8.61/1.29	NR	NR	NR	NR
	Duration (days)	20.73	NR	NR	NR	NR
	Disutilities	-0.05	NR	0.050	NR	NR
Asthenia	Incidence (%)	5.30/2.58	0.7/3.5	0/3.8	0.3/1.9	0
	Duration (days)	16.56	NR	NR	NR	NR
	Disutilities	-0.073	-0.073	0.073	-0.073	NR
Neutropenia	Incidence (%)	33.11/22.58	11.8/14.6	0/15.2	0/12.3	4.39/1.79
	Duration (days)	16.06	NR	NR	NR	15.50
	Disutilities	-0.09	-0.09	0.090	-0.09	0.0900
Leukopenia	Incidence (%)	11.26/3.23	NR	0/15.2	NR	NR
	Duration (days)	12.4	NR	NR	NR	NR
	Disutilities	-0.09	NR	0.090	NR	NR
Rash	Incidence (%)	11.26/0	0/0	0/NR	0.3/0	2
	Duration (days)	26.94	NR	NR	NR	NR
	Disutilities	-0.032	-0.032	0.032	-0.032	NR
Thrombo-cytopenia	Incidence (%)	9.93/10.32	7.4/0	NR	NR	NR
	Duration (days)	11.51	NR	NR	NR	NR

	Disutilities	-0.108	-0.108	0.050	NR	NR

Footnotes: ^a Assumed same as rash in the current evaluation for disutility; ^b Incidence is reported in current appraisal as ACP/PBC; ^c In TA850, amivantamab AEs are confidential, thus PBC/non-PBC chemotherapy values have been used; ^d Incidence values have been reported as osimertinib monotherapy/PBC; ^e Incidence values have been reported as pembrolizumab/docetaxel; ^f Incidence is reported in TA855 as mobocertinib/pembrolizumab.

Abbreviations: amivantamab, carboplatin and pemetrexed; AE: adverse event; NR: Not reported.

- c) Please provide an updated economic model and scenario analyses informing AE incidences based on the NECTAR study and other KEYNOTE trials in NSCLC.

Johnson & Johnson maintain that the AE incidences for amivantamab with chemotherapy and chemotherapy should be primarily sourced from the PAPILLON study.² The PAPILLON study is the only RCT available that provides data for amivantamab in combination with carboplatin and pemetrexed in the untreated EGFR Exon20 insertion mutation-positive advanced NSCLC population. The NECTAR study does not report AE incidence data and therefore a scenario analyses cannot be performed using NECTAR to inform these data.

As discussed in B13a), the KEYNOTE-189 trial is the most relevant trial to inform AE incidence for pembrolizumab in combination with carboplatin and pemetrexed.³⁹ It is therefore not considered appropriate to update the model with AE incidence data from a different KEYNOTE trial.

Based on the above justification, an updated economic model and scenario analysis has not been provided.

- B 14. In the cost-effectiveness model, the effect of AEs was applied as a one-off utility decrement to each treatment arm upon entry to the progression-free health state.

- a) Based on the nature of the disease, please elaborate on the appropriateness of applying the AEs utility decrement after each treatment cycle until treatment discontinuation.

Johnson & Johnson consider this assumption to be primarily reliant upon the nature of the treatment rather than the nature of the disease. As AEs are usually observed shortly after initiation of treatment in clinical practice, it was considered appropriate to apply utility decrements as a one-off in the first cycle upon entry into the progression-free health state (i.e. upon starting treatment).

The cumulative incidence of AEs, as well as the daily rate of AEs, observed within the amivantamab with chemotherapy arm and the chemotherapy arm of the PAPILLON trial are presented in the figures below.² These figures show that AEs predominantly occur shortly after initiation of treatment, within the first year after randomisation to amivantamab with chemotherapy and within the first six months after randomisation to chemotherapy. The AE occurrences become sparser as the trial progresses. It should be noted that the figures below show the number of new AEs occurring each day over the duration of maximum follow-up in each cohort. The data reflect the AEs included in the model which comprise treatment emergent, Grade 3+ AEs from the safety population.

Figure 62: Cumulative incidence of treatment emergent, grade 3+ AEs observed within the amivantamab with chemotherapy arm of the PAPILLON trial (reflecting the AEs included within the economic model)

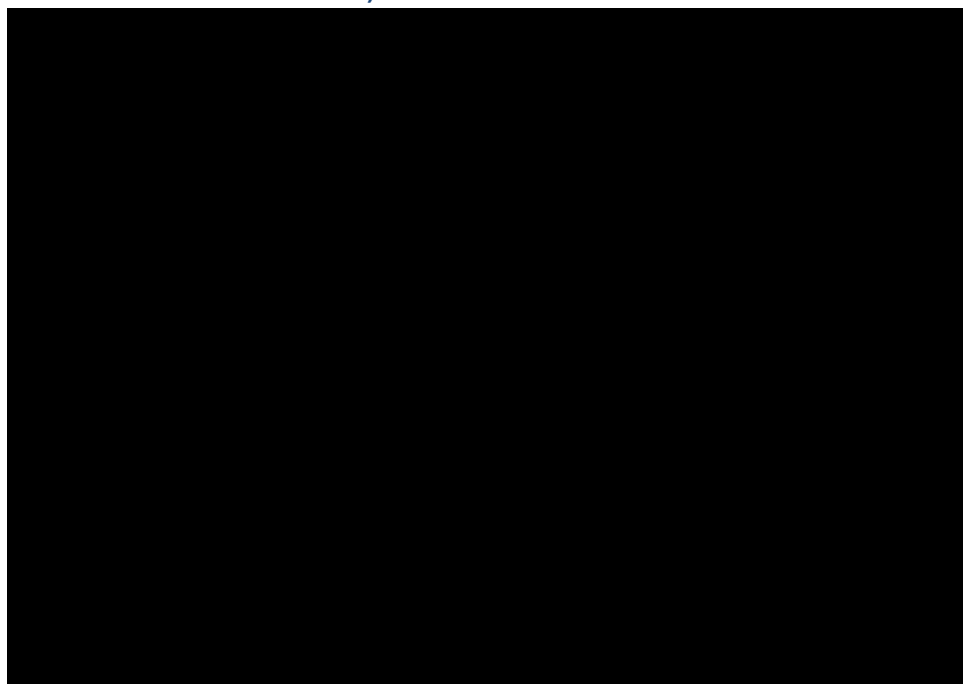


Figure 63: Cumulative incidence of treatment emergent, grade 3+ AEs observed within the chemotherapy arm of the PAPILLON trial (reflecting the AEs included within the economic model)

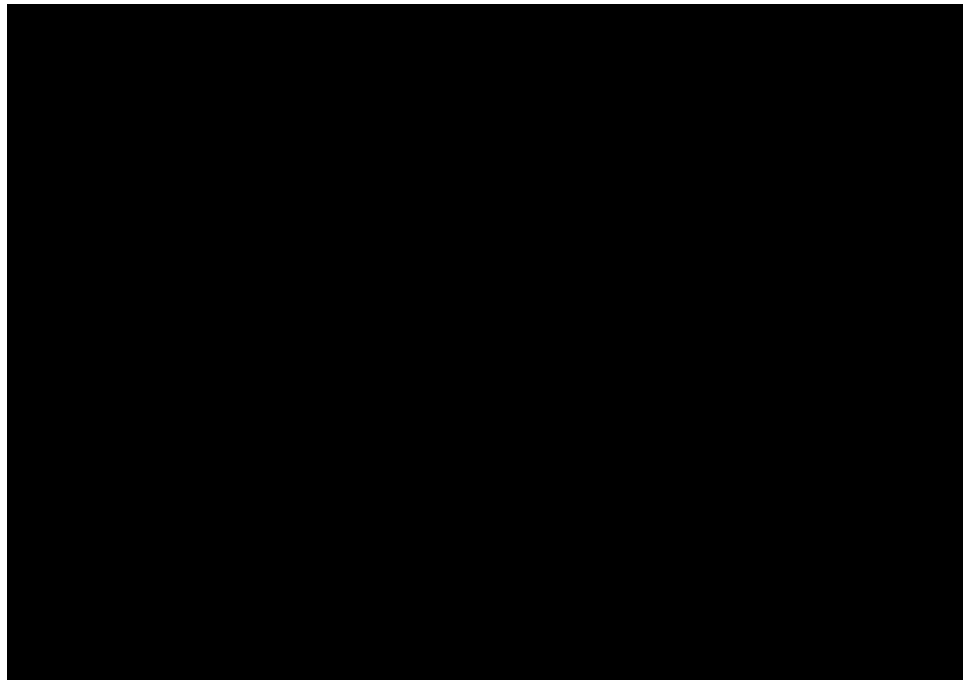


Figure 64: Daily rate of treatment emergent, grade 3+ AEs observed within the amivantamab with chemotherapy arm of the PAPILLON trial (reflecting the AEs included within the economic model)

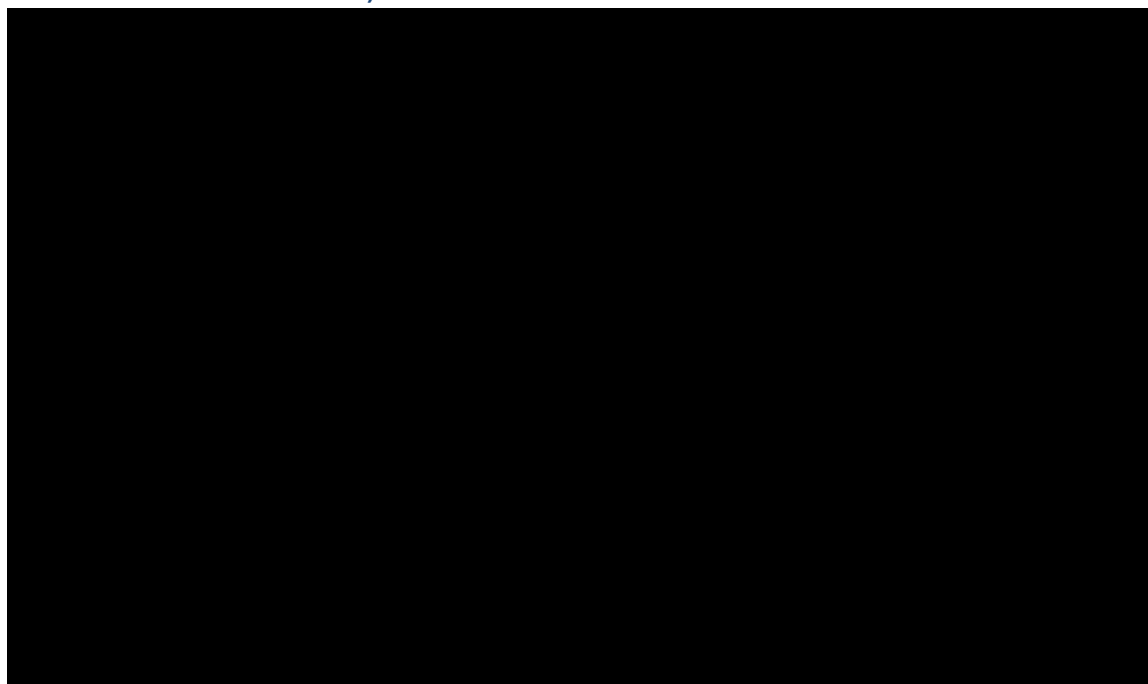
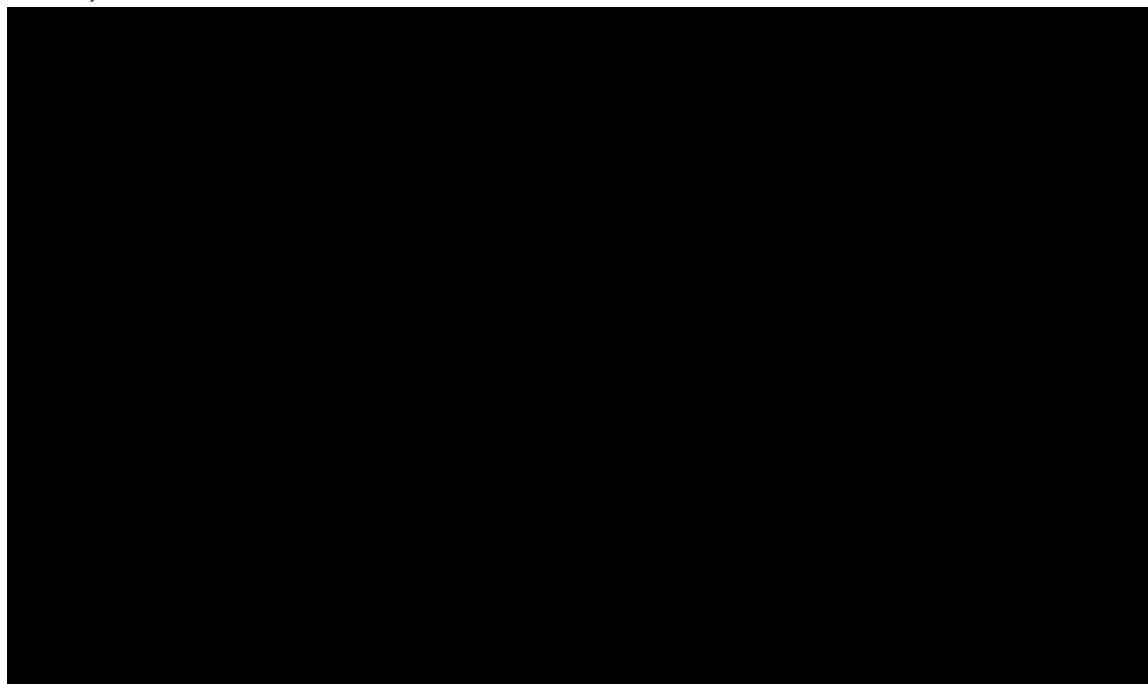


Figure 65: Daily rate of treatment emergent, grade 3+ AEs observed within the chemotherapy arm of the PAPILLON trial (reflecting the AEs included within the economic model)



- b) Please compare the current approach (i.e., one-off disutilities) with an AE disutility approach calculating the impact of AEs per-cycle (i.e., QALY loss and costs applied while patients remained on treatment in every cycle) until treatment discontinuation. Please comment on the impact on the cost-effectiveness and the appropriateness of this approach.

The observed AE incidence rates presented in part a show that the frequency of AE occurrences diminish over time for both treatment arms. Therefore, applying AE incidences per cycle for the duration of treatment would overestimate the disutility and costs. This approach would also disproportionately affect the amivantamab with chemotherapy arm due to the longer TTDD compared to the chemotherapy arm. Another reason why a per cycle approach would overestimate the AE management costs is that, in this approach, AE events with very close start and end dates are costed separately. However, in practice, they may have incurred a management cost only once. As such, applying a per-cycle approach to calculate the impact of the AEs would not be appropriate.

This approach is considered to be minimally impactful as supported by the conclusion of the EAGs and Committees in both TA850 and TA484,^{11, 42} in which AE utilities were applied as a one-off decrements within the first cycle of the model, and the approach to the modelling of AE disutilities did not have a major impact on the ICER.

c) Please provide a scenario analysis using a per-cycle approach to calculate the impact of the AEs.

As noted above, this approach is considered to be minimally impactful and as such, a scenario analysis has not been conducted.

Health-related quality of life

B 15. Priority question. Health state utility values (HSUVs) for each health state were derived from EQ-5D-5L data from the PAPILLON trial, cross-walked to EQ-5D-3L using the method reported by Hernández Alava et al.

a) Please provide an overview of the data included (i.e. the number of observations in PF and PD), the number and pattern of missingness, and how missing data were handled.

Table 26 provides an overview of EQ-5D-5L questionnaire completion and proportion of missing questionnaires (based on the number of patients expected to provide questionnaires at any time point) up to cycle 27 (21-day cycles), which was the last time point included in the utility analysis. The proportion of missing data is similar in both trial arms and there is no clear pattern over time in missingness. Missing data were not explicitly imputed. The number of patients with missing data in the PF estimation averaged to ■■■ across cycles, indicating that missingness would have little impact on the overall mean.

Table 26. EQ-5D questionnaire completion over time in PAPILLON for pre-progression

	Pooled			ACP			CP		
21-Day Cycle	No. expected	No. received	% Missing	No. expected	No. received	% Missing	No. expected	No. received	% Missing
Cycle 0	■■■	■■■	■■■	■■■	■■■	■■■	■■■	■■■	■■■
Cycle 3	■■■	■■■	■■■	■■■	■■■	■■■	■■■	■■■	■■■

Cycle 5	■	■	■	■	■	■	■	■	■
Cycle 7	■	■	■	■	■	■	■	■	■
Cycle 9	■	■	■	■	■	■	■	■	■
Cycle 11	■	■	■	■	■	■	■	■	■
Cycle 13	■	■	■	■	■	■	■	■	■
Cycle 15	■	■	■	■	■	■	■	■	■
Cycle 17	■	■	■	■	■	■	■	■	■
Cycle 19	■	■	■	■	■	■	■	■	■
Cycle 21	■	■	■	■	■	■	■	■	■
Cycle 23	■	■	■	■	■	■	■	■	■
Cycle 25	■	■	■	■	■	■	■	■	■
Cycle 27	■	■	■	■	■	■	■	■	■

Abbreviations: ACP: amivantamab in combination with carboplatin and pemetrexed; CP: carboplatin and pemetrexed; EQ-5D: EuroQoL 5 Dimensions.

Table 27 shows the expected number of patients who have progressed and are alive (N), the number of subjects with at least one questionnaire completed after progression (R) and the percentage of missing observations. In total, there were ■ missing observations within the progressed disease health state.

Table 27: EQ-5D questionnaire completion in PAPILLON for post-progression

Number expected (N)	Number received (R)	% Missing
■	■	■

Abbreviations: EQ-5D: EuroQoL 5 Dimensions.

Given the similarity in baseline characteristics between the two cohorts (patients with and without at least one post-PD EQ-5D assessment), it is not expected that the degree of missingness within the PD state will introduce bias into the results, as shown in Table 28 below..

Table 28: Baseline characteristics (number of subjects with at least one value after progression vs missing), progressed and still alive population

Characteristic	With utilities	Without utilities	Total
Age			
Median	■	■	■
Age (category 1)			
<65	■	■	■
>=65	■	■	■
Age (category 2)			
<75	■	■	■
>=75	■	■	■
Gender			
Male	■	■	■
Female	■	■	■
Weight			
Median	■	■	■
Weight category			

<80			
>=80			
Ethnicity			
Asian			
No-Asian			
Unknown			
Baseline ECOG			
0			
1			
History of smoking			
No			
Yes			
Cancer stage at initial diagnosis (for stages III-IV)			
IIIA			
IIIB			
IIIC			
IVA			

Abbreviations: ECOG: Eastern Cooperative Oncology Group.

b) Please elaborate on the risk of bias introduced by (handling of) missing data.

Mixed models for repeated measures (MMRM) impute missing observations by assuming that patients with non-missing data are representative of patients with missing data across all MMRMs.

c) Please provide an updated model and scenario analyses using imputed data and elaborate on the method of data imputation used and the reasons it was chosen.

A scenario based on last observation carried forward (LOCF) was explored as an alternative approach for handling the missing data (Table 29). A multiple imputation (MI) approach was also tested but due to low number of patient in later cycles, the MI algorithm failed to produce estimates. MMRM approach (used in the base case) leverages data not only from the last observation of the patient with missing data, but from all past observations, and is more likely to reduce bias due to missingness. An imputation based on LOCF was still implemented. This approach has a negligible impact on the utility values.

Table 29: Utility values by health state with and without LOCF approach on handling missing data

Health state	Base case (SE)	Scenario with LOCF (SE)
PF		
PD		

Abbreviations: LOCF: last observation carried forward; SE: standard error; PD: progressive disease; PF: progression-free.

The results from the scenario using the LOCF approach are presented in Table 30 below. The scenario demonstrates that using this approach has a very small impact and increases the ICER slightly. This therefore confirms the approach in the company base-case is robust, due to the limited impact of alternative methodologies.

Table 30: Scenario analysis results (amivantamab with chemotherapy versus the weighted comparator in the base-case and in scenario using LOCF)

	With PAS		
	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Base-case	■	■	24,839
Scenario with LOCF approach	■	■	24,861

Abbreviations: ICER: incremental cost-effectiveness ratio; Inc.: Incremental; LOCF: last observation carried forward; PFS: progression-free survival; PAS: patient access scheme; QALY: quality adjusted life year

B 16. Priority question. In the CS it is stated that the area under the curve (AUC) of the time-specific PF state utilities was used to inform the PF utility. PD state utilities were estimated from patients who progressed in the PAPILLON trial, using a mixed-model repeated measures (MMRM) model that accounted for correlations between measurements from the same patients.

a) Please provide detailed methods for the estimation of utility values in the PF and PD health states and elaborate on the different approaches used for obtaining PF (i.e. based on a AUC approach) and PD (i.e. based on MMRM) utility values. For the MMRM, please provide an overview of which models were considered, which covariates were included, and which model was selected (including rationale)?

Johnson & Johnson would like to provide more information on the approach on estimating PF- and PP utility values (please see below). We would like to clarify that covariates were not included for estimating utility in PF or PD states.

Progression-free utility

Cycle specific MMRM analyses were conducted so that utility estimates of patients who have progressed before a cycle do not influence the utility estimate for that cycle: First, for each EQ-5D-5L collection time point, a separate MMRM was fit using information only from patients who stayed progression free until that time point, including all their available EQ-5D-5L results up to and including that time point, and using visit as a categorical predictor, to get time specific utility estimates. Second, from each of these MMRMs, the least squares (LS) mean estimate of the last time point was used as the utility estimate for that time point. These time specific LS estimates (each of which was obtained from a different MMRM) are plotted in Figure 66. Each of the MMRMs had the compound symmetry correlation structure, which assumes that variances are

homogenous. This means that variability of utility measurements is constant at each cycle. Compound symmetry (CS) structure was selected based on the correlation structure with the lowest AIC from an MMRM that included all PRO values during PFS (Table 32).

The area under the curve of the progression-free estimates presented in Figure 66 and Table 32 was used as the mean state utility in progression-free state (██████, standard error: ██████).

Figure 66: Mean utility estimates (while PF and at risk of progression) over time

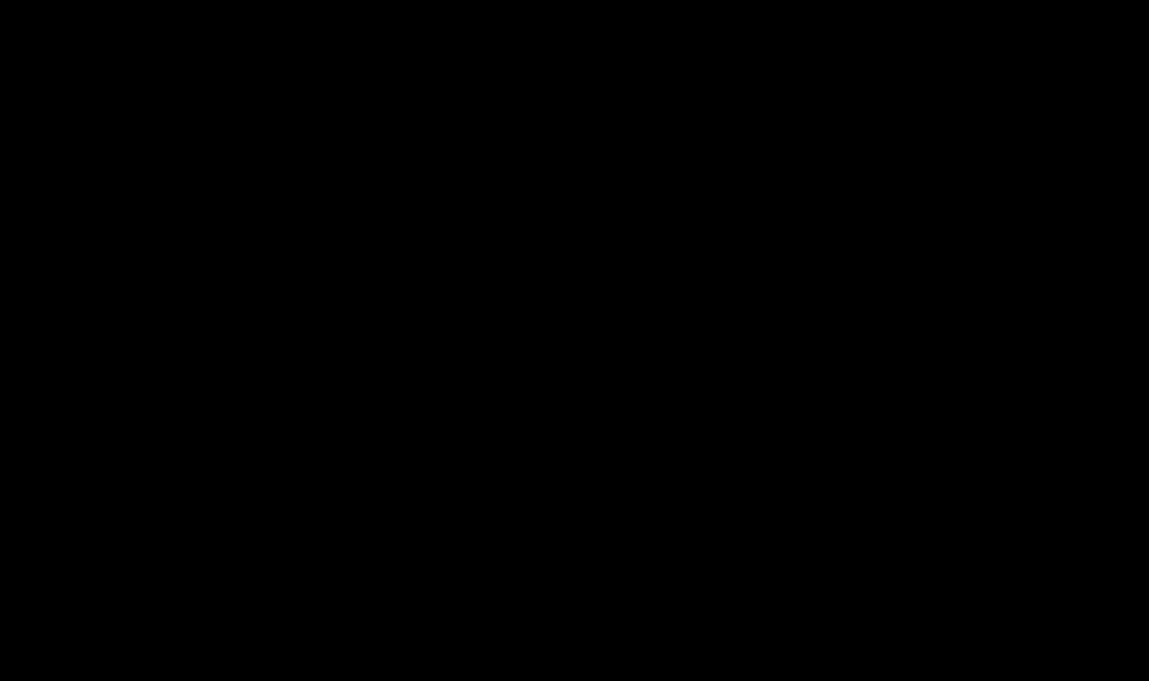


Table 31. Modelled mean utility estimates over time in PF state

21-Day Cycle	Mean, SE
Cycle 0	██████████
Cycle 3	██████████
Cycle 5	██████████
Cycle 7	██████████
Cycle 9	██████████
Cycle 11	██████████
Cycle 13	██████████
Cycle 15	██████████
Cycle 17	██████████
Cycle 19	██████████
Cycle 21	██████████
Cycle 23	██████████
Cycle 25	██████████
Cycle 27	██████████

Abbreviations: PF: progression-free; SE: standard error.

The purpose of the models is to estimate the PF state utility rather than estimating the impact of specific baseline characteristics on utility. This is why the model only includes time as a categorical variable.

Post-progression utility

Post-progression health state utilities were estimated from patients who progressed in PAPILLON data, using a MMRM model that accounted for correlations between PRO measurements from the same patients. Similarly to pre-progression, CS structure was selected based on the correlation structure with the lowest AIC from an MMRM that included all PRO values during post-progression (Table 32).

Table 32. AIC values of correlation structure in MMRM

	Compound symmetry structure	AIC	Rank
Progression-free	Autoregression (1) ¹	-1613.61	2
	Compound symmetry ²	-1684.42	1
	Variance components ³	-1018.04	3
Progressed disease	Autoregression (1) ¹	-183.819	2
	Compound symmetry ²	-202.604	1
	Variance components ³	-93.8604	3

Footnotes: Bold indicates lowest AIC value, 1) Homogenous correlations that decline exponentially with each time step, 2) Homogenous correlation between measurements over time 3) Zero correlation between measurements over time.

b) Please justify why different approaches were used for the estimation of PF and PD.

Different approaches were considered when estimating PF versus PD state utility, given that while patients are in pre-progression there is a defined start date (baseline), and generally more data is available across time compared to PD state.

The health economic model estimates proportion of patients who are still in PF state over time, therefore the composition of the PF state changes over time. Estimating per cycle MMRMs that use data only from patients still in PF state makes sure that patients who progress early do not impact mean utility estimates in later cycles (i.e. through the correlation structure that would be defined in a single MMRM). The AUC of the last time points from each of these time-specific MMRMs were then calculated and was used as the mean PF state utility.

In contrast to the PF health state, patients are assumed (implicitly in a partition survival model) to enter the PD health state throughout the model time horizon. At any time point in the model, the PD health state will include patients who have been in PD health state for different duration of time. For this reason, instead of estimating time-dependent PD utilities, we directly estimated a single mean PD utility using an MMRM. Correlations between the observations from each patient were still taken into account through the CS correlation structure.

c) Please provide an updated economic model and scenario analysis estimating PF and PD health state utilities within one (multivariable)

mixed model (i.e. by including a covariate for progression status, as well as other potentially confounding factors).

In a single MMRM estimation, utility values from patients who progressed early would still influence the mean PF utility estimates in later cycles, which is inconsistent with the health economic model, where the composition of the PF cohort changes over time.

Johnson & Johnson would like to note that the objective of the analysis is to estimate mean PF and PD health state utility values for the cohort, estimation of the impact of progression or baseline characteristics on utility values per se (i.e. after controlling for other characteristics) are not of interest. This is why confounding is not a relevant concern in this context. We have fit an MMRM model with treatment (randomised to ACP vs. CP), time, progression status (PF vs. PD) and treatment and time interaction (Table 33 and Table 34). As indicated by the p-value for the treatment and time interaction term (0.2200), there is no statistically significant impact of treatment on utility estimates.

Table 33. Type 3 test of fixed effects

Type 3 Tests of Fixed Effects				
Effect	Num DF	Den DF	F value	Pr>F
RT01P	1	294	0.21	0.6494
Cycle	14	1441	1.64	0.0635
Status PD	1	107	14.92	0.0002
TRT01P*cycle	14	1441	1.27	0.2200

Abbreviations: DF: degrees of freedom; F: F statistic; PD: progressed disease; PR(>F): p value of the F statistic; TRT01P: Planned Treatment for Period 01

The covariate for the PD health state is statistically significant, and the difference between the least-square mean estimate of PF and PD utility values in this model is very close to the difference between the single MMRM with PF-only utility estimates and the MMRM with only PD utility estimates (Table 34) (though the PF utility estimate from the single MMRM model is influenced by patients who progressed in earlier cycles, and is not appropriate to use in the health economic model).

Table 34. Comparison of MMRM model results for progression-free and progressed disease

Method	Mean PD	Mean PF	Mean PD – mean PF
Model with treatment, treatment*time, time, PF status	████	████	████
Single MMRM	████	████	████
Per cycle MMRM	NA	████*	

Footnotes: * used in model base case.

Abbreviations: NA: Not available; PF: Progression-free; PD: Progressed disease

d) From Figure 10 in document A it appears that over time, HRQoL for chemotherapy seems slightly better than for amivantamab + chemotherapy. Please comment on this observation and provide an updated economic model and scenario analysis exploring treatment-

dependent utility values using a mixed effect model including treatment as a covariate (as well as other potentially confounding factors such as progression status).

Please see combined response in part c.

B 17. A summary of the company's base-case PF and PD utility values was provided in Table 66 of the CS.

a) Please provide justification for the relatively small standard errors reported in CS Table 66.

In AUC, mean utility values obtained from the per-cycle MMRMs were first interpolated to each cycle. This provided 28 mean estimates (27 cycles plus baseline). The standard error reported is the standard error of these 28 mean estimates.

b) Please elaborate on the plausibility of the relatively high PF utility value (██████) compared to the UK age and gender matched general population utility (female: 0.791, male: 0.809, average for the modelled population: 0.799; McNamara et al <https://doi.org/10.1016/j.jval.2022.07.005>) .

The utility analysis informing the model made use of the best available EQ-5D data for the patient population relevant to the decision problem; patients with untreated EGFR Exon 20 insertion mutation-positive advanced NSCLC from the PAPILLON trial.

With regards to sourcing UK age- and gender-matched population EQ-5D-3L utilities to inform cost-effectiveness models, NICE TSD 23 proposes that the most suitable source is the Health Service for England (HSE) 2014, and is preferred over the HSE 2018 dataset published by McNamara.⁴³ The sex- and age-matched general population utility value from HSE 2014 (0.8392) is higher than PAPILLON PF-utility (██████). Johnson & Johnson therefore consider that it is not necessary to apply a cap on the PF utility value in the cost-effectiveness model, and this has not been implemented.⁴⁴

c) Please provide an updated economic model and scenario analyses capping the PF utility value based on these UK general population utility values.

Please see combined response in part b.

d) Please comment on how the company's base case PF and PD utility values compare with utility values of other relevant TAs in NSCLC and elaborate on the implications for the cost-effectiveness results. Please comment on potential reasons for the different utility values based on the population characteristics.

A comparison of utility values in the CS with previous relevant TAs in NSCLC is presented in Table 35. The utility values for TA850 reflect patients at a more advanced stage of disease (as the progression free utility represents a second-line state) and therefore intuitively are lower than

those used in the current model.¹¹ TA653 (osimertinib for treating EGFR T790M mutation-positive advanced non-small-cell lung cancer) captures a patient population with EGFR-positive advanced NSCLC post-TKI use (not Exon20-specific), and utilised utility values similar to those used in the current appraisal.⁴⁰ TA683 (pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic NSCLC) adopted time-to-death approach for utilities, with the utility value ranges adopted for each health state presented in the table, although these utility values are for a different population of patients who do not have EGFR mutations.²³

Table 35: Comparison of health state utility values

	Current appraisal	TA850¹¹	TA653⁴⁰	TA683²³
Population	Patients with untreated advanced NSCLC who have activating EGFR Exon 20 insertion mutations	Patients with EGFR exon 20 insertion mutation-positive advanced NSCLC after platinum-based chemotherapy	Patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC only if disease has progressed after first-line treatment with an EGFR TKI	Patients with untreated, metastatic, non-squamous non-small-cell lung cancer
PF utility value	■	0.62	0.831	Utilities were applied based on time-to-death with an additional decrement applied for progression. Values for PF ranged from 0.397 to 0.79.
PD utility value	■	0.57	0.751	Values for PD ranged from 0.300 to 0.693.
Source	PAPILLON	CHRYSLIS (PF) & TA713 (PD)	AURA + IMPRESS	KEYNOTE-189

Abbreviations: NSCLC: non-small cell lung cancer; PF: progression-free; PD: progressed disease; PD-L1: programmed death-ligand 1; TKI: tyrosine kinase inhibitor.

Resource use and costs

B 18. Priority question. The calculation of the drug acquisition and administration costs included adjustments for Relative Dose Intensity (RDI) and skipped doses. Providing a detailed explanation is essential to ensure that the assumptions made in the economic model can be replicated and validated independently.

a) Please provide step-by-step instructions as well as appropriate references to reproduce the results reported in CS Table 68, 69 and 70, specifically the “RDI” and “Dose skipping (%)” columns.

Aggregate level calculations on dose skipping and RDI/dose reduction are provided in the reference pack to the responses.⁴⁵ .

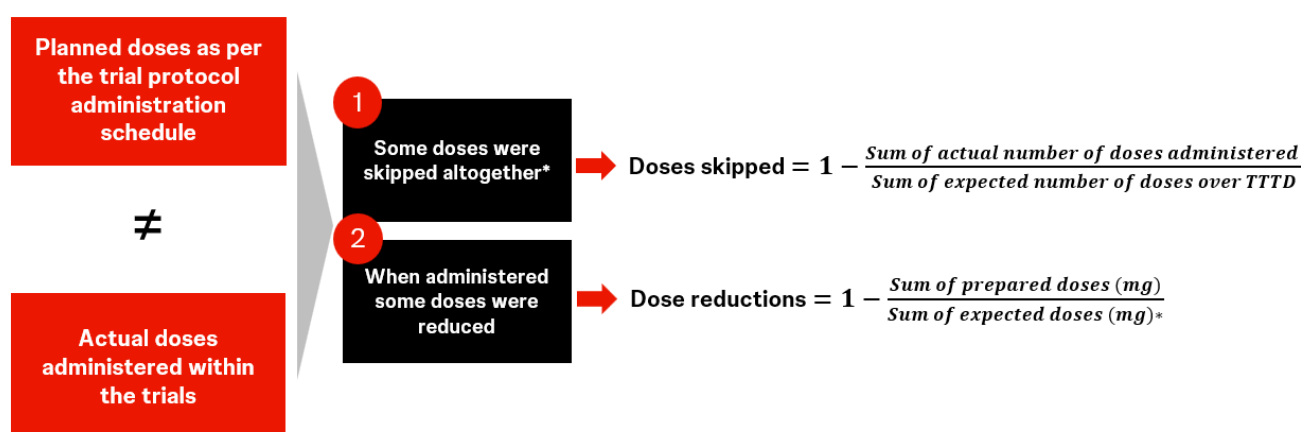
Dose skipping is calculated based on the total number of doses actually administered in the trial and the expected number of administration based on time on treatment as of the time of data-cut for each patient and the licenced dosing schedule (Figure 67). For example, for patients receiving amivantamab based on the schedule and dosing of weight <80 kg at baseline (n=132), the total expected number of dose administrations is 2536 but only [REDACTED] administrations occurred meaning that [REDACTED] administrations visits ([REDACTED]) e.g. [REDACTED] of the administrations were skipped. In the economic model [REDACTED] is used to calculate the average number of treatment administration visits per scheduled administration day ([REDACTED]) and will then have an impact on the treatment acquisition, administration and monitoring costs.

Dose reduction and RDI are calculated by comparing the total dose prepared to the total expected dose based on the planned trial dosing (Figure 67), given that an amivantamab administration did take place. We considered dose reductions for amivantamab to estimate the average number of vials received because dose reductions of amivantamab are based on the number of full vials (350mg) e.g. are not related to the assumptions on vial sharing. For example, a patient <80kg receives a dose of 1400 mg instead of 1750 mg would have incurred cost of 4 vials, instead of 5. In the economic model the dose reduction percentage is multiplied by the number of vials of amivantamab received per administration.

As the dose reductions of carboplatin and pemetrexed do not correspond to full vials, we calculated an RDI that only impacts the treatment costs when vial sharing is allowed. Expected doses of carboplatin and pemetrexed were not known exactly as BSA and AUC were not recorded for each visit which required an assumption that the dose prepared corresponded exactly to the dose level recorded for that visit.

Johnson & Johnson would like to highlight that dose skipping accounts for the administration visits that are being skipped whereas dose reductions or RDI considers the administered dose given that an administration visit did take place, and therefore, there is no double counting between them.

Figure 67: Illustrations of dose reduction and dose skipping calculations



* Expected doses of carboplatin and pemetrexed were not known exactly as BSA and AUC were not recorded for each visit, so an assumption was made that the dose prepared corresponded exactly to the dose level recorded for that visit

Abbreviations: AUC: area under the curve; BSA: body surface area; TTDD: time to treatment discontinuation or death.

b) Please provide step-by-step explanations how the “RDI” and “Dose skipping (%)” were implemented in the economic model.

Please see combined response in part a.

c) Please clarify that including both “RDI” and “Dose skipping (%)” does not result in double counting.

Please see combined response in part a.

d) In the CS it is stated: “Accounting for the RDI for these treatments and the occurrence of dose skipping was validated in the May 2024 advisory board, with clinical experts supporting that this reflects UK clinical practice”. Please clarify in detail how the clinical expert opinion was derived to inform “RDI” and “Dose skipping (%)”. This should include (but not limited to), per advisor:

- i. what advisor was consulted,
- ii. why this advisor qualified as expert for this topic,
- iii. what information was provided to the advisor,
- iv. what questions were asked,
- v. exact statements as well as point estimates (%) and/or ranges provided by the advisor (separately per treatment).

The May 2024 advisory board had three key objectives: to understand how to bring better outcomes to newly diagnosed patients with EGFR Exon20 insertion mutations and common EGFR mutations; to understand how to differentiate Johnson & Johnson treatment options for patients with EGFR Exon20 insertion mutations and also EGFR common mutations from other licensed treatment options; to validate clinical assumptions within the NICE submission within patients with EGFR Exon20 insertion mutation-positive NSCLC.

Johnson & Johnson cannot compliantly share personal data related to individual advisors beyond what was presented within the data on file. Therefore, Johnson & Johnson cannot provide names, qualifying criteria for attendance, or verbatim comments attributed to individual advisors.

Johnson & Johnson can disclose that six oncologists practicing at large, tertiary centres within the UK, with leading experience in managing patients with EGFR Exon20 insertion mutated advanced NSCLC. Advisor selection was conducted according to Johnson & Johnson standard operating procedure, which specifies that advisors must be experts in their areas and each participant should be chosen according to their expertise, such that they will be able to contribute meaningfully to the purpose and expected outcomes of the meeting.

Information relating to dose skipping and the relative dose intensity were shared with advisors during the advisory board meeting. Screenshots of the information presented to the advisors (PowerPoint slides) are detailed in Figure 68 and Figure 69 below.

Figure 68: Screenshot of information presented to advisors during the May 2024 advisory board detailing information on dose skipping

Dose skipping

- In the model, we have accounted for skipped doses of study treatments
- The proportion of skipped doses (i.e., dose administrations that are skipped and not made up are based on trial data)
- Dose skipping percentages have been estimated separately for amivantamab, pemetrexed, and carboplatin, by dividing the number of doses received by the expected number of doses (maximum for the recorded number of cycles)
- However, this calculation does not account for any dose gaps or time between the last exposure to treatment and decision to discontinue treatment

Discussion:

- Please could you discuss whether we should account for dose gaps or time between the last exposure to treatment and the decision to discontinue treatment when calculating dose skipping

J&J EGFR; epidermal growth factor receptor, NSCLC; non-small-cell lung cancer, TTDD; time to treatment discontinuation or death **Oncology**

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Figure 69: Screenshot of information presented to advisors during the May 2024 advisory board detailing information on the relative dose intensity calculation

Dose reduction

- In the model, we have accounted for the impact of dose reductions/relative dose intensity on top of the dose skipped
- A value for the relative dose intensity has been applied to the required number of vials for each study treatment (amivantamab, carboplatin, and pemetrexed) based on the dose reductions observed in the trial

Discussion:

- Please could you discuss whether you agree with the current approach for calculating the impact of dose reductions

From the May 2024 advisory board, the following insights were gained and were used to inform dose skipping and an RDI adjustment within the economic model:

- **Dose skipping:** Advisors agreed that dose skipping is seen in practice and that this should be accounted for in the cost calculation in the model. Advisors also agreed that it is appropriate to use trial data on skipped doses within the economic model.

- **Dose reduction:** Advisors agreed that dose reductions are seen in practice, and these should be accounted for in the cost calculation in the model; incorporating a relative dose intensity adjustment is appropriate. Advisors agreed to follow the trial data for dose reductions.

Furthermore, dose adjustments based on trial data have been similarly applied and accepted by the committees in previous NICE evaluations in untreated, advanced NSCLC, such as TA428, TA653, TA654 and TA898.^{40, 46, 47} This established precedent highlights the appropriateness of incorporating these adjustments into the current submission.

There were no point estimates related to the topics of dose skipping or RDI assumptions that were elicited at the May 2024 advisory board. The information and questions related to these topics that were presented to advisors have been detailed in Figure 68 and Figure 69 and a summary of the discussion has been provided above. Johnson & Johnson cannot compliantly provide verbatim comments attributed to individual advisors regarding these topics.

e) Please justify the 100% RDI for pembrolizumab, the exact source and whether this is clinically plausible.

There were no published data available to inform the RDI of pembrolizumab. Based on the SmPC of pembrolizumab, dose reductions are not recommended and, therefore, an assumption of 100% RDI can be considered plausible.¹⁷

Johnson & Johnson would also like to note that RDI only impacts the treatment costs if vial sharing is allowed. In the company base case we do not assume that vial sharing is allowed.

f) Please justify the stratification (before and after 4 weeks) for amivantamab related to “RDI” and “Dose skipping (%)” (CS Table 68):

i. General justification for a different approach for amivantamab compared with the other treatments.

ii. Please justify the time-point (4 weeks) that was selected

iii. Please report the data available for the four amivantamab “RDI” and “Dose skipping (%)” calculations.

Johnson and Johnson would like to clarify that RDI or dose skipping estimates are not stratified by time-point for amivantamab with chemotherapy. The stratification is based on the different dosing schedules of amivantamab in patients <80kg and ≥80kg.

The cost calculations are split by 4-week time-point given patients have a different dosing schedule of amivantamab for that period, but dose skipping/RDI values are the same regardless of the time-point.

g) Please provide an updated economic model and scenario analysis without the stratification (before and after 4 weeks) for amivantamab related to “RDI” and “Dose skipping (%)”.

No additional analysis is needed as there is no stratification by the time-point of 4 weeks.

B 19. The economic model included costs related to subsequent treatments in both the second line setting and third line setting (CS Tables 75 and 76).

- a) Please provide the durations of subsequent therapies as well as the total costs (separately for all treatments reported in CS Table 75 and 76), for patients that stay alive for the whole subsequent treatment duration.

Johnson and Johnson would like to clarify that subsequent treatment costs are assigned as one-off cost to patients who progressed and have not died in pre-progression. Therefore, separate costs are not assigned depending on the survival of individual patients in post-progression.

- b) Please clarify how the economic model takes into account that patients can die before finishing the subsequent treatment.

The model does not explicitly account for some patients dying prior to the estimated subsequent treatment duration. The approach taken in the model is a simplification and commonly used and accepted approach. Given subsequent treatment costs are not major drivers of costs in the model, this is expected to have a limited impact on the model results/ICER.

- c) Please clarify and justify when the third line treatment is initiated and how this is technically implemented in the economic model.

Similarly to the second line treatment costs, the third line costs consist of three different components: 1) the proportion of patients starting 3L+ treatment based on the UK advisory board estimates, 2) the distribution of the subsequent treatment based on the initial treatment and 3) the duration of each of the subsequent treatments based on median PFS data derived from literature.

As the model does not explicitly track patients who initiate 3L+ therapy, a simplified approach was adopted where the proportion starting 3L+ accounts also for the proportion of patients who die prior to the 2nd progression.

Together with the dosing and the treatment cost information a one-off subsequent treatment cost is derived, and it is summed up together with 2L subsequent treatment cost. Detailed calculations are available in the cost-effectiveness Excel model (Detailed Cost Inputs_SubTx). The total one-off subsequent treatment cost is applied to the proportion of patients who have discontinued the prior line of therapy and did not die prior to the discontinuation (Excel CE model: Engine Ami+CP column AP).

- d) It is stated that “Patients not receiving subsequent treatment following progression are assumed to receive BSC, which has a £0 cost assumed in the base case of the model”. Please justify this assumption of £0 for BSC.

This is a simplifying assumption applied within the model as it is assumed that BSC would have no associated costs given these costs are captured in existing monitoring and resource use

costs. This approach has also been taken in previous NICE appraisals and should be considered appropriate in this submission.^{11, 40, 41}

B 20. The AEs unit costs and resource use were mostly derived from the non-elective short stay admissions from the 2021/22 National Schedule of NHS Costs.

a) In CS Table 80 it is stated “*Weighted average of National Schedule of NHS Costs 2021/22*”. Please clarify how this was weighted.

The National Schedule of NHS Costs for 2022/2023 were republished on the NHS website after the CS but prior to receiving the clarification questions.¹ Johnson & Johnson have therefore updated the reference costs in the model to reflect the 2022/23 costs to ensure the model captures the latest data and is, to the fullest extent, reflective of current costs.

Weighted average costs of adverse events followed the standard approach of calculating the total costs of the codes and weighting them based on the number of units. This was done by summing the total costs of all codes then dividing by the summed units. An example is given for Anaemia, using the 2022/23 NHS costs in Table 36 below:

Table 36: Weighted average cost calculations: anaemia example

Code	Code Descriptor	Number	Costs (£)	Weighted cost
SA01G	Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia, with CC Score 8+	904	705983.09	
SA01H	Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia, with CC Score 5-7	444	340680.65	
SA01J	Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia, with CC Score 2-4	414	281253.48	
SA01K	Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia, with CC Score 0-1	190	114710.56	
Total		1952	1442627.78	£739.05

b) For every AE, a series of codes were selected (e.g., Anaemia used codes SA01G-SA01K). However, it is unclear why these particular codes were selected (e.g., AEs of anaemia can be represented with SA04G-SA04L) over other realistic codes. Please justify the selected codes per individual AE, include supporting evidence (apart from being used in other TAs) if necessary.

The codes were sourced based on evidence from other Technology Appraisals (TAs), which follows the precedent set in recent TAs within EGFR mutated advanced NSCLC such as TA850 and TA654.^{11, 46} All AE codes were taken from the most recent TA (TA850) except where that AE was not present in the submission; in this case other similar TAs in NSCLC where the AE and a

suitable code were available were used.¹¹ The codes, when not sourced from other TAs, were validated with medical opinion, to ensure they were appropriate to the specified adverse event.

- c) Please compare the AE unit costs used in other TAs (e.g., TA653, TA713, TA850, TA855) and elaborate on its appropriateness.

Table 37 has been provided showing each AE, the code used, which TA it was taken from and its appropriateness. As stated in the response to question B20b, TA850 is the most relevant appraisal as it is the most recent published guidance and in the relevant population of EGFR Exon20 insertion mutations. For TA713 the source of adverse event codes are not listed. Where TA850 did not report the adverse event, other TAs within NSCLC were used.

Table 37: Adverse event codes in prior TAs

Adverse Event	Codes	Use in Prior TAs	Comments
Anaemia	SA01G-SA01K	TA850 TA653 TA898	Note, there was an error in TA850 committee papers on pg 124 Table 58 (where SA04 codes were incorrectly written). The actual model used the code SA01G-SA01K and using the 2019/20 reference codes gives the number in Table 58 of £859.55. This code is also aligned with other NSCLC appraisals, as stated in the left column.
Paronychia	JD07A-JD07K (assumed same as rash)		Assumption
Hypokalaemia	KC05G-KC05N	TA737	No NSCLC TAs with hypokalaemia therefore alternative Oncology TA used.
Asthenia	SA01G-SA01K (assumed same as anaemia)	TA653 TA898	
Neutropenia	SA35A-SA35E	TA850 TA653 TA898	
Leukopenia	SA08G-SA08J	TA653	
Rash	JD07A-JD07K	TA850 TA654 TA653 TA898	
Thrombocytopenia	SA12G-SA12K	TA850 TA898	
Fatigue	SA01G-SA01K (assumed same as anaemia)	TA850 TA654 TA653 TA898	
Diarrhoea	FD01A-FD01J	TA850 TA654 TA653 TA898	

B 21. Some aspects related to CS Section B.3.5 were not completely clear to the EAG.

- a) Please justify the clinical plausibility of the types and frequencies of resource use reported in CS Table 79. In case of expert opinion, please clarify in detail how the clinical expert opinion was derived.

The resource use and frequencies were taken from other recent TAs within untreated advanced NSCLC. The resource use type and frequency inputs were sourced from the following TAs:

- TA683 Pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, non-squamous non-small-cell lung cancer.²³
- TA531 Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer.⁴⁸
- TA584 Atezolizumab in combination for metastatic non-squamous non-small-cell lung cancer.⁴⁹

This demonstrates the appropriateness of the resource use within this appraisal, as it follows the frequencies used within other untreated NSCLC appraisals.

TA850 and TA713 were deemed less relevant TAs to guide resource use and frequency as they were in a second-line population.

- b) Please clarify why pembrolizumab is not associated with administration costs.

Given patients receive pembrolizumab in combination with carboplatin and pemetrexed, the model assigns administration costs to pemetrexed to avoid double counting in administration costs. Johnson & Johnson would therefore like to clarify that pembrolizumab is associated with administration costs, within the model they are just applied through the pemetrexed component.

- c) Please clarify that including end-of-life costs does not result in double counting (e.g. with health state costs for the progressed disease health state).

The inclusion of end-of-life costs does not include double counting with the resource use costs in the progressed disease health state. The end-of-life costs are representative of the costs associated in the final months of life, including final hospitalisation costs, Macmillan nurse support and hospice care. This follows the approach taken in other NSCLC NICE appraisals including TA850, TA855 and TA428.^{24, 41, 50}

- d) Please provide the sources/references for all estimates in all Tables in the cost healthcare resource sections (CS section B.3.5)

As stated in B20a, the NHS reference costs have been recently republished and have therefore been updated in the cost-effectiveness model. Johnson & Johnson have provided updated versions for the costs in Table 71, Table 77, Table 79 and Table 81 of the original CS to show the new costs and have clearly stated the source for where the code has come from.

Table 38: Drug administration unit costs and source (update of Table 71)

Description	Cost (£)	Source
Cost per IV administration, monotherapy	191.96	National Schedule of NHS Costs 2022/23, SB12Z - Deliver Simple Parenteral Chemotherapy at First Attendance; outpatient, Medical Oncology service
Cost per IV administration, combination therapy	335.66	National Schedule of NHS Costs 2022/23, SB14Z - Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance; outpatient, Medical Oncology service
Oral therapy one-off cost	316.22	National Schedule of NHS Costs 2022/23, SB11Z - Deliver Exclusively Oral Chemotherapy, Medical Oncology service

Abbreviations: IV: intravenous; NHS: National Health Service.

Table 39: Drug monitoring unit costs (update of Table 77)

Mode of administration	Cost (£)	Source
Lab test - Full blood count	2.75	National Schedule of NHS Costs 2022/23 DAPS05 Directly Accessed Pathology Services, Haematology, (as per TA850)
Lab test - Liver function	1.61	National Schedule of NHS Costs 2022/23 DAPS04 Directly Accessed Pathology Services, Clinical biochemistry; (as per TA850)
Lab test - Renal function	1.61	National Schedule of NHS Costs 2022/23 DAPS04 Directly Accessed Pathology Services, Clinical biochemistry; (as per TA850)

Abbreviations: NHS: National Health Service; TA: technical appraisal.

For resource use, the codes used from the NHS reference costs were the same as the codes used in TA850, and where not present in TA850, were sourced from other relevant NSCLC appraisals. However, as stated in B21a, the frequencies were sourced from more relevant appraisals in untreated NSCLC. As the frequencies were not updated, these are not included in Table 40. The PSSRU index has also not been recently updated, so there have been no changes for costs sourced from there.

Table 40: Resource use and costs for routine follow-up care by health state (update of Table 79)

Resource	Unit cost (£)	Source
Oncology outpatient visit	190.53	National Schedule of NHS Costs 2022/23. WF01A. Consultant Led, Non-Admitted Face-to-Face Attendance, Follow-up, Medical Oncology Service (as per TA850)
Clinical nurse specialist (hours)	88.00	No change PSSRU 2023: Cost per hour Band 8B nurse P.61 (as per TA705)
GP surgery visit	49.00	No change PSSRU 2023: Unit costs for a GP Per surgery consultation lasting 10 minutes incl. direct care staff costs & qualifications p.64, (as per TA850)

Resource	Unit cost (£)	Source
Therapist visit	52.00	No change PSSRU 2023: Cost per hour for a community occupational therapist (local authority), incl. qualification p.77, (as per TA850)
GP home visit	49.00	No change PSSRU 2023: Unit costs for a GP. Assumed the same costs as per surgery consultation lasting 10 minutes incl. direct care staff costs & qualifications p.64 (as per TA850)
Community nurse home visit	76.00	No change PSSRU 2023: Cost per hour Band 8A nurse P.61, (as per TA705)
Chest radiography	73.79	National Schedule of NHS Costs 2022/23, IMAGCDC Plain Film (as per TA654)
CT scan (chest)	154.13	National Schedule of NHS Costs 2022/23, RD24Z, IMAG Computerised Tomography Scan of Two Areas, with Contrast (as per TA850)
CT scan (other)	172.76	National Schedule of NHS Costs 2022/23, RD26Z, IMAG Computerised Tomography Scan of Three Areas, with Contrast (as per TA850)
Electrocardiogram	177.96	National Schedule of NHS Costs 2022/23, EY51Z, Outpatient, Electrocardiogram Monitoring or Stress Testing (as per TA705)

Abbreviations: CT: computed tomography; NHS: National Health Service; PSSRU: Personal Social Services Research Unit; TA: technical appraisal.

Table 41: Cost components in end-of life costs (Update of Table 81)

Component	Frequency	Patients receiving care (%)	Unit cost (£)	Weighted costs (£)	Source
Hospitalisation admission and excess bed days	1	55.8	5,410.7	3,019.2	National Schedule of NHS Costs 2022/23, DZ17S Respiratory
Macmillan Nurse (home setting)	50	27.3	38.0	518.7	No change Assumed two thirds of the cost of a community nurse (£57 per working hour, PSSRU 2023)
Hospice care	1	16.9	6,763.4	1,143.0	Assumed 25% increase on hospitalisation setting
Total cost (£):				4,680.87	Calculation

Abbreviations: NHS: National Health Service; PSSRU: Personal Social Services Research Unit.

Results

B 22. Priority question. The company provided the results of their base-case, sensitivity, and scenario analyses including a 1.2x severity modifier. Please also provide the results of all analyses (reported in CS sections B3.10 and B3.11), without severity modifier.

Johnson & Johnson do not consider that providing results without a severity modifier is an appropriate analysis given the QALY shortfall calculated for all comparators met the criteria for the 1.2x severity modifier, including the basket of treatments within the NCRAS dataset (England-specific RWE). Johnson & Johnson would like to reiterate that the method used in B.3.6, which uses the total discounted QALYs calculated for patients in the NCRAS dataset (n=24), is the most suitable approach for determining the severity modifier. This method accurately represents the real-world population dataset specific to England.

Results from the QALY shortfall analysis are detailed in Table 42.

Table 42: QALY shortfall calculations for all comparators

	NCRAS	Weighted comparator	Chemotherapy	Pembrolizumab plus chemotherapy	Pembrolizumab monotherapy
QALE after model starting age	12.58	12.58	12.58	12.58	12.58
QALYs for SoC	■	■	■	■	■
Absolute shortfall	■	■	■	■	■
Proportional shortfall	■	■	■	■	■
Severity modifier	1.20	1.20	1.20	1.20	1.20

Abbreviations: QALE: quality adjusted life expectancy; QALY: quality adjusted life year; SoC: standard of care

The fact that a 1.2x severity modifier was met for all comparators and scenarios demonstrates the high unmet need faced by patients with EGFR Exon20 insertion mutation-positive advanced NSCLC and further demonstrates why an analysis without a severity modifier applied is inappropriate.

B 23. Priority question. Considering the CS base-case results

- a) Please provide a comparison of the observed survival as well as progression free survival (e.g. using restricted mean survival time; RMST) and the undiscounted life years (LYs) as well as undiscounted progression free LYs (estimated in the model) by filling out the Table below using different periods/truncation points (with justification) to calculate the RMST.

Table 43 presents the comparison of the observed survival versus the modelled survival based on the selected time points. TTNT instead of PFS has been used as there is observed TTNT KM data based on pembrolizumab-chemotherapy. The highest time-point for the RMST was based on the maximum follow-up time (months) of the chemotherapy group. The other two time points were selected based on the event time percentiles when 33% and 66% of events observed have occurred in amivantamab-chemotherapy and chemotherapy arms together.

Table 43: Comparison of observed and modelled outcomes (OS and TTNT) using RMST

	Observed	Modelled	
	Restricted mean survival time (RMST)	Estimated undiscounted life-years	Estimated undiscounted Quality-adjusted life-years
OS - RMST period / truncation point: 9.50 months (selected based on event time percentiles, 33% of the ACP and CP OS events)			
Amivantamab-chemotherapy	■■■	■■■	■■■
Chemotherapy	■■■	■■■	■■■
Increment	■■■	■■■	■■■
Pembrolizumab-chemotherapy	■■■	■■■	■■■
Increment	■■■	■■■	■■■
OS - RMST period / truncation point: 14.66 months (selected based on event time percentiles, 66% of the ACP and CP OS events)			
Amivantamab-chemotherapy	■■■	■■■	■■■
Chemotherapy	■■■	■■■	■■■
Increment	■■■	■■■	■■■
Pembrolizumab-chemotherapy	■■■	■■■	■■■
Increment	■■■	■■■	■■■
OS - RMST period / truncation point: 28.58 months (selected based on maximum follow-up period of CP (PCW))			
Amivantamab-chemotherapy	■■■	■■■	■■■
Chemotherapy	■■■	■■■	■■■
Increment	■■■	■■■	■■■
Pembrolizumab-chemotherapy	■■■	■■■	■■■
Increment	■■■	■■■	■■■
TTNT - RMST period / truncation point: 6.47 months (selected based on event time percentiles, 33% of the ACP and CP TTNT events)			
Amivantamab-chemotherapy	■■■	■■■	■■■
Chemotherapy	■■■	■■■	■■■
Increment	■■■	■■■	■■■
Pembrolizumab-chemotherapy	■■■	■■■	■■■

Increment			
TTNT - RMST period / truncation point: 10.25 months (selected based on event time percentiles, 66% of the ACP and CP TTNT events)			
Amivantamab-chemotherapy			
Chemotherapy			
Increment			
Pembrolizumab-chemotherapy			
Increment			
TTNT - RMST period / truncation point: 23.56 months (selected based on maximum follow-up period of CP)			
Amivantamab-chemotherapy			
Chemotherapy			
Increment			
Pembrolizumab-chemotherapy			
Increment			

Abbreviations: ACP: amivantamab in combination with carboplatin and pemetrexed; CP: carboplatin and pemetrexed; IPCW: Inverse probability of censoring weight; OS: overall survival; RMST: restricted mean survival time; TTNT: time to next treatment.

b) Please elaborate on the plausibility of the differences between observed and modelled outcomes (proportion accumulated beyond observed data) for:

i. Amivantamab-chemotherapy

ii. Chemotherapy and its increment

iii. Pembrolizumab-chemotherapy and its increment

For all three indications, the observed and modelled life years are generally comparable with the modelled outcomes slightly lower than the observed. Differences are therefore minimal between the observed and modelled outcomes.

c) Regarding the model estimated differences between the intervention and the comparator (in terms of PFS, LYs and quality-adjusted life years (QALYs)); please provide an explanation of the mechanism by which the model generated these differences as well as a justification for why they are plausible based upon available evidence (NICE DSU TSD 19 recommendation 13).

A summary of disaggregated QALYs is presented for amivantamab-chemotherapy versus the weighted comparator in Table 59 in the appendices of the CS. The results illustrate the overall

number of QALYs accumulated over the model time horizon is greater with amivantamab with chemotherapy vs the weighted comparator, and that this gain is accumulated in both the PF and PD health states. This result is aligned with clinical trial evidence observed in PAPILLON and from the ITC, where amivantamab-chemotherapy demonstrates statistically significantly superior clinical outcomes versus the relevant comparators, including for OS, PFS and TTNT. Such superior results are in line with expectations for a therapy that targets the underlying oncogenic driver of disease, as compared to non-targeted therapies.

Sensitivity and scenario analyses

B 24. According to CS Table 83, parameters related to efficacy data were not included in the probabilistic sensitivity analysis (PSA). Please provide an updated economic model including the coefficients of the parametric survival models in the PSA.

Johnson & Johnson can confirm that parameters related to parametric models used to extrapolate survival are included as part of PSA. Covariance matrices together with Cholesky compositions are available in the economic model (sheet Data Storage) and varied in PSA. For example, parametric fits to PFS of amivantamab-chemotherapy are set to '4' (denotes probabilistic analysis in VBA) in 'Parameters sheet' (cells P70:P72) and the values using Cholesky composition are drawn in 'Data Storage' sheet (cells AV48:AV49). These values are then fed back to the model in 'Data Storage' sheet (cells I49:I62).

Validation

B 25. The (results of the) validity assessments are not described nor are detailed validation exercises (i.e. specific black-box tests) described.

a) Please provide a detailed description of the validity assessment performed as well as the results

The model structure was developed based on insight gained from a global advisory board held in November 2023 comprising two health economic experts and two clinical experts; advisor names cannot be shared for compliance reasons.

Additionally, the UK model underwent an in-depth technical validation (including a 'stress-test'), quality check, and input review with an external vendor. The 'stress-test' represented a 'black-box' test as it involved setting model input values to their extremes, and confirming the model returned the appropriate values on the results page. Any errors in the model programming could be identified where the appropriate results values were not returned. Any items to be addressed from the technical validation and QC were actioned prior to developing the version of the model that was included within the company submission.

b) Please complete the TECH-VER checklist (Büyükkaramikli et al. 2019, <https://pubmed.ncbi.nlm.nih.gov/31705406/>) and provide the results.

Given the model structure aligns with prior models within advanced NSCLC, has been validated at an advisory board with health economists and clinical experts, and has undergone in-depth technical validation plus QC, Johnson & Johnson consider the model has gone through appropriate and extensive validation. Therefore, given the limited timeframe for response to questions and the fact that this checklist is not part of the guidance to manufacturers prior to submission, the checklist has not been retrospectively completed.

B 26. Please provide cross validations, i.e. comparisons with other relevant NICE TAs focussed on similar, potentially relevant, diseases (including related NICE recommendations and NICE Pathways listed in the final scope) and elaborate on the identified differences

a) Model structure and assumptions

b) Input parameters related to:

- i. Clinical effectiveness
- ii. Health state utility values
- iii. Resource use and costs

c) Estimated (disaggregated) outcomes per comparator/ intervention

- i. Life years
- ii. QALYs
- iii. Costs

Table 44 presents a comparison with TA850 and TA855, two recent evaluations of treatments for EGFR Exon 20 insertion mutation-positive advanced NSCLC.

Table 44: Cross validation of model assumptions between current and previous evaluations

Factor	Previous evaluations		Current evaluation	
	TA850 ¹⁹	TA855 ¹¹⁰	Chosen values	Comparison
Evaluation title	Amivantamab for treating EGFR exon 20 insertion mutation-positive advanced non-small-cell lung cancer after platinum-based chemotherapy	Mobocertinib for treating EGFR exon 20 insertion mutation-positive advanced non-small cell lung cancer after platinum-based chemotherapy	n/a	n/a
Model structure	PSM; three health states: PFS, post-progression survival and death	PSM; three health states: progression-free, progressed disease, death	PSM; three health states: progression-free, progressed disease, death	All three evaluations utilise a PSM structure. All three evaluations use the same health states. The PSM was utilised for the CS as it is representative of the natural history and clinical pathway for NSCLC, see response to Question B5.
Clinical Effectiveness	PFS and OS were the key clinical effectiveness inputs within the model. The CHRYSALIS trial was the primary data source for the amivantamab arm. PFS and OS were derived from real-world data for the comparator arm (SoC)	OS and PFS were used as clinical effectiveness inputs. Inputs for mobocertinib were informed by IPD from the Study AP32788-15-101 PPP cohort. Inputs for the comparator, standard of care, were sourced from real-world evidence sources.	Clinical data from the PAPILLON trial (PFS and OS) were used to model these inputs for ACP and CP. OS and TTDD (adjusted to inform the PFS health state) data for the pembrolizumab with chemotherapy comparator were sourced from real-world data sources.	All evaluations made use of trial data to inform PFS and OS where possible. Where comparator interventions were not included in the trial, real-world data sources were utilised.
Health State Utility Values (HSUVs)				
Value (SE)	Progression-free survival: 0.713 Post-progression survival: 0.569	Progression-free: 0.807 (0.0117) Progressed disease: 0.763 (0.0258)	Progression-free: [REDACTED] Progressed disease: [REDACTED]	The current appraisal and TA855 have similar HSUVs for both progression-free and progressed disease. TA850 has lower HSUVs than those in the CS, which is intuitive given TA850 captures patients with more advanced disease (see response to Question B17).

Source	Sourced from previous appraisals (TA484/TA713) due to limited EQ-5D-5L collection in the CHRYSALIS trial	Estimated from the prior platinum treated population in the EXCLAIM trial. EQ-5D-5L mapped to EQ-5D-3L	PAPILLON EQ-5D-5L data mapped to EQ-5D-3L	Both the current evaluation and TA855 utilise health state utilities from trial data whereas TA850 utilises previous evaluations. NICE reference case recommends the use of patient data for the measurement of health state utilities as it ensures the HSUVs are specific to the patient population and as such, the chosen approach is appropriate.
Resource use and costs				
Cost categories included	Drug acquisition Drug administration Subsequent treatments Follow-up and monitoring AE management End-of-life	Drug acquisition Drug administration Subsequent treatments Follow-up and monitoring AE management End-of-life	Drug acquisition Drug administration Subsequent treatments Follow-up and monitoring AE management End-of-life	The cost categories included across the evaluations were comparable.
Source of costs	NHS Reference costs 2019/20 PSSRU eMIT BNF	NHS Reference costs 2019/20 PSSRU eMIT BNF	NHS Reference costs 2021/22 (updated base case results have been provided that incorporate the latest costs available [2022/23]) PSSRU eMIT BNF	Cost sources are replicated across submissions, with the exception of the year of NHS reference costs used, due to differing years of submission
Cost assumptions	No vial sharing is assumed given the small patient population	In the base case, drug wastage is calculated using the method of moments to determine the combination of vial sizes that produce the lowest wastage in the patient population	Drug wastage (no vial sharing) is accounted for in drug costs	The current appraisal and TA850 use similar approaches for vial sharing, with the reasoning that due to the small population. TA855 used a method of moments to minimise wastage. This results in a more complex calculation for vial use which may not be replicated in a clinical setting
Model results				

Life Years	Amivantamab: 1.34* SoC: 0.80 (deterministic, discounted)	Mobocertinib: 2.09** SoC: 1.29 (deterministic, discounted)	ACP: 3.76 Weighted comparator: 2.00 (deterministic, discounted)	Life years gained for all treatments arms are greater in the current appraisal and TA855 vs TA850, which is as expected for treatments administered first-line relative to those given at second-line. ACP demonstrated a greater number of life years gained relative to mobocertinib.
QALYs	Redacted	Redacted	ACP: [REDACTED] Weighted comparator: [REDACTED] (deterministic, discounted)	N/A
Costs	Redacted	Redacted	ACP: £[REDACTED] Weighted comparator: £[REDACTED] (deterministic, discounted)	

*Values taken from company response to clarification questions. ** Values taken from company submission.

Abbreviations: ACP: amivantamab in combination with carboplatin and pemetrexed; BNF: British National Formulary; CP: carboplatin and pemetrexed; eMIT: electronic market information tool; HSUV: health state utility value; NHS: national health service; OS: overall survival; PSM: partitioned survival model; PFS: progression-free survival; PSSRU: Personal Social Services Research Unit; QALYs: quality adjusted life years; SE: standard error; SoC: standard of care TTD: time to treatment discontinuation; TTDD: time to treatment discontinuation or death.

Severity modifier

B 27. The EAG were unable to reproduce the results reported in CS Table 82, utilising the QALY shortfall calculator (<https://shiny.york.ac.uk/shortfall/>) recommended in NICE DSU TSD 23 providing guidance to calculate the severity shortfall for NICE evaluations.

a) Please provide step-by-step instructions to reproduce the results reported in CS Table 82.

Johnson & Johnson can reproduce the results of the remaining QALYs without disease with a negligible difference when the ONS life table is switched to 2017–2019 in the economic model. The estimated QALYs without disease are 12.73 and 12.71 with the QALY shortfall calculator and the economic model, respectively.

b) Please provide the severity shortfall calculations (results from CS Table 82 + an overview of input parameters) separately based on chemotherapy and pembrolizumab-chemotherapy.

The QALY shortfall calculations for all comparators are presented below; these have already been presented in the response to question B22.

Table 45: QALY shortfall calculations for all comparators

	NCRAS	Weighted comparator	Chemotherapy	Pembrolizumab plus chemotherapy	Pembrolizumab monotherapy
QALY after model starting age	12.58	12.58	12.58	12.58	12.58
QALYs for SoC	■	■	■	■	■
Absolute shortfall	■	■	■	■	■
Proportional shortfall	■	■	■	■	■
Severity modifier	1.20	1.20	1.20	1.20	1.20

Abbreviations: QALE: quality adjusted life expectancy; QALY: quality adjusted life year; SoC: standard of care

The QALY shortfall analysis shows that, for all comparators, the criteria for the 1.2 x severity modifier was met. Further, the 1.2x severity modifier was still met when the model incorporated the baseline characteristics from patients in the NCRAS dataset.

- c) Please provide the severity shortfall calculations (results from CS Table 82 + an overview of input parameters) separately based on chemotherapy and pembrolizumab-chemotherapy, using the NECTAR study as source.

[Please see combined response in part b.](#)

- d) Please clarify that the QALY shortfall analysis is consistent with the guidance provided in NICE DSU TSD 23

[QALY shortfall analysis is consistent with the recommendations detailed in NICE DSU TSD 23. The only difference is that Johnson & Johnson are using the latest ONS life table \(2020–2022\).](#)

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Single Technology Appraisal

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

Patient Organisation Submission

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

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

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

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

Information on completing this submission

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

About you

1. Your name	[REDACTED]
2. Name of organisation	EGFR+ UK
3. Job title or position	[REDACTED]
4a. Brief description of the organisation (including who funds it). How many members does it have?	EGFR+ UK is a patient driven charity established to provide information and support for EGFR mutation positive lung cancer patients, their families and loved ones. We are also dedicated to supporting research and advocacy, and are working to raise awareness of EGFR positive lung cancer and end the stigma associated with lung cancer in general. We currently have approximately 850 members, and are largely funded by fundraising activities, charitable donations, and some grants.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] If so, please state the name of the company, amount, and purpose of funding.	Yes. In the last month we received £3,508 from Janssen to cover some of our patient support activities.

Patient organisation submission

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

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Patients share their experiences of treatment pathways and drug toleration on our private patient support forum, which is the main forum for the exchange of information and support. As we have approx. 850 members we are able to present a representative view of the experience of living with EGFR mutation positive lung cancer. We recently ran a survey with our membership exploring the experiences of EGFR+ patients in the UK in terms of their diagnosis, treatment, surveillance and wellbeing (n=234). For this submission I have drawn on the experiences of our Exon 20 patients, alongside my own personal experience.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Non-small cell lung cancer (NSCLC) with an EGFR mutation is an aggressive disease that has a considerable physical, psychological, economic and social impact on patients and their families. Patients affected by EGFR positive NSCLC are generally younger than typical lung cancer patients, non-smokers, more likely to be female, often still working and with dependent children. The diagnosis therefore is particularly devastating, often coming as a total shock. The majority of our members have EGFR mutations on Exons 19 and 21, which are typically treated with TKIs. However, patients with Exon 20 mutations usually have a worse prognosis than those with other EGFR mutations, as they don't usually respond well to TKIs. In our annual survey of EGFR+ UK members (n=234), 9% had a mutation on Exon 20. This finding confirms estimates in the academic literature that suggests Exon 20 affects up to 10% of EGFR cases (Chan and Hughes, 2015; Oxnard et al, 2013; Remon et al, 2020). As part of our survey, we used standardised measures (the GAD7 and PHQ9) to estimate levels of anxiety and depression in our membership. The results showed that lung cancer causes significant psychological distress, with 1-in-3 of patients scoring over the cut-off for diagnosable anxiety; and 1-in-4 showing likely clinical depression. Both prevalence rates are significantly higher than that seen in the general population. In addition, when anxiety and depression scores were broken down by mutation type, Exon 20 patients were found to have significantly higher levels of both (both $p < .01$) – showing that the psychological distress associated with this specific mutation is particularly problematic. This coupled with the burden of disease and uncertainty about treatment options impacts enormously on the quality of life of the patient and their families. For example, from our communications with Exon 20 patients, one patient highlights the link between their distress and lack of treatment options available to them: <i>"I am struggling with the EXON 20 diagnosis, and would like to know more about what the future might hold. My oncologist hasn't given me any information about it. Everything I access online is quite frightening, eg average life expectancy is 16.2 months, it doesn't respond to available treatments and such like... This had caused me continuing anxiety, especially as the consultant does not seem to understand my questions when I ask, and I feel I am being brushed aside."</i>

	In addition to being psychologically challenging, Exon 20 also has a significant social impact. For example, one of our younger patients describes just how isolating having Exon 20 can feel: <i>“It all feels so alienating. Both because my friends who don’t have cancer just don’t understand how much it affects me. How huge it all is. But I also feel alienated with other lung cancer patients, because most people have the Exon 21 mutation and take osi, and don’t understand that that’s not possible for me. It’s just so scary.”</i> The diagnosis also has a significant impact on the family relationship and income. Many patients are diagnosed at Stage 4, and are often unable to work as a result of their treatment (which in the case of Exon 20, is often chemo with or without radiotherapy) or symptoms of the disease. This in itself can be very distressing, and significantly impacts normal family life. <i>“When I was diagnosed, my world around me just felt like it came crashing down. I had to do chemo and radio, which meant that I couldn’t really do anything or go anywhere. I felt like I was letting them down, because I was either always in hospital or too sick to do things with them. I also couldn’t work, and some months we didn’t know whether we could pay the bills or not. It was terrifying!”</i> For patients who have had treatment, fear of progression and/or recurrence of disease is enormous, and has a significant psychological burden on the patient and their families. <i>“I was given chemoradiation after diagnosis, because that is all that was available. While I’m lucky enough to have responded well to my initial treatment, I live in constant fear of what will happen when it comes back. There are no other treatment options at the moment... immunotherapy isn’t an option, as my PDL1 levels are less than 1%. So what do I do? I thought things might get easier as time moves on, but actually I am getting more anxious the further away we get from my last treatment. I’m just waiting for the other shoe to drop... it’s like living in a constant state of fear and terror, praying that a new treatment will be in place when I need it.”</i> Patients deserve the chance of treatments which will give them as much time as possible with their families and the ability to continue to actively their lives as long as possible.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	There is no standard of care currently available on the NHS. This means patients often feel very uncertain and confused about what their treatment options are. One of the most common themes seen in the posts on our patient forum from Exon 20 patients is them trying to better understand what is available, and navigate the fear and uncertainty around it. Patients also often feel that their oncology teams don't understand the idiosyncrasies of an Exon 20 diagnosis, which just adds to the feeling of uncertainty. For example, one recent communication stated: <i>"I'm sorry for the rant, but I am just so confused. My oncology team don't seem to think Exon 20 is any different to other EGFR mutations. I just have so many questions. Was I given the correct drugs? Are there any new treatments? Are there any trials?"</i> Overall, patients are deeply unhappy with the current options (or lack thereof) available. For example, they are aware that there is very little NICE guidance for Exon 20, and they know that responses to current treatment options (like chemo) can be very variable. As such, they are very anxious to secure access to additional, evidence-based treatment lines. In some cases, patients are so determined to access treatments outside of the NHS that they resort to crowd-funding. This really highlights the unmet need in the NHS.
8. Is there an unmet need for patients with this condition?	Yes. An evaluation of the clinical and cost effectiveness of amivantamab in combination with carboplatin and pemetrexed for EGFR exon 20 patients is not just appropriate, but necessary, as there is a huge unmet need for this patient population. As described above, unlike other EGFR patients who respond to TKIs and have a number of different treatment options and drug lines available to them, Exon 20 patients have very few treatment options available. They have significantly poorer outcomes than patients with more common EGFR mutations as a result of this. The lack of an agreed standard of care in relation to how an Exon 20 patient is treated is likely to result in some patients being disadvantaged and risking progression due to inappropriate treatment. As such, there is a huge unmet need for this patient groups.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	As part of our newsletters, we summarise results of recent research. Since reporting on the results of the Papillion trial (which showed a significantly improved PFS with the combination of amivantamab and chemotherapy, compared to chemo alone), we have had a number of Exon 20 patients asking how they can access this treatment option. Even with the knowledge that this treatment combination may result in not insignificant toxicity-related side effect, patients' main priority seems to be the existence of efficacious treatment options, which are currently lacking. From our patient support forums, we know that some of our patients are already receiving Amivantamab (with or without chemo, either through trials, or through expanded access programs). Generally, this drug is really well received by patients who are taking it – and those who are not receiving it often ask for advice about how they might be able to get it on the NHS. When they discover they currently can't, patients also often express their frustrations that the UK seems to be behind other countries in terms of drugs available to Exon 20 patients. For example, one patient says: <i>“It just feels so unfair. I’m on the Exon 20 Facebook Group, which is largely American. They all seem to have access to lots of different drugs – like most of them have been on Ami at some point. I just don’t understand why we can’t have it here? It doesn’t make sense.”</i>

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	As with chemo alone, patients can be quite nervous about IV drugs, both from the perspective of possible side effects, but also in terms of the logistical and time-related factors associated with treatment. While our members who have received this treatment (via trial) did experience significant GI and skin-related issues, they have also managed to get these under control with a combination of systemic and local antibiotic treatment. As such, they feel that the positives of the treatment greatly outweigh the negatives.

Patient population

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

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Potentially. Only untreated patients are included in the current appraisal, however there is a huge unmet need amongst patients who have previously received chemotherapy. Please see the next section for more detail here.

Other issues

Patient organisation submission

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

13. Are there any other issues that you would like the committee to consider?	This appraisal needs to be considered in the context of the huge unmet need in Exon 20 patients. There is currently no standard pathway for these patients, and there is a dearth of treatment options available for Exon 20 mutations. The impact of this 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. While this appraisal is for untreated patients only, there is also a substantial unmet need in pretreated patients, and we are disappointed to see that only first line is being considered here. In March this year, the UK entered an unprecedented situation where the withdrawal of a drug (Mobocertinib – Takeda) left a treatment gap and an unmet need for Exon 20 patients. Mobocertinib was the only NICE-approved treatment option for this patient group after initial chemotherapy, and its removal has significantly increased the psychological distress experienced by this group, and will certainly increase mortality rates unless access to an alternative treatment option is implemented. We therefore want to advocate, in the strongest possible terms, that Amivantamab (with or without chemotherapy) should be considered for use in pre-treated Exon 20 patients to fill the gap left by Mobocertinib's withdrawal. Particularly as we have evidence from members of our charity and the Exon 20 group in the USA that many patients are on this drug for years before seeing progression.
14. What treatments are people with untreated EGFR exon20 insertion mutation positive NSCLC currently having in the NHS? (If possible please give any estimates of proportions having different treatments)	Our patient survey highlights a lack of standard care, with: • ~70% received chemotherapy (most commonly carbo/pem, but carbo/vino and carbo/paclitaxel were also cited) • ~30% received TKIs (most commonly Osimertinib, but also erlotinib and afatinib), despite a lack of research to support TKI use in this patient groups • Only 28.6% received radiotherapy • 9.5% of Exon 20 patients were on Mobocertinib, which is no longer available • None of our Exon 20 members, who responded to our annual survey, reported receiving immunotherapy

14b. Are there any particular reasons why people and clinicians might choose one of these treatments over the others?	Choosing TKIs for Exon 20 patients may be due to a lack of awareness of the research around Exon 20 patients. That said, there is a growing body of evidence that suggests the exact location of the Exon 20 mutations may indicate how well (or not) a patient is likely to respond to treatment. Considering the different sub-mutations of Exon 20, along with co-mutations and TP53 might also be informing treatment options. For example, some sub-mutations may have some activity when given Osimertinib or Afatanib.
15. In your experience, do all people diagnosed with advanced or metastatic NSCLC have a test that can confirm the presence or absence of an EGFR exon20 insertion mutation?	Yes.

Key messages

16. In up to 5 bullet points, please summarise the key messages of your submission.	• There is currently no standard of care of Exon 20 patients, following the withdrawal of Mobocertinib • Exon 20 patients lack access to efficacious treatments in the UK • The uncertainty around treatment options leads to significant anxiety and depression in Exon 20 patients • Offering patients an additional treatment line, which has proven efficacy, is likely to have a positive impact on patients' wellbeing and quality of life • Amivantamab (with or without chemotherapy) should also be considered for use in pre-treated Exon 20 patients to fill the gap left by Mobocertinib's withdrawal

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

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Single Technology Appraisal

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

Patient Organisation Submission

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

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1. Your name	██████████
2. Name of organisation	Roy Castle Lung Cancer Foundation
3. Job title or position	██████████
4a. Brief description of the organisation (including who funds it). How many members does it have?	Roy Castle Lung Cancer Foundation is a UK wide lung cancer charity. We fund lung cancer research, work in lung cancer patient care (information, support and advocacy activity) and raise awareness of the disease and issues associated with it. Our funding base is a broad mixture including community, retail, corporate, legacies and charitable trusts. Clearly, our patient group members and contacts are a self-selected group, who have taken the step to seek out information or have accessed specialist support services. As most lung cancer sufferers tend to be older, from lower social class groups and with the five year survival being around 15%, less physically well, we acknowledge that our patients are perhaps not representative of the vast majority of lung cancer patients, who are not so well informed. It is, however, important that the opinions expressed to us, be passed on to NICE, as it considers the place of this product in the management of lung cancer.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in	RCLCF has received the following funding : - Amgen (£30,000 for 1 year funding of Global Lung Cancer Coalition (GLCC) project; £15,000 grant for Information Services; £165 Advisory Meeting Honorarium) - BMS (£30,000 for 1 year funding of GLCC project; £1100 for Advisory board Honorarium) - Lilly (£30,000 for 1 year funding of GLCC project) - Boehringer Ingelheim (£30,000 for 1 year funding of GLCC project; £1040 Advisory board Honorarium) - Novartis (£30,000 for 1 year funding of GLCC project); £3656.50 for 4 Advisory Boards and Quarterly Consultations) - Sanofi (£30,000 for 1 year funding of GLCC project) - Pfizer (£30,000 for 1 year funding of GLCC project)

Patient organisation submission

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

the appraisal stakeholder list.] If so, please state the name of the company, amount, and purpose of funding.	- Astra Zeneca (£30,000 for 1 year funding of GLCC project; £19,500 for GLCC Project Translation; £300 for Advisory Board Honorarium) - Daiichi Sankyo (£30,000 for 1 year funding of GLCC project; £131.50 for Advisory Board Honorarium) - Takeda (£30,000 for 1 year funding of GLCC project; £260 Speaker Fee) - Janssen (£24,000 grant funding for Ask The Nurse Service)
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	no
5. How did you gather information about the experiences of patients and carers to include in your submission?	The Foundation has contact with patients/carers through its UK wide network of Lung Cancer Patient Support Groups, Patient Information Days, patient/carer panel, online forums, Keep in Touch' service and its nurse-led Lung Cancer Information Helpline.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	According to the National Lung Cancer Audit, the one year survival for lung cancer at all stages, is 48% (for those diagnosed in England in 2022). Thus, this group of lung cancer patients, with advanced disease have a particularly poor outlook, with an obvious impact on family and carers. Symptoms such as breathlessness, cough and weight loss are difficult to treat, without active anti-cancer therapy. Furthermore, these are symptoms which can be distressing for loved ones to observe. Insertions in exon 20 are the third most common type of EGFR mutation, representing up to 12% of all EGFR mutated non small cell lung cancers (NSCLC). Because of an altered conformation at the kinase-active site that limits the binding of tyrosine kinase inhibitors, NSCLC with insertions in EGFR exon 20 is largely insensitive to TKIs that have been approved for the treatment of patients with common EGFR mutated NSCLC.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	As above, despite current therapy, outcomes for those with advanced disease remains poor. The first line standard treatment for advanced NSCLC with EGFR exon 20 insertions remains platinum based chemotherapy, owing to a lack of targeted therapy and currently no demonstrated benefit with Immunotherapy. We understand that patients with exon 20 insertions have a poorer prognosis than those with other EGFR-TKI sensitive mutations.
8. Is there an unmet need for patients with this condition?	yes

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Outcomes of treatment are seen as an advantage of this technology. We do not have any additional data, beyond that publicly available. We note, however, the results of the PAPILLON Study, of patients with EGFR exon 20 insertion mutations. Patients received either Amivantamab with carboplatin and pemetrexed or carboplatin and pemetrexed. The median PFS was 11.4 months in the Amivantamab arm and 6.7 months in the chemotherapy alone arm. At 18 months, PFS was reported in 31% of patients in the Amivantamab-Chemotherapy group and in 3% of the chemotherapy alone group.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Side effects associated with the addition of Amivantamab to the chemotherapy. We understand the most common adverse reactions were rash, nail toxicity, stomatitis, infusion related reaction, fatigue, oedema, constipation, decreased appetite , nausea, diarrhoea and vomiting.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues

13. Are there any other issues that you would like the committee to consider?	
14. What treatments are people with untreated EGFR exon20 insertion mutation positive NSCLC currently having in the NHS? (If possible please give any estimates of proportions having different treatments)	
14b. Are there any particular reasons why people and clinicians might choose one of these treatments over the others?	
15. In your experience, do all people diagnosed with advanced or metastatic NSCLC have a test that can confirm the presence or absence of an EGFR exon20 insertion mutation?	

Key messages

16. In up to 5 bullet points, please summarise the key messages of your submission.	• Amivantamab with chemotherapy shows an improvement in PFS, as compared with chemotherapy alone. • Amivantamab with chemotherapy would be the first NICE recommended therapy targeted for NSCLC with EGFR exon 20 insertion mutations.

Thank you for your time.

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Single Technology Appraisal

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

Professional organisation submission

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

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
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- Your response should not be longer than 13 pages.

About you

1. Your name	
2. Name of organisation	British Thoracic Oncology Group
3. Job title or position	
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	Funded by sponsorship and registration fees. The British Thoracic Oncology Group (BTOG) is the multi-disciplinary group for healthcare professionals involved with thoracic malignancies throughout the UK.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	Yes platinum sponsorship BTOG 2024 April 2024, £30,000 +VAT
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	no

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To improve disease related symptoms To shrink cancer To delay progression To improve overall survival To improve or maintain quality of life
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Partial response is defined by recist as a 30% reduction in target lesion diameters, but more minor responses and prolonged disease stability are clinically significant
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There is a very large unmet need as there are currently no targeted therapies for this population of patients in the NHS

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Patients are currently treated with platinum doublet chemotherapy in first line therapy. There is no targeted second line treatment since mobocertinib was withdrawn. Second line treatment is with docetaxel+/- nintedanib. There is also some use of post chemotherapy immunotherapy although the effectiveness of checkpoint inhibitors in this patient group is uncertain.

9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE Guidance and TAs ESMO Guidelines for oncogene addicted NSCLC – Last updated April 2023 <i>Recommends Amivantamab as single agent following failure of first line therapy. Not yet updated for Amivantamab following publication of Papillon</i> ASCO Therapy for Stage IV NSCLC with driver alterations: version 2023.2 <i>Not yet updated for Amivantamab following publication of Papillon</i> NCCN version 7.2024 <i>recommends Amivantamab in combination with carboplatin and pemetrexed as 1st line treatment and or as a single agent as second line treatment if not received in first line</i>
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The current pathway is standard across the NHS, but if the technology is approved there will need to be efforts to ensure full NGS testing is carried out to identify patients who would benefit (some current methods of testing do not detect EGFR exon 20 insertions). The NHS England ctDNA testing in NSCLC programme will also help identify patients.
9c. What impact would the technology have on the current pathway of care?	There would be no pathway change, the technology is added to the chemotherapy backbone of first line treatment. Other options remain unchanged.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes it will be used in patients suitable for platinum doublet chemotherapy
10a. How does healthcare resource use differ between the technology and current care?	Longer chair time (2 hours) for amivantamab infusion Drugs to treat infusion reactions may be required (steroids, antihistamines, bronchodilators, adrenaline, oxygen) Treatment will continue for longer than current treatment as it is more effective, with longer PFS
10b. In what clinical setting should the technology be	Secondary care

Professional organisation submission

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

used? (For example, primary or secondary care, specialist clinics.)	
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Staff must have up to date training in the management of infusion reactions. Nil else
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes The technology is added to the current standard of care (platinum doublet chemotherapy) and so many aspects of technology are similar to current SoC. The main advantages are improvements in outcomes compared to chemotherapy (data from Papillon Trial, Girard et al ESMO 2023, Zhou et al NEJM October 2023): • ORR 73% vs 47% • mPFS 11.4 months vs 6.7 months (HR 0.395; 95% CI 0.30-0.53) • mDoR 9.7months vs 6.7 months • OS NE vs 24.4months (HR 0.67)
11a. Do you expect the technology to increase length of life more than current care?	Yes The technology is added to the current standard of care (platinum doublet chemotherapy) and so many aspects of technology are similar to current SoC. The main advantages are improvements in outcomes compared to chemotherapy (data from Papillon Trial, Girard et al ESMO 2023, Zhou et al NEJM October 2023): • mPFS 11.4 months vs 6.7 months (HR 0.395; 95% CI 0.30-0.53) • OS NE vs 24.4months (HR 0.67)
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes, due to improved efficacy, QoL data not yet published

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No, all subgroups presented demonstrated benefit in PFS

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	The technology is added to the current standard of care (platinum doublet chemotherapy) and so many aspects of technology are similar to current SoC. There are potentially additional side effects related to EGFR inhibition (eg rash) with which clinicians are very familiar. The challenges are: • delivery of amivantamab - infusion reactions not uncommon on first cycle. Drugs to treat infusion reactions may be required (steroids, antihistamines, bronchodilators, adrenaline, oxygen) • ensuring patients with EGFR EXON 20 insertions are picked up on diagnostic sample (NGS required) as some labs carry out more limited testing which may lead to patients not being identified
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No rules Testing is available and funded for all patients but not currently consistently delivered
15. Do you consider that the use of the technology will result in any	no

substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes – there is no targeted therapy available for this group of patients whose cancers have an oncogenic driver. Although there are some challenges with identification of patients in the front line, improvements are being made with more patients having full NGS testing and NHSE ctDNA testing will play a part in improving pick up of EGFR exon 20 Insertions
16a. Is the technology a ‘step-change’ in the management of the condition?	yes
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient’s quality of life?	The healthcare professionals need to be aware of the risk of infusions reactions and patients counselled before the first treatment of the risk and reassured that if a reaction occurs it can be managed and the treatment can usually continue. Of note, a subcutaneous preparation of the technology has been developed which abrogates the infusion reaction problem and is currently in trials.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	yes
18a. If not, how could the results be extrapolated to the UK setting?	na
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	PFS, OS, adverse events Yes
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	PFS was primary endpoint and is appropriate as OS can be confounded by crossover. There was 66% cross over at the time of reporting.
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	no
20. Are you aware of any new evidence for the	no

Professional organisation submission

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

comparator treatment(s) since the publication of NICE technology appraisal guidance TA770?	
21. How do data on real-world experience compare with the trial data?	I'm not aware of any published real world data in this setting

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	no
22b. Consider whether these issues are different from issues with current care and why.	

Topic-specific questions

23. Further to question 9, could you offer any insight into the proportions of people who have the different treatment options which are currently available for this condition?	There is only one SoC (platinum doublet chemotherapy) and these patients will be eligible. Patients will currently receive platinum doublet or BSC. There are no other options to offer proportions
24. Are there any particular clinical or other reasons why a person might have one of the current treatment options over another?	NA
25. Could you comment on the usage and efficacy of “conventional” EGFR tyrosine kinase inhibitors (erlotinib, gefitinib, afatinib, dacomitinib and osimertinib) in untreated advanced/metastatic NSCLC that is EGFR Exon20 insertion positive?	Exon 20 EGFR insertions are not sensitive to standard TKI therapy. High dose Osimertinib (for which there is limited data) is not commissioned. Genomic testing reports have been improved and now usually comment on the type of mutation and sensitivity to treatment, therefore EGFR TKIs should not be used and if there is use it will be very limited.
26. Do all people diagnosed with advanced or metastatic NSCLC have a test that can confirm the presence or absence of an EGFR exon20 insertion mutation?	See previous comments. Some labs are still carrying out limited panel rather than full NGS testing and although the situation is changing there is a current risk that up to 30% of cases may not be identified (personal opinion based on local data of insufficient tissue for testing and discussion with colleagues)

27. Would you expect any differences in the efficacy of amivantamab with carboplatin and pemetrexed for untreated EGFR Exon20 insertion positive NSCLC based on the type of Exon20 insertion alteration?	There is insufficient data to influence decision making according to the location of insertion.

Key messages

28. In up to 5 bullet points, please summarise the key messages of your submission.	• There is no current targeted therapy available for patients with NSCLC harbouring EGFR EXON 20 insertions - Amivatamab would be a step change in treatment for these patients • Phase 3 randomised controlled trial has demonstrated improved outcomes compared to current standard of care chemotherapy: ○ Response rate 73% vs 47% ○ Median progression free survival 11.4 months vs 6.7 months ○ Duration of response 9.7months vs 6.7 months ○ Overall Survival was not reached at the time of follow up vs 24.4months

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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Professional organisation submission

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

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Single Technology Appraisal

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

Clinical expert statement

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Clinical expert statement

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

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 also send a second version of your comments with that information redacted. See [Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals](#) (section 3.2) for more information.

The deadline for your response is **5pm** on **<insert deadline>**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, 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 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.

Clinical expert statement

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

Part 1: Treating untreated EGFR exon 20 insertion mutation-positive advanced non-small-cell lung cancer and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Professor Sanjay Popat
2. Name of organisation	Royal Marsden Hospital
3. Job title or position	Consultant Medical Oncologist, Professor of Thoracic Oncology
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with advanced non-small-cell lung cancer? ☒ A specialist in the clinical evidence base for advanced non-small-cell lung cancer or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil

Clinical expert statement

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

8. What is the main aim of treatment for advanced NSCLC? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To prolong life, to shrink cancer, to control cancer growth, to improve quality of life
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	a 30% shrinkage in tumour size on CT is regarded as significant shrinkage
10. In your view, is there an unmet need for patients and healthcare professionals in advanced NSCLC?	Yes, especially for EGFR exon20 insertion positive NSCLC for whom no targeted therapies are approved and for whom immunotherapy has modest if any activity
11. How is exon 20 insertion positive advanced NSCLC currently treated in the NHS? - Are any clinical guidelines used in the treatment of the condition, and if so, which? - Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) - What impact would the technology have on the current pathway of care?	Patients are currently treated first line with platinum doublet chemotherapy. They are generally not treated with chemo-immunotherapy. There are no approved targeted therapies funded in the NHS. Second line patients are treated with docetaxel +/- nintedanib. Some oncologists use immune checkpoint inhibitors but the activity is modest/minimal at best, May patients elect for supportive care at joint decision-making. Patients are treated according to NICE guidelines in the UK. ESMO, ASCO, and NCCN guidelines recommend the technology in the indication being appraised. The technology would be easy to implement, although the initial weekly administration results in increased visits over chemotherapy alone, and the initial longer infusion time results in longer chair time utilization than with chemotherapy alone.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes

Clinical expert statement

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

• How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Amivantamab is added to standard chemotherapy. The additional of amivantamab will currently require longer chair time for initially doses and increased weekly attendances initially. A subcut formulation is pending license which will improve chair time and minimize infusion reactions. It will be used in the chemo day unit There will be little additional investment needed
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes, the efficacy advantage for the addition of amivantamab is large and clinically meaningful Yes, I expect it to increase length of life in due course Yes, I expect it to increase some domains in quality of life related to disease but decrease some aspects due to toxicities
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	It should be used for the licensed indication, EGFR exon 20 insertion NSCLC
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? • (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Like all new drugs, it will need some learning for physicians when initially using it; eg prophylaxing against infusion reactions with high dose steroids, prophylaxing against skin toxicities with emollients, antibiotics and soap substitutes; managing nail toxicities. When the subcut form is licensed in due course, this will reduce the infusion reaction rate and the chair time.

Clinical expert statement

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

16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No, systemic therapy will be administered as per usual clinical practice. EGFR genotyping to OPTIMALLY detect exon 20 insertions is patchily implemented in the NHS despite adequate lab resource.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	No
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? - Is the technology a 'step-change' in the management of the advanced NSCLC? - Does the use of the technology address any particular unmet need of the patient population?	Yes- this is innovative treatment and would be the first NHS approved targeted therapy for this group of mutation-selected patients with poor outcomes otherwise, for whom amivantamab will make a clear and meaningful difference. I would consider the implementation of amivantamab a step change for EGFR exon 20 insertion positive advanced NSCLC Yes, it addresses a large unmet need as survival is terrible currently for this group of patients
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Healthcare professionals need to be able to manage thee toxicities but these are similar to that seen for drugs already used in oncology; ie infusion reactions (mitigated by high dose steroid prophylaxis), skin and nail toxicities. Patient education is also key, but the adverse event profile is offset well against the marked efficacy seen with the drug.
20. Do the clinical trials on the technology reflect current UK clinical practice?	Yes

Clinical expert statement

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

• If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	N/A ORR, PFS, OS- yes measured N/A No
21. Would you expect the treatment effect of amivantamab to diminish once treatment has stopped?	Yes
22. What treatment options do you consider would be displaced if amivantamab were recommended?	Amivantamab is an addition to standard chemotherapy in most oncological expert practice. Some more “generalist” oncologist do give chemotherapy with immunotherapy (pembrolizumab) and amivantamab would displace pembrolizumab
23. Does the blended comparator (70% chemo to 30% pembro) reflect what might occur in clinical practice?	Yes
24. Do exon20 insertions appear in squamous disease and if so, at what prevalence?	Very rarely but occasionally these are observed
25. Would you expect amivantamab to have the same efficacy in squamous NSCLC as non-squamous?	Yes

Clinical expert statement

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

26. Would you want to offer this as a treatment option in squamous disease?	Yes, but these are very rare cases
27. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
28. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA683?	No
29. How do data on real-world experience compare with the trial data?	Real world datasets generally tend to have poorer PFS and OS than trial data, due to patient selection on prognostic factors by trials unlike real world
30. NICE considers whether there are any equality issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation	No

Clinical expert statement

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

- lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population
- lead to recommendations that have an adverse impact on disabled people.

Please consider whether these issues are different from issues with current care and why.

More information on how NICE deals with equalities issues can be found in the [NICE equality scheme](#).

[Find more general information about the Equality Act and equalities issues here.](#)

Clinical expert statement

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

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

1. EGFR exon 20 insertion mutant advanced NSCLC has a large unmet need with poor outcomes, currently
2. Amivantamab-chemotherapy is a step-change treatment for EGFR exon 20 insertion mutant advanced NSCLC
3. Amivantamab is highly active in EGFR exon 20 mutant advanced NSCLC with clinically meaningful benefit in progression-free survival
4. The skin, nail and infusion toxicities of amivantamab are manageable with appropriate prophylaxis

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Clinical expert statement

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

Single Technology Appraisal

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

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Clinical expert statement

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

Part 1: Treating untreated EGFR exon 20 insertion mutation-positive advanced non-small-cell lung cancer and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Spyridon Gennatas
2. Name of organisation	Guy's and St Thomas' NHS Foundation Trust
3. Job title or position	Consultant Medical Oncologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with advanced non-small-cell lung cancer? ☐ A specialist in the clinical evidence base for advanced non-small-cell lung cancer or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Clinical expert statement

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

8. What is the main aim of treatment for advanced NSCLC? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	The main aim of treatment for advanced NSCLC is to improve quality of life and prolong survival.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	I consider a clinically significant treatment response one that is durable, so not measured in percentage of shrinkage or drop in SUV on PET. A clinically significant response is one that increases the progression free survival for that intervention Vs no intervention or the standard of care treatment.
10. In your view, is there an unmet need for patients and healthcare professionals in advanced NSCLC?	In my view, there is an unmet need for patients and healthcare professionals in advanced NSCLC. In very broad terms, this includes both treatments and biomarkers of response for all subtypes of advanced NSCLC.
11. How is exon 20 insertion positive advanced NSCLC currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Currently exon 20 insertion positive advanced NSCLC in the NHS is treated with platinum-based chemotherapy (commonly carboplatin) and pemetrexed. Immunotherapy can be but is not commonly used as such tumours are known to be relatively resistant to immunotherapy. The most commonly used clinical guidelines are those from the European Society for Medical Oncology (ESMO). The current pathway of care is very well-defined. The only variation can be that of the use of immunotherapy together with chemotherapy or not in this patient cohort. The technology would not have a big impact on the current pathway of care. It would only add an extra 3 hospital visits as amivantamab is given weekly for the first four weeks and the first dose has a Day 1 and 2. In due course, it is likely that amivantamab will also be used subcutaneously that will further simplify the treatment pathway.

Clinical expert statement

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

12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	As above, the technology would only add an extra 3 hospital visits. The technology, as is the case with all systemic anticancer therapies, should be used in a specialist chemotherapy day unit and as part of a specialist Lung Oncology outpatient clinic. No additional/ new investment is needed to introduce the technology.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	I expect the technology to provide clinically meaningful benefits compared to the current standard of care (SoC). The progression free survival with this technology is significantly longer than with the current SoC. The same is very likely with health-related quality of life that I would expect to be increased compared with SoC.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Those with NSCLC and exon 20 EGFR mutations.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? • (For example, any concomitant treatments needed, additional clinical requirements, factors affecting	The technology will be as easy to use as the current, SoC treatment. As noted above there is a subcutaneous formulation of amivantamab that when used will further simplify administration.

Clinical expert statement

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

patient acceptability or ease of use or additional tests or monitoring needed)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	There will be nothing outside current, routine clinical practice, in terms of outpatients appointments, blood tests needed and the imaging used for response assessment.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	As stated above, the current route of administration is IV. However when the subcutaneous preparation of amivantamab is available and licensed, this will further improve quality of life for these patients. They will need to spend less time in hospital, they have a shorter treatment duration and importantly will have no infusion reactions, as there will be no infusion of the amivantamab. This formulation is already shown to be non-inferior to IV in some settings.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? - Is the technology a 'step-change' in the management of the advanced NSCLC? - Does the use of the technology address any particular unmet need of the patient population?	This is a technology that addresses a current unmet need as patients with EGFR Exon 20 insertions do not have access to any targeted treatment for their disease. Access to amivantamab (together with chemotherapy) will significantly improve their responses and progression free survival and is likely to also improve their overall survival although these data from the trial are still pending.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Amivantamab adverse events are already well documented and understood. Patient, physician and nurse education is key. Giving patients supportive medications up from will be crucial in making sure that any toxicity is dealt with in a timely manner and patient awareness is also key in that.
20. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, they do. Important outcomes as per the PAPILLON trial: "Progression-free survival was significantly longer in the amivantamab–chemotherapy group than in the

Clinical expert statement

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• If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	chemotherapy group (median, 11.4 months and 6.7 months, respectively; hazard ratio for disease progression or death, 0.40; 95% confidence interval [CI], 0.30 to 0.53; $P < 0.001$). At 18 months, progression-free survival was reported in 31% of the patients in the amivantamab–chemotherapy group and in 3% in the chemotherapy group; a complete or partial response at data cutoff was reported in 73% and 47%, respectively (rate ratio, 1.50; 95% CI, 1.32 to 1.68; $P < 0.001$). In the interim overall survival analysis (33% maturity), the hazard ratio for death for amivantamab–chemotherapy as compared with chemotherapy was 0.67 (95% CI, 0.42 to 1.09; $P = 0.11$)." These results are impressive for such a cohort of patients. As far as I am aware, there are no adverse events that have come to light since the clinical trial was conducted/ reported.
21. Would you expect the treatment effect of amivantamab to diminish once treatment has stopped?	Yes.
22. What treatment options do you consider would be displaced if amivantamab were recommended?	None.
23. Does the blended comparator (70% chemo to 30% pembro) reflect what might occur in clinical practice?	Yes.
24. Do exon20 insertions appear in squamous disease and if so, at what prevalence?	EGFR mutations are rare in squamous cell lung cancer. This is in the order of 5-7% even in populations with a high prevalence of EGFR mutations. Of those EGFR mutant cases, Exon 20 insertions are less than 10%.

Clinical expert statement

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25. Would you expect amivantamab to have the same efficacy in squamous NSCLC as non-squamous?	Extrapolating the data and experience we have from common EGFR mutations and their treatments, I would expect amivantamab to have similar efficacy in squamous NSCLC.
26. Would you want to offer this as a treatment option in squamous disease?	For the above reasons, I would like to be able offer this option to patients with squamous NSCLC and EGFR exon 20 insertions.
27. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Not at present but this would be part of the real-world evidence we would want to collect as soon as we have access to this regimen.
28. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA683?	No.
29. How do data on real-world experience compare with the trial data?	There are currently real-world data to support that amivantamab is safe in patients with EGFR exon 20 insertions but to my knowledge, there are no published real-world data in combination with chemotherapy in the first line setting.
30. NICE considers whether there are any equality issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could	I do not think there are any groups of people with this condition that are particularly disadvantaged. Access to molecular diagnostics is key for all potentially actionable mutations in NSCLC and the only group that would be disadvantaged would be one that doesn't, whichever the molecular aberration may be.

Clinical expert statement

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

- exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation
- lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population
- lead to recommendations that have an adverse impact on disabled people.

Please consider whether these issues are different from issues with current care and why.

More information on how NICE deals with equalities issues can be found in the [NICE equality scheme](#).

[Find more general information about the Equality Act and equalities issues here.](#)

Clinical expert statement

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

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

There is huge unmet need for NSCLC patients with EGFR exon 20 insertions, who currently have no access to targeted therapies and poor outcomes.

The PAPILLON trial showed amivantamab–chemotherapy has a significant PFS advantage over chemotherapy alone (median, 11.4 Vs 6.7 month; HR 0.40; 95% confidence interval 0.30 to 0.53; $P < 0.001$).

Amivantamab-chemotherapy can cause reversible adverse events that led to a very low discontinuation rate amongst trial participants.

Upon approval of this regimen all centres will need to contribute to real-world data for the efficacy and toxicity of its use.

In the future, access to subcutaneous amivantamab will further improve the ease of administration and minimise adverse reactions.

Thank you for your time.

Your privacy

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Clinical expert statement

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

Single Technology Appraisal

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

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

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

Information on completing this form

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Patient expert statement

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

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Your response should not be longer than 15 pages.

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Patient expert statement

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

Part 1: Living with this condition or caring for a patient with untreated EGFR exon 20 insertion mutation-positive advanced non-small-cell lung cancer?

Table 1 About you, advanced NSCLC, current treatments and equality

1. Your name	Gini Harrison
2. Are you (please tick all that apply)	☒ A patient with advanced NSCLC? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with advanced NSCLC? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	EGFR+ UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and do not wish to complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and do not wish to complete this statement ☐ I agree with it and will be completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience:

Patient expert statement

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

	☐ I have completed part 2 of the statement after attending the expert engagement teleconference ☐ I have completed part 2 of the statement but was not able to attend the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with advanced NSCLC? If you are a carer (for someone with advanced NSCLC) please share your experience of caring for them	In December 2021, whilst on maternity leave and after experiencing shoulder pain for 10 months that was put down to bad breastfeeding posture, I had an MRI that revealed a tumour in the apex of my right lung, and another in my scapular. Shortly after this, a biopsy revealed it to be EGFR+ NSCLC. While most EGFR mutations are treatable with TKIs, my biopsy revealed that I had a rare subtype - Exon 20 which does not typically respond to this type of treatment. As such, I was treated with chemoradation, and am now off treatment (which, in itself, is terrifying). When I was first diagnosed, I was shocked and terrified by the lack of treatment options for Exon 20 mutations in the UK – and I still am. This uncertainty has caused an immense stress and upset – particularly after Mobocertinib was withdrawn. And this stress has dramatically impacted my quality of life, and that of my family. This lack of treatment options also feels really unfair, particularly as I am able to see that other countries offer effective targeted treatments (including Amivantamab) that aren't available here. I am also a trustee for EGFR+ UK, where I work with and advocate for patients. I am also a Professor of Psychology and have recently been carrying out research with EGFR patients, exploring their wellbeing needs.

Patient expert statement

7a. What do you think of the current treatments and care available for advanced NSCLC on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	There's no standard treatment pathway available on the NHS, and that uncertainty is incredibly overwhelming. I've come to realise how limited the treatment options really are in the UK. There's currently barely any guidance from NICE on Exon 20, and the treatments that are available—like chemo—don't work the same way for everyone. It's frustrating and terrifying to know that even the "standard" options might not help. Having spoken to other Exon 20 patients, this is absolutely the experience of other patients. I'm lucky, as my oncology team are up-to-date on the research, and know a lot about Exon 20. But one of the biggest challenges others face is that their oncology teams don't always seem to understand how different Exon 20 is from other EGFR mutations. This often leaves them with more questions than answers. Are they on the right treatment? Are there new treatments they don't know about? What about clinical trials? The fear of missing out on something that could help them (and me!) is constant. I've seen patients in my position turn to crowdfunding to access treatments outside the NHS. It's heartbreaking because it shows how much we're willing to fight for a chance—any chance—at better care. Current treatments just aren't meeting our needs, and every day feels like a race against time to find something, anything, that could make a difference.
8. If there are disadvantages for patients of current NHS treatments for advanced NSCLC (for example, how they are given or taken, side effects of treatment, and any others) please describe these	As I said above, there isn't a current standard of care. But most Exon 20 patients in the UK have either been put on TKIs, or given chemo. The disadvantages are being given an ineffective drug (like Osimertinib), or being given chemo alone. Obviously chemo involves having to go to hospital (which has logistical challenges) and suffering the side-effects.

Patient expert statement

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

9a. If there are advantages of amivantamab with carboplatin and pemetrexed over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does amivantamab with carboplatin and pemetrexed help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these	The increased effectiveness of this treatment! When I first read about the Papillon trial, which showed that combining amivantamab with chemotherapy significantly improved progression-free survival compared to chemo alone, it gave me a glimmer of hope. Even though the combination might come with some serious side effects, what really matters to me—and I know I'm not alone in this—is having an effective treatment option. Right now, those options are so limited. From what I've seen on patient forums, some people in the UK have managed to get amivantamab, either through clinical trials or expanded access programs, and the feedback from those patients is generally really positive. And in most cases, side effects have been effectively managed, allowing people to maintain a decent quality of life. It's clear that this treatment could make a real difference for people like me.
10. If there are disadvantages of amivantamab with carboplatin and pemetrexed over current treatments on the NHS please describe these. For example, are there any risks with <<this treatment>>? If you are concerned about any potential side effects you have heard about, please describe them and explain why	I don't really see any disadvantages over current treatments, as the main one is likely to be chemo – which will have similar side effects to this treatment combination. Obviously, there will be a degree of additional toxicity from the Amivantamab, so clinicians will need to take that into account when making treatment decisions. And there are more hospital visits in the first month – but these are things most patients are willing to go through to access an effective treatment.
11. Are there any groups of patients who might benefit more from amivantamab with carboplatin and pemetrexed or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	The combination of chemo and amivantamab may be too toxic for some patients, so this would need to be carefully managed.

Patient expert statement

12. Are there any potential equality issues that should be taken into account when considering advanced NSCLC and amivantamab with carboplatin and pemetrexed ? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	Potentially. Only untreated patients are included in the current appraisal, however there is a huge unmet need amongst patients who have previously received treatment. Please see the next section for more detail here.
13. Are there any other issues that you would like the committee to consider?	Exon 20 patients face a significant unmet need, as there is no standard treatment pathway and very few options available. This lack of care leads to higher rates of anxiety and depression compared to patients with more common EGFR mutations. While this appraisal focuses on untreated patients, there is also a critical need for effective treatments in pretreated patients. The situation has worsened since the withdrawal of Mobocertinib—previously the only NICE-approved post-chemotherapy treatment for Exon 20 patients—left a significant treatment gap. This has amplified psychological distress and is likely to increase mortality rates unless alternative options are made available.

Patient expert statement

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

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- There is currently no standard of care of Exon 20 patients, following the withdrawal of Mobocertinib
- Exon 20 patients lack access to efficacious treatments in the UK
- The uncertainty around treatment options causes significant anxiety and impacts quality of life
- Offering patients an additional treatment line, which has proven efficacy, is likely to have a positive impact on patients' wellbeing and quality of life
- Amivantamab (with or without chemotherapy) should also be considered for use in pre-treated Exon 20 patients to fill the gap left by Mobocertinib's withdrawal

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Patient expert statement

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

Single Technology Appraisal

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

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Patient expert statement

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

Part 1: Living with this condition or caring for a patient with untreated EGFR exon 20 insertion mutation-positive advanced non-small-cell lung cancer?

Table 1 About you, advanced NSCLC, current treatments and equality

Patient expert statement

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

1. Your name	Sophie McCluskey
2. Are you (please tick all that apply)	☐ A patient with advanced NSCLC? Yes ☐ A patient with experience of the treatment being evaluated? Yes ☐ A carer of a patient with advanced NSCLC? No ☐ A patient organisation employee or volunteer? No ☐ Other (please specify):
3. Name of your nominating organisation	EGFR Positive UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and will be completing
5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience Yes ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: Yes, I make reference to others experiences, taken from being apart of online communities such as EGFR Positive UK and Exon20 Group ☐ I have completed part 2 of the statement after attending the expert engagement teleconference Yes

Patient expert statement

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

6. What is your experience of living with advanced NSCLC?

If you are a carer (for someone with advanced NSCLC) please share your experience of caring for them

In May 2021 I contacted my GP regarding symptoms of a rattling chest at night and night sweats, I was referred for a chest X-ray. At the X-ray appointment they discovered I had right lung collapse and plural effusion. A needle biopsy confirmed a lung cancer diagnosis in July 2021. I was 24 years old, had not smoked more than a handful of cigarettes and was otherwise fit and active. I was told it was stage 4 as it appeared in all lung lobes.

I was started on cisplatin and vinorelbine. After two cycles the drug was stopped due to toxicity and the cancer not responding.

I had signed up to the National Lung Cancer Matrix at the time of my diagnosis and further testing was done on my biopsy sample. The results identified an exon 20 insertion on the EGFR gene. My oncologist provided me with the option of going on amivantamab (single agent) on a Post Approval Named Patient Programme. I started IV amivantamab end of October 21. The first CT, 2 months into treatment showed a small reduction to the cancer, my right lung collapsed had cleared and the plural effusion had reduced. For the next 2 and half years I had scans every 2-3 months and the disease remained stable. During that time I was fairly independent, I had no rattle in my chest or night sweats, I could walk reasonable distances and looked healthy. I did struggle to continue working as I had recurrent chest infections in 2022 leading to community acquired pneumonia and then a lung abscess (November 2022) but once I was treated for the abscess and prescribed a saline nebuliser for clearing my chest, I went without an infection throughout 2023 and was living an active lifestyle.

May 2024 I became symptomatic with breathlessness and a CT scan showed possible greater density of disease, this was followed up with a PET scan and further biopsy confirming that the cancer had progressed and amivantamab was stopped in September, 35 months after starting.

I was started on carboplatin and pemetrexed and received 2 cycles but my breathing greatly worsened after each dose. Further imagining led to the chemo being stopped at the end of November 24 and I was further diagnosed with pulmonary hypertension. I am currently

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having support from my local hospice for symptom management as well as commencing Osimertinib which was agreed on compassionate use given there is some evidence of its effectiveness in my sub-mutation of exon 20.

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7a. What do you think of the current treatments and care available for advanced NSCLC on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	a. There currently is no standard of care for Exon 20 on the NHS. My cancer did not respond to the platinum chemotherapy given for NSCLC and I was unable to tolerate the toxicity (see 8. disadvantage section). I was able to access amivantamab on a post approval named patient basis. It was devastating when mobocertinib was pulled from the market as my oncologist had hoped that would be my next option of treatment, after amivantamab, in order to extend my life. The lack of treatments makes me anxious, I am fearful I won't live to see my 30th birthday and I will be leaving my family behind. b. There were many others in the EGFR+ and Exon 20 communities who mourned the loss of mobocertinib. Similarly to myself, I've noted a wish amongst other exon 20 patients, for therapies that target the gene mutation rather than (or rather than solely) chemotherapy drugs with their potential side effects and impact on daily life.
8. If there are disadvantages for patients of current NHS treatments for advanced NSCLC (for example, how they are given or taken, side effects of treatment, and any others) please describe these	The lack of treatments that specifically target exon 20 causes means there are poorer outcomes for patients with exon 20. When I was treated with the platinum chemotherapy regime for NSCLC (cisplatin and vinorelbine) I was extremely unwell. After cycle one I developed gastroenteritis and after cycle two I was admitted to intensive care due to sepsis (not neutropenia) and pneumonia and had 2 weeks on a respiratory ward. A CT scan showed the 2 cycles of chemo had not made a difference to the cancer and it was ceased. With another chemotherapy- carboplatin and pemetrexed, I experienced extreme fatigue and lung inflammation. This was not given to me at the same time as amivantamab, it was given a month after stopping and at a time I was more symptomatic and diagnosed with pulmonary hypertension.

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9a. If there are advantages of amivantamab with carboplatin and pemetrexed over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does amivantamab with carboplatin and pemetrexed help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these	a. Effectiveness- amivantamab had an impact on my cancer where platinum chemo hadn't worked. I had a small reduction to the density of cancer in my lung lobes and my right lung collapse and plural effusion were cleared up with receiving amivantamab. I therefore felt well again; I had no rattling chest at night or night sweats, I was able to manage my self care and activities of daily living such as shopping, housework and being present for my loved ones. The side effects were either mild for me or with the support of the right professionals, became manageable even over the long term. I received amivantamab for 35 months, giving me time to do things I wanted to do like visit my sister in Edinburgh, go with my Dad to a football match and look after my cats. For myself and others, amivantamab gives hope as extending prognoses could result in being able to try next generations of therapies targeted for exon 20 and improve overall outcomes for patients. b. The biggest advantages for me were tolerability of the drug and effectiveness of the drug to keep my disease stable over 35 months because I felt like I got my life back after very nearly losing it at 24 years of age. c. Yes absolutely because patients would be given a targeted therapy, amivantamab, which in trials has performed well for exon 20 and from personal experience and the experience of individuals I speak to, provides good results with generally tolerated side effects.

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10. If there are disadvantages of amivantamab with carboplatin and pemetrexed over current treatments on the NHS please describe these. For example, are there any risks with <<this treatment>>? If you are concerned about any potential side effects you have heard about, please describe them and explain why	Develop resistance Cost (particularly of amivantamab) The risk of infusion related reactions with amivantamab which needs careful monitoring and means the first infusion is given very slowly over 2 days. The risks associated with carboplatin and pemetrexed. When I was taking those drugs I completely isolated myself at home during the most high risk period as I was fearful of infections and sepsis. I experienced the following side effects on amivantimab (please note they were mild or managed for me): Rash Constipation Dry eyes Paronychia
11. Are there any groups of patients who might benefit more from amivantamab with carboplatin and pemetrexed or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	I feel all exon 20 patients could benefit from amivantimab (solely or with chemotherapy) as it could improve their quality of life and extend their life. It fills the gap left by mobocertinib which resulted in no standard of care for exon 20 patients.

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12. Are there any potential equality issues that should be taken into account when considering advanced NSCLC and amivantamab with carboplatin and pemetrexed ? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	Regular hospital trips required for the regime, could be difficult for certain groups of people such as those with mobility or cognitive difficulties or people with child care responsibilities. From exon 20 patients I talk to on a social level, there seems to be issues around geographical location. A gentleman in London has much easier access to lung cancer specialised hospitals who see more exon 20 patients than another person I speak to in Wales. I was extremely grateful Janssen provided in-person training to my local chemo unit so I did not have to travel far for treatment.
13. Are there any other issues that you would like the committee to consider?	From my own experience and talking to others (particularly patients in the US where Amivantamab is more widely used) I would say there are significantly better outcomes for people taking the drug where their medical care teams are trained and very aware of the guidance and prococols around administering amivantamab and managing its side effects and giving comprehensive information to their patients and other health professionals involved in their care. My oncologist liaised closely with dermatology and using guidance provided by Janssen in order to get on top the rash I developed on my face so treatment could continue.

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- For the close to 3 years I was taking amivantamab, my quality of life was invaluabley improved; I was able to live fairly independently and to be present and able to show up for my family and friends and make new memories with them.
- Myself and other exon 20 patients wish for a greater arsenal of treatments, with good efficacy for exon 20, that will improve quality of life and life expectancy.
- The current lack of treatment options for exon 20 mutations increases fear and anxiety and leads to feelings of hopelessness regarding our futures.
- As someone who managed well with the side effects of amivantamab but (separately) was unable to tolerate the side effects of the carboplatin and pemetrexed regime, I wonder, under the current proposal, what the guidance or process would be for continuation of either amivantamab or carboplatin and pemetrexed should one of them have too high of a toxicity profile in someone?
- I feel there is a huge importance in the oncology and care team of the patient being specifically trained on the administration of amivantamab and management of side effects and being aware of the nuances of exon 20 mutations.

Thank you for your time.

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in collaboration with:

Erasmus School of
Health Policy
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Maastricht University

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

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Abbreviations

AACR	American Association for Cancer Research
ABCP	Atezolizumab, bevacizumab, carboplatin and paclitaxel
AE	Adverse event
AESI	Adverse event of special interest
AIC	Akaike information criterion
ASCO	American Society of Clinical Oncology
ATC	Average treatment effect in the control
ATT	Average treatment effect for the treated
AUC	Area under the curve
BIC	Bayesian information criterion
BICR	Blinded independent central review
BNF	British National Formulary
BOR	Best overall response
BSA	Body surface area
BSC	Best supportive care
BTOG	British Thoracic Oncology Group
C	Cycle
CADTH	Canadian Agency for Drugs and Technologies in Health
CBR	Clinical benefit rate
CDSR	Cochrane Database of Systematic Reviews
CE	Cost effectiveness
CEA	Cost effectiveness analysis
CEM	Cost effectiveness model
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CP	Carboplatin plus pemetrexed
CR	Complete response
CRD	Centre for Reviews and Dissemination
CS	Company submission
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
D	Day
DARE	Database of Abstracts of Reviews of Effects
DCO	Data cut-off
DCR	Disease control rate
DFS	Disease-free survival
DOR	Duration of response
DP	Decision problem
DSU	Decision Support Unit
DSA	Deterministic sensitivity analysis
EAG	Evidence Assessment Group
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EGFR	Epidermal growth factor receptor
ELCC	European Lung Cancer Annual Congress
EMA	European Medicines Agency
EO	Expert opinion
EORTC QLQ C-30	European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30
EPAR	European Public Assessment Report
EQ-5D-5L	European Quality of Life-5 Dimensions-5 Levels

ESME	Epidemiological Strategy and Medical Economics
ESMO	European Society of Medical Oncology
EUR	Erasmus University Rotterdam
FE	Fixing error
FV	Fixing violation
GHS	Global health score
HERC	Health Economics Research Centre
HR	Hazard ratio
HRQoL	Health-related quality of life
HSE	Health Survey England
HTA	Health technology assessment
IASLC WCLC	International Association for the Study of Lung Cancer World Conference on Lung Cancer
ICER	Incremental cost-effectiveness ratio
ICH	International Council for Harmonization
ILD	Interstitial lung disease
Incr.	Incremental
IO	Immunotherapy
IPCW	Inverse Probability of Censoring Weighting
IPW	Inverse probability weighting
IPD	Individual participant data
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous
KM	Kaplan-Meier
KSR	Kleijnen Systematic Reviews
LOCF	Last observation carried forward
LYs	Life years
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency
MIMS	Monthly Index of Medical Specialities
MJ	Matters of judgement
MMRM	Mixed-model repeated measures
N/A	Not applicable
N/A	Not available
NCI	National Cancer Institute
NCRAS	National Cancer Registration and Analysis Service
NE	Not estimable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NL	The Netherlands
NMA	Network meta-analysis
NMB	Net monetary benefit
NR	Not reported
NSCLC	Non-small cell lung cancer
NSCLC-SAQ	Non-Small Cell Lung Cancer Symptom Assessment Questionnaire
OECD	Organisation for Economic Co-operation and Development
ONS	Office for National Statistics
ORR	Objective response rate
OS	Overall survival
PAS	Patient access scheme
PC-IO	platinum chemotherapy–immune-oncology
PCP	Pembrolizumab with carboplatin and pemetrexed

PD	Progressed disease
PD-L1	Programmed cell death ligand 1
PF	Progression free
PFS	Progression-free survival
PFS2	Time to second progression
	progression-free survival after first subsequent therapy
PGIC	Patient Global Impression of Change Scale
PGIS	Patient's Global Impression of Severity
PH	Proportional hazards
PR	Partial response
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PRO	Patient reported outcome
PROMIS-PF	Patient-Reported Outcomes Measurement Information System – Physical Function
PS	Performance status
PS	Propensity score
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PSW	Propensity score weighting
QALE	Quality-adjusted life expectancy
QALY	Quality-adjusted life year
QoL	Quality of life
QW	Once a week
RCT	Randomised controlled trial
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumours
RFS	Relapse/recurrent-free survival
RMST	Restricted mean survival time
ROBINS-I	Risk of Bias in Non-randomized Studies of Interventions
RPSFT	Rank preserving structural failure time
RWCP	Real-world clinical practice
RWD	Real-world data
RWE	Real-world evidence
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SD	Stable disease
SE	Standard error
SF-36	36-Item Short Form Survey
SLR	Systematic literature review
SMD	Standardised mean difference
SmPC	Summary of Product Characteristics
SoC	Standard of care
SR	Systematic review
STA	Single technology appraisal
TA	Technology assessment
TEAE	Treatment emergent adverse event
TKI	Tyrosine kinase inhibitor
TSD	Technical Support Document
TSE	Two-stage estimation
TTD	Time to treatment discontinuation
TTDD	Time to treatment discontinuation or death

TTNT	Time to next treatment
TTP	Time to progression
TTSP	Time to symptomatic progression
TTST	Time to subsequent treatment
UK	United Kingdom
UMC+	University Medical Center+
US	United States
WDAE	Withdrawals due to adverse event

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1. Executive summary

This summary provides a brief overview of the key issues identified by the Evidence Assessment Group (EAG) as being potentially important for decision making. If possible, it also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 presents the key model outcomes. Section 1.3 discusses the decision problem, Section 1.4 issues related to the clinical effectiveness, and Section 1.5 issues related to the cost effectiveness. A summary is presented in Section 1.6.

Background information on the condition, technology and evidence and information on key as well as non-key issues are in the main EAG report, see Sections 2 (decision problem), 3 (clinical effectiveness) and 4 (cost effectiveness) for more details.

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

Table 1.1: Summary of key issues

ID5110	Summary of issue	Report Sections
1	Application of the CS evidence that excludes squamous histology to all patients regardless of histology	2.1, 3.2, 3.3, 4
2	Uncertainty as to the appropriate comparators	2.3, 3.3, 3.4, 4
3	There was a lack of adjustment for some important prognostic variables in the base-case average treatment effect for the treated (ATT) analyses.	3.3 and 3.4
4	Sensitivity analyses by using alternative adjustment methods were not conducted for the data of base-case ATT analyses.	3.3 and 3.4
5	The additional ITC analysis for the comparison of amivantamab plus chemotherapy versus immunotherapy alone was not conducted by using ATT adjustment and/or alternative adjustment methods.	3.3 and 3.4
6	Intervention and comparators – blended comparator approach	4.2.4
7	Treatment effectiveness - survival extrapolation for amivantamab with chemotherapy and chemotherapy only	4.2.6
8	Treatment effectiveness - assuming no waning of the relative treatment effect	4.2.6
9	Health-related quality of life - missing data	4.2.8
10	Resource use and costs - implementation of dose frequency	4.2.9
11	Resource use and costs - assumption of no vial sharing	4.2.9
12	Company's cost effectiveness results - extrapolated benefits	5.1
13	Model validation – technical verification of economic model	5.3
ATT = average treatment effect for the treated; CS = company submission; EAG = Evidence Assessment Group; ITC = indirect treatment comparison		

1.2 Overview of key model outcomes

Overall, the technology is modelled to affect quality-adjusted life years (QALYs) by:

- Increased health state occupancy duration in the progression free (PF) and progressed disease (PD) health states, with incremental QALYs of [REDACTED] ([REDACTED]% of the total incremental QALYs) and [REDACTED] ([REDACTED]% of the total incremental QALYs) for the progression free and progressed disease states, respectively for the weighted comparator. Similar percentages were seen in the chemotherapy (PF: [REDACTED]% PD: [REDACTED]%) and pembrolizumab-chemotherapy arms (PF: [REDACTED]% PD: [REDACTED]%).

Overall, the technology is modelled to affect costs by:

- Increased acquisition costs of amivantamab with chemotherapy (additional costs of [REDACTED], [REDACTED]% of the total incremental costs for the weighted comparator). These were mainly due to the chemotherapy arm (additional costs of [REDACTED], [REDACTED] of the total incremental costs compared to the chemotherapy arm).
- Increased resource use of the progression free state for amivantamab with chemotherapy ([REDACTED], [REDACTED]% of the total incremental costs compared to the weighted comparator)
- Increased resource use of the progressed disease state for amivantamab with chemotherapy ([REDACTED], [REDACTED]% of the total incremental costs compared to the weighted comparator)
- Virtually no difference in the subsequent treatment costs (additional costs of [REDACTED], [REDACTED]% of the total incremental costs compared to the weighted comparator). However, there was a significant difference between the chemotherapy arm (incremental costs: [REDACTED], [REDACTED] of the total incremental costs compared to the chemotherapy arm) and the pembrolizumab with chemotherapy ([REDACTED], [REDACTED] of the total incremental costs compared to the pembrolizumab with chemotherapy arm).

The modelling assumptions that have the greatest effect on the ICER (based on scenario analyses included in the CS) are:

- The use of an alternative comparator distributions in the weighted comparison (90% IO+CP and 10% CP; reflecting insight from some experts in advisory board) ([REDACTED]% decrease on the ICER)
- Using National Cancer Registration and Analysis Service (NCRAS) data to model comparator efficacy and treatment distribution, using the full dataset to model efficacy and the distribution of treatments ([REDACTED]% decrease on the original ICER)
- The use of gamma distribution to extrapolate the overall survival (OS) of amivantamab-chemotherapy ([REDACTED]% decrease on the ICER).

1.3 The decision problem: summary of the EAG's key issues

The decision problem addressed in the company submission (CS) is broadly in line with the final scope issued by NICE. However, there is a lack of evidence on adult patients (Table 1.2) as well as on certain comparators (Table 1.3).

Table 1.2: Key issue 1: Application of the CS evidence that excludes squamous histology to all patients regardless of histology

Report Section	2.1, 3.2, 3.3, 4
Description of issue and why the EAG has identified it as important	The key trial, PAPILLON, does not include patients with squamous histology. On the basis that squamous histology is rare (the company cited a figure of 3.05%) and the lack of inclusion of patients with it in PAPILLON, the company stated that, in line with the trial, they have excluded squamous histology from the decision problem.
What alternative approach has the EAG suggested?	Adapt the decision problem to exclude squamous histology or provide clinical and cost effectiveness evidence for this population.
What is the expected effect on the cost effectiveness estimates?	None if the NICE decision does not apply to patients with squamous histology.
What additional evidence or analyses might help to resolve this key issue?	Additional evidence can only be helpful if the NICE decision applies to patients with squamous histology.
CS = company submission; EAG = Evidence Assessment Group; NICE = National Institute for Health and Care Excellence	

Table 1.3: Key issue 2: Uncertainty as to the appropriate comparators

Report Section	2.3, 3.3, 3.4, 4
Description of issue and why the EAG has identified it as important	Pembrolizumab monotherapy is listed as a comparator in the DP and a treatment that patients in the population of the DP have received in England as recorded in the NECTAR study. However, the company originally did not include it as a comparator in the cost effectiveness analysis and argued in response to the request for clarification that the NECTAR study data are too few and too old and therefore only clinical expert opinion should guide choice of comparator, such opinion being recorded essentially excluding pembrolizumab monotherapy. The EAG also noted that there was some clinical expert opinion that the combination of atezolizumab, bevacizumab, carboplatin and paclitaxel (ABCP) was listed as comparator by some clinical experts. Although the company stated that this was only in a survey and never mentioned in any of the advisory board meetings, the EAG noted that there is no record of actual questions asked in the meetings or of the degree of overlap in clinical experts between meetings.
What alternative approach has the EAG suggested?	The EAG recommended the inclusion of all treatments used in NHS clinical practice and the company did include results of ITC for an unadjusted overall survival and time to next treatment for immunotherapy (assumed to be pembrolizumab monotherapy) in response to the request for clarification. These were based on the 20 patients in the overall dataset from the NECTAR study (not only England).
What is the expected effect on the cost effectiveness estimates?	Unknown.

Report Section	2.3, 3.3, 3.4, 4
What additional evidence or analyses might help to resolve this key issue?	A comparison with ABCP might be helpful, although the EAG know of no relevant data source.
ABCP = atezolizumab, bevacizumab, carboplatin and paclitaxel; DP = decision problem; EAG = Evidence Assessment Group; NHS = National Health Service	

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

The EAG identified three major concerns with the evidence presented on the clinical effectiveness: a) there was a lack of adjustment for some important prognostic variables in the base-case average treatment effect for the treated (ATT) analyses (see Table 1.4); b) sensitivity analyses by using alternative adjustment methods such as the regression adjustment method and/or a doubly robust method were not conducted for the data of base-case ATT analyses (see Table 1.4); and c) the additional indirect treatment comparison (ITC) analysis for the comparison of amivantamab plus chemotherapy versus immunotherapy alone was not conducted by using ATT adjustment and/or alternative adjustment methods (see Table 1.5).

Table 1.4: Key issue 3: There was a lack of adjustment for some important prognostic variables in the base-case average treatment effect for the treated (ATT) analyses

Report Section	3.3 and 3.4
Description of issue and why the EAG has identified it as important	The ITC used propensity score weighting (PSW) to estimate the ATT in the comparison of amivantamab plus chemotherapy versus pembrolizumab plus chemotherapy. Eight baseline characteristics were listed for consideration in estimating the propensity score (PS). However, summary data were only provided for four baseline characteristics. The EAG requested the company to clarify which baseline characteristics were used to estimate the PS. In responding to the EAG's request, the company provided details of baseline characteristics that were used to estimate the PS. The company also provided reasons (e.g., not available across databases) for excluding some baseline characteristics to estimate the PS. It should be noted that the prognostic variables of any other metastatic locations, Asian ethnicity and smoking history were not adjusted for in the base-case ATT analyses due to the limited availability of these variables across RWE databases. Therefore, there was a lack of adjustment for these important prognostic variables in the base-case ATT analyses. Due to this issue, there were uncertainties in these results of ITC.
What alternative approach has the EAG suggested?	All relevant prognostic variables should be adjusted for in the base-case ATT analysis where possible.
What is the expected effect on the cost effectiveness estimates?	The effect on the cost effectiveness estimates is difficult to predict.
What additional evidence or analyses might help to resolve this key issue?	The EAG recommends that all important prognostic variables should be adjusted for in the base-case ATT analysis if data are available.

Report Section	3.3 and 3.4
ATT = average treatment effect for the treated; EAG = Evidence Assessment Group; ITC = indirect treatment comparison; PS = propensity score; PSW = propensity score weighting; RWE = real-world evidence	

Table 1.5: Key issue 4: Sensitivity analyses by using alternative adjustment methods such as regression adjustment method and/or a doubly robust method were not conducted for the data of base-case ATT analyses

Report Section	3.3 and 3.4
Description of issue and why the EAG has identified it as important	The EAG requested the company to conduct sensitivity analyses by using regression adjustment method and/or a doubly robust method for the base-case ATT analyses. In responding to the EAG's request, the company stated that covariate adjustment and doubly robust regression required centralised pooling of all individual participant data (IPD). Due to the remote access setup of the IPD in one real-world dataset (Epidemiological Strategy and Medical Economics [ESME]), these analyses could not be performed on the pooled NECTAR data. Given that the sensitivity analyses by using alternative adjustment methods such as regression adjustment method and doubly robust method were not conducted for the data of the base-case ATT analyses, it was unclear whether the results of base-case ATT analyses were robust.
What alternative approach has the EAG suggested?	Sensitivity analyses by using regression adjustment method and/or a doubly robust method should be conducted for the data of base-case ATT analyses where possible.
What is the expected effect on the cost effectiveness estimates?	The effect on the cost effectiveness estimates is difficult to predict.
What additional evidence or analyses might help to resolve this key issue?	The EAG recommends that sensitivity analyses by using regression adjustment method and/or a doubly robust method should be conducted for the data of base-case ATT analysis if data are available.
ATT = average treatment effect for the treated; EAG = Evidence Assessment Group; ESME = Epidemiological Strategy and Medical Economics; IPD = individual participant data	

Table 1.6: Key issue 5: The additional ITC analysis for the comparison of amivantamab plus chemotherapy versus immunotherapy alone was not conducted by using ATT adjustment and/or alternative adjustment methods

Report Section	3.3 and 3.4
Description of issue and why the EAG has identified it as important	The EAG requested the company to present the ITC results for comparisons with all relevant comparators. In responding to the EAG's request, the company provided the ITC results for the comparison of amivantamab plus chemotherapy versus immunotherapy alone as a comparator. However, it should be noted that these ITC analyses were not conducted by using ATT adjustment and/or alternative adjustment methods due to a small number of patients within the immunotherapy alone treatment class. Given that the additional ITC analysis for the comparison of amivantamab plus chemotherapy versus immunotherapy alone was not conducted by using ATT adjustment and/or alternative

Report Section	3.3 and 3.4
	adjustment methods such as regression adjustment method and a doubly robust method, there were considerable uncertainties on these results of ITC analyses.
What alternative approach has the EAG suggested?	ATT adjustment and/or alternative adjustment methods such as regression adjustment method and doubly robust should be conducted for the ITC analyses of the comparison of amivantamab plus chemotherapy versus immunotherapy alone.
What is the expected effect on the cost effectiveness estimates?	The effect on the cost effectiveness estimates is difficult to predict.
What additional evidence or analyses might help to resolve this key issue?	The EAG recommends that ATT adjustment and/or alternative adjustment methods such as regression adjustment method and a doubly robust should be conducted for the comparison of amivantamab plus chemotherapy versus immunotherapy alone where possible.
ATT = average treatment effect for the treated; EAG = Evidence Assessment Group; ITC = indirect treatment comparison	

1.5 The cost effectiveness evidence: summary of the EAG's key issues

The EAG's summary and detailed critique can be found in Section 4, the company's cost effectiveness results are presented in Section 5, and the EAG's amendments to the company's model and results are in Section 6. The key issues in the cost effectiveness evidence are discussed below.

Table 1.7: Key issue 6: Intervention and comparators – blended comparator approach

Report section	4.2.4
Description of issue and why the EAG has identified it as important	The company used a blended comparator approach which hides important differences in estimated cost effectiveness.
What alternative approach has the EAG suggested?	The EAG requested the company to provide all results presented in CS sections B.3.10 and B.3.11 for the treatment options within the blended comparator separately.
What is the expected effect on the cost effectiveness estimates?	The pairwise comparison versus carboplatin and pemetrexed increases the ICER substantially, whereas the pairwise comparison versus pembrolizumab plus carboplatin and paclitaxel results in amivantamab being dominant.
What additional evidence or analyses might help to resolve this key issue?	Results of all future analyses should be provided for the treatment options within the blended comparator separately.
CS = company submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio	

Table 1.8: Key issue 7: Treatment effectiveness - survival extrapolation for amivantamab with chemotherapy and chemotherapy only

Report section	4.2.6
Description of issue and why the EAG has identified it as important	The CS base-case overestimated OS for amivantamab with chemotherapy and underestimated OS for chemotherapy only based on the company's advisory board report as well as clinical opinion obtained by the EAG. Moreover, none of the standard parametric

	distributions did align very well with the long-term expert estimates obtained for amivantamab with chemotherapy.
What alternative approach has the EAG suggested?	It is recommended that the company explores alternative parametric models to estimate OS for amivantamab with chemotherapy in line with this statement: <i>“During the August 2024 advisory board, UK clinical experts aligned on a consensus that around 27.5% of patients receiving amivantamab-chemotherapy were expected to be alive after 5-years and 7.5% were expected to be alive after 10-years”</i> According to CS Table 52, none of the distributions aligned well with the 5-year survival estimate provide by clinical opinion. Nor with the clinical opinion obtained by the EAG indicating 10-15% survival after five years.
What is the expected effect on the cost effectiveness estimates?	Alternative assumptions can potentially increase the ICER.
What additional evidence or analyses might help to resolve this key issue?	See above.
CS = company submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; OS = overall survival	

Table 1.9: Key issue 8: Treatment effectiveness - assuming no waning of the relative treatment effect

Report Section	4.2.6
Description of issue and why the EAG has identified it as important	The company did not provide scenario analyses exploring alternative assumptions related to treatment effect waning. 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.
What alternative approach has the EAG suggested?	Provide scenario analyses while assuming treatment waning (at different time points), as requested in clarification question B11.
What is the expected effect on the cost effectiveness estimates?	Alternative assumptions can potentially increase the ICER.
What additional evidence or analyses might help to resolve this key issue?	See above.
EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio	

Table 1.10: Key issue 9: Health-related quality of life – missing data

Report section	4.2.8
Description of issue and why the EAG has identified it as important	For the estimation of the PF health state utility, the average number of patients with missing data across treatment cycles was [REDACTED], whereas for the PD health state utility, a total of [REDACTED] missing observations were reported.

Report section	4.2.8
	It is unclear to the EAG whether these data were missing (completely) at random and hence whether and to what extent the missing data impacted the estimated PF and PD health state utility values
What alternative approach has the EAG suggested?	The EAG requested an updated model and scenario analyses using data imputation methods.
What is the expected effect on the cost effectiveness estimates?	A scenario analysis based on last observation carried forward resulted in similar cost-effectiveness estimates.
What additional evidence or analyses might help to resolve this key issue?	The EAG would like to see further evidence to support the company's assumption that data was missing (completely) at random to address this issue.
EAG = External Assessment Group; PD = progressed disease; PF = progression free	

Table 1.11: Key issue 10: Resource use and costs - implementation of dose frequency

Report section	4.2.9
Description of issue and why the EAG has identified it as important	Patients were modelled to receive a fraction of the dose per model cycle, instead of receiving a full dose at the start of each treatment cycle followed by a period of no doses. This approach does not accurately represent real-world clinical practice, and may lead to an underestimation of the per-cycle costs.
What alternative approach has the EAG suggested?	Accurately reflect treatment administration over time (i.e., patients receiving full dose at the required time-point followed by stipulated period of no administration).
What is the expected effect on the cost effectiveness estimates?	The EAG is uncertain on the magnitude on the cost effectiveness estimates but would expect an increase on the ICER.
What additional evidence or analyses might help to resolve this key issue?	See above.
EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio	

Table 1.12: Key issue 11: Resource use and costs - assumption of no vial sharing

Report section	4.2.9
Description of issue and why the EAG has identified it as important	The company implicitly allowed vial sharing for amivantamab with chemotherapy, but not for the comparators, without providing sufficient justification.
What alternative approach has the EAG suggested?	Update the CEM to not include vial sharing in the amivantamab with chemotherapy arm.
What is the expected effect on the cost effectiveness estimates?	Increase on the ICER.
What additional evidence or analyses	See above.

Report section	4.2.9
might help to resolve this key issue?	
CEM = cost-effectiveness model; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio	

Table 1.13: Key issue 12: Company's cost effectiveness results - extrapolated benefits

Report section	5.1
Description of issue and why the EAG has identified it as important	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.
What alternative approach has the EAG suggested?	The EAG would like to see an explanation of the mechanism by which the economic model generated these results.
What is the expected effect on the cost effectiveness estimates?	N/A
What additional evidence or analyses might help to resolve this key issue?	N/A
EAG = Evidence Assessment Group; LY: life year; N/A = not applicable; QALY: quality-adjusted life year	

Table 1.14: Key issue 13: Model validation – technical verification of economic model

Report section	5.3
Description of issue and why the EAG has identified it as important	The EAG is concerned that the technical verification of the model was insufficient. The company did not provide the TECH-VER checklist despite being asked in the request for clarification.
What alternative approach has the EAG suggested?	Complete the TECH-VER and provide further information on the technical verification on the economic model
What is the expected effect on the cost effectiveness estimates?	N/A
What additional evidence or analyses might help to resolve this key issue?	N/A
EAG = Evidence Assessment Group; N/A = not applicable	

1.6 Summary of the EAG's view

The company's cost-effectiveness model partly complied with the NICE reference case. Deviations from the NICE reference case related to the use of a 'blended' comparator, and it was unclear whether the UK tariff was used for the health state utility values. The most prominent issues highlighted by the

EAG related to 1) the estimation of OS and time to treatment discontinuation or death (TTDD), 2) the estimation of health-related quality of life (HRQoL), 3) the estimation of treatment costs, and 4) the technical verification of the economic model.

The CS base-case probabilistic ICERs (with severity modifier) for amivantamab with chemotherapy versus chemotherapy only and versus pembrolizumab with chemotherapy were £34,368 per QALY gained and dominant respectively. The estimated EAG base-case probabilistic ICERs (with severity modifier), based on the EAG preferred assumptions highlighted in Section 5.1, for amivantamab with chemotherapy versus chemotherapy only and versus pembrolizumab with chemotherapy were £52,482 and £9,759 per QALY gained. The probabilistic EAG base-case analyses indicated cost effectiveness probabilities of [REDACTED] at willingness to pay thresholds of £20,000 and £30,000 per QALY gained for amivantamab with chemotherapy. The most influential adjustments were alternative TTDD approach for amivantamab with chemotherapy, alternative approach for the estimation of treatment costs and alternative approach to estimate OS for chemotherapy only. The ICER increased most in the scenario analysis with alternative assumptions regarding the estimation of OS for amivantamab with chemotherapy, alternative TTDD approach for pembrolizumab with chemotherapy and using utility values from TA683. Notably, in the EAG base-case pembrolizumab with chemotherapy is less effective than chemotherapy only, this illustrates the uncertainty related to the unanchored comparison with pembrolizumab with chemotherapy. The EAG has identified a number of key issues with ATT weighting, used for pembrolizumab with chemotherapy, for the ITC: a) there was a lack of adjustment for some important prognostic variables in the base-case ATT analyses; b) Sensitivity analyses by using alternative adjustment methods were not conducted for the data of base-case ATT analyses; and c) the additional ITC analysis for the comparison of amivantamab plus chemotherapy versus immunotherapy alone was not conducted by using ATT adjustment and/or alternative adjustment methods. Due to these issues, there were uncertainties in the results of ITC.

There is large remaining uncertainty about the effectiveness and relative effectiveness of amivantamab chemotherapy, which can be at least partly resolved by the company by conducting further analyses.

Table 1.15: EAG base-case with severity modifier

Technologies	Total costs	Total LY	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)
CS base-case (updated in clarification response)							
Amivantamab - chemotherapy	[REDACTED]	3.762	[REDACTED]				
Platinum chemotherapy	[REDACTED]	1.958	[REDACTED]	[REDACTED]	1.804	[REDACTED]	35,820
Pembrolizumab-chemotherapy	[REDACTED]	2.089	[REDACTED]	[REDACTED]	1.673	[REDACTED]	Dominant
Blended comparator	[REDACTED]	1.997	[REDACTED]	[REDACTED]	1.765	[REDACTED]	24,839
Matter of judgement (1- Log-logistic distribution for estimating OS for chemotherapy only)							
Amivantamab - chemotherapy	[REDACTED]	3.762	[REDACTED]				
Platinum chemotherapy	[REDACTED]	2.204	[REDACTED]	[REDACTED]	1.558	[REDACTED]	40,074
Pembrolizumab-chemotherapy	[REDACTED]	2.089	[REDACTED]	[REDACTED]	1.673	[REDACTED]	Dominant

Technologies	Total costs	Total LY	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Matter of judgment (2- Log-logistic distribution for estimating TTDD for amivantamab AND Exponential distribution for estimating TTDD for chemotherapy (administered with amivantamab))							
Amivantamab - chemotherapy	██████	3.762	██████				
Platinum chemotherapy	██████	1.958	██████	██████	1.804	██████	45,829
Pembrolizumab-chemotherapy	██████	2.089	██████	██████	1.673	██████	7,919
Matter of Judgment (3 – No vial sharing for amivantamab and RDI based on TA683 for pembrolizumab)							
Amivantamab - chemotherapy	██████	3.762	██████				
Platinum chemotherapy	██████	1.958	██████	██████	1.804	██████	37,719
Pembrolizumab-chemotherapy	██████	2.089	██████	██████	1.673	██████	Dominant
Matter of judgement (4 -Use of severest AE unit costs for non-elective short stay)							
Amivantamab - chemotherapy	██████	3.762	██████				
Platinum chemotherapy	██████	1.958	██████	██████	1.804	██████	35,873
Pembrolizumab-chemotherapy	██████	2.089	██████	██████	1.673	██████	Dominant
EAG base-case							
Amivantamab - chemotherapy	██████	3.762	██████				
Platinum chemotherapy	██████	2.204	██████	██████	1.558	██████	54,577
Pembrolizumab-chemotherapy	██████	2.089	██████	██████	1.673	██████	10,719
EAG base-case probabilistic							
Amivantamab - chemotherapy	██████	3.881	██████				
Platinum chemotherapy	██████	2.234	██████	██████	1.647	██████	52,482
Pembrolizumab-chemotherapy	██████	2.144	██████	██████	1.737	██████	9,759
AE = adverse event; CS = company submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; LY = life year; OS = overall survival; QALY: quality-adjusted life year; TTDD = time to treatment discontinuation or death							

Table 1.16: Scenario analyses (conditional on EAG base-case) with severity modifier

Technologies	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)
EAG base-case							
Amivantamab - chemotherapy	██████	3.762	██████				

Technologies	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Platinum chemotherapy	██████	2.204	██████	██████	1.558	██████	54,577
Pembrolizumab-chemotherapy	██████	2.089	██████	██████	1.673	██████	10,719
Scenario 1 (Gompertz for estimating OS for amivantamab with chemotherapy)							
Amivantamab - chemotherapy	██████	2.724	██████				
Platinum chemotherapy	██████	2.204	██████	██████	0.519	██████	119,117
Pembrolizumab-chemotherapy	██████	2.089	██████	██████	0.635	██████	456
Scenario 2 (Gompertz for estimating TTNT for pembrolizumab with chemotherapy)							
Amivantamab - chemotherapy	██████	3.762	██████				
Platinum chemotherapy	██████	2.204	██████	██████	1.558	██████	54,577
Pembrolizumab-chemotherapy	██████	2.089	██████	██████	1.673	██████	15,341
Scenario 3 (Utility values based on single MMRM)							
Amivantamab - chemotherapy	██████	3.762	██████				
Platinum chemotherapy	██████	2.204	██████	██████	1.558	██████	55,389
Pembrolizumab-chemotherapy	██████	2.089	██████	██████	1.673	██████	10,854
Scenario 4 (Utility values based on TA683)							
Amivantamab - chemotherapy	██████	3.762	██████				
Platinum chemotherapy	██████	2.204	██████	██████	1.558	██████	57,691
Pembrolizumab-chemotherapy	██████	2.089	██████	██████	1.673	██████	11,354
EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; LY = life year; MMRM = mixed-model repeated measures; OS = overall survival; QALY: quality-adjusted life year; TTNT = time to next treatment							

2. Critique of company's definition of decision problem

Table 2.1: Statement of the decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with untreated, locally advanced or metastatic NSCLC with an EGFR exon 20 insertion mutation.	First-line treatment of adult patients with advanced NSCLC with activating EGFR exon 20 insertion mutations.	Aligned to the licensed indication for amivantamab, as per the marketing authorisation from the MHRA.
Intervention	Amivantamab in combination with carboplatin and pemetrexed.	As per NICE scope.	Not applicable.
Comparator(s)	Chemotherapy such as docetaxel, gemcitabine, paclitaxel or vinorelbine in combination with a platinum drug (carboplatin or cisplatin), with or without pemetrexed maintenance treatment Pembrolizumab (monotherapy or in combination with chemotherapy according to PD-L1 expression) Atezolizumab TKIs (gefitinib, erlotinib, afatinib, dacomitinib, osimertinib and osimertinib with chemotherapy [subject to NICE appraisal]).	Carboplatin with pemetrexed Pembrolizumab with carboplatin and pemetrexed Pembrolizumab monotherapy UK RWE (collected from the NCRAS dataset) – as scenario.	Advisory boards with UK oncologists (held in June 2023, May 2024, and August 2024) and UK RWE (collected from the NCRAS dataset) have highlighted that carboplatin with pemetrexed and pembrolizumab in combination with carboplatin and pemetrexed are the predominant treatment regimens used in the patient population considered in this appraisal. Chemotherapy: Clinical expert opinion has highlighted that carboplatin with pemetrexed is the dominant chemotherapy regimen being used, with negligible to no use of cisplatin-based chemotherapy or other chemotherapy regimens such as docetaxel, gemcitabine, paclitaxel or vinorelbine. Therefore, Johnson & Johnson does not consider other chemotherapy regimens aside from

			carboplatin with pemetrexed to constitute relevant comparators. IO monotherapy: Atezolizumab is not NICE-recommended within the population covered by this decision problem (patients with untreated EGFR exon 20 insertion mutation-positive advanced NSCLC) and clinical expert opinion plus UK RWE data have highlighted there is no use of this therapy in clinical practice. Therefore, Johnson & Johnson does not consider atezolizumab to constitute a relevant comparator. Clinical expert opinion as well as UK RWE have shown that there is limited use of pembrolizumab monotherapy in clinical practice. EGFR TKIs: EGFR exon 20 insertion mutations are associated with de novo resistance to EGFR TKIs. Additionally, there are no EGFR TKIs that are specifically recommended within patients with EGFR exon 20 insertion mutation-positive NSCLC at any line. Although there is limited use of EGFR TKIs seen in UK RWE, clinical expert opinion has highlighted EGFR TKIs should not be used in these patients. Additionally, the response from the British Thoracic Oncology

			Group (BTOG) on the draft scope for this appraisal highlighted that use of standard EGFR TKIs in this population was inappropriate. Further, in the appraisal of amivantamab for treating EGFR exon 20 insertion mutation-positive advanced NSCLC after platinum-based chemotherapy (TA 850), clinical experts explained that EGFR TKIs have limited efficacy when there are EGFR exon 20 insertion mutations and, because of this, are rarely and inappropriately used in this population. Therefore, Johnson & Johnson does not consider EGFR TKIs to constitute relevant comparators.
Outcomes	• OS • PFS • Overall response rate (ORR) • Time to subsequent treatment (TTST) • Adverse events (AEs) • HRQoL.	• PFS (primary endpoint) • ORR • Duration of response (DOR) • OS • TTST • Progression-free survival after first subsequent therapy (PFS2) • Time to symptomatic progression (TTSP) • Incidence and severity of AEs and laboratory abnormalities, assessment of vital signs, and physical examination abnormalities • HRQoL.	The outcomes listed in the NICE final scope represent those collected in the PAPILLON trial. Additional outcomes are suggested, to capture the full extent of outcomes assessed in the Phase 3 PAPILLON trial and used within the economic model to demonstrate the most important health benefits associated with amivantamab in combination with carboplatin and pemetrexed.

		Exploratory: • Time to treatment discontinuation (TTD) • EuroQol-5 Dimensions-5 Levels (EQ-5D-5L).	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year (QALY). The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services (PSS) perspective. EGFR testing costs: The final NICE scope highlights that the economic modelling should include the costs associated with diagnostic testing for EGFR exon 20 insertions in people with locally-advanced or metastatic NSCLC who would not otherwise have been tested.	A de novo cost-utility model will be developed for the economic analysis. As per the NICE reference case: results will be expressed in terms of incremental cost per QALY. As per the NICE reference case: The time horizon in the model will be of sufficient length to capture all important differences in costs or outcomes between the technologies being compared. The economic model uses a 40-year time horizon. Less than 0.01% of patients are expected to survive beyond this period. EGFR testing costs: EGFR testing costs are not included within the base-case economic model.	EGFR testing costs: The introduction of amivantamab with carboplatin and pemetrexed is not expected to incur additional costs to the NHS over and above the current SoC for EGFR testing requirements for all patients with NSCLC. Testing for EGFR exon 20 insertion mutations is included in the National Genomic Test Directory. Therefore, EGFR exon 20 insertion mutations are tested routinely in clinical practice as part of a panel of genes, alongside other oncogenic drivers in NSCLC, in a standardised and fully validated approach across the GLHs and different hospitals throughout the UK. Testing for EGFR exon 20 insertion mutations is included in the testing panel as part of the reflex EGFR testing pathway that is conducted at diagnosis for all patients with NSCLC. Therefore, introducing amivantamab-chemotherapy is not expected to incur additional testing costs and as such, the costs associated with diagnostic testing for EGFR in people with NSCLC are not

			anticipated to be included within the base case economic analysis.
Subgroups to be considered	If the evidence allows, the following subgroups will be considered: • Disease stage • Histology • Type of exon 20 alteration present and presence of co-mutations	Subgroup analyses are not considered appropriate.	Subgroups based on disease stage (squamous or non-squamous), histology, EGFR exon 20 insertion mutation type, or co-mutations are not available. Histology: The PAPILLON trial excludes squamous NSCLC and, since 99% of the trial population was of adenocarcinoma histology type, these subgroups could not be explored. Disease stage: Disease stage subgroups could not be explored as efficacy data stratified by this group are not available. Type of EGFR exon 20 alteration or presence of co-mutations: Subgroups based on mutation alteration could not be explored as available sample sizes do not permit such analyses.
Special considerations including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	Amivantamab is presented within the first-line marketing authorisation for the treatment of adult patients with advanced NSCLC with activating EGFR exon 20 insertion mutations. The impact of stigma on people living with lung cancer, including patients and caregivers, is also of relevance to this submission and is not inherently captured in the cost/QALY measure.	Lung cancer is associated with substantial stigma owing to the perception that it is ‘self-inflicted’ due to the public perceiving a link between lung cancer and smoking. This stigma is compounded when considering patients with EGFR exon 20 insertion mutation-positive NSCLC given that EGFR exon 20 insertion mutations are more likely

			to be associated with never-smokers compared with other mutations It should further be considered that EGFR exon 20 insertion mutations are particularly associated with women, non-smokers and people of Asian ethnicity. There is evidence that symptoms of lung cancer are stigmatised in Asian communities, which could reinforce treatment delaying behaviour. A recent study assessing differences in screening, diagnosis, and initial care between patients with newly diagnosed with lung cancer of Asian and White ethnicity reported that, compared with patients of White ethnicity, patients of Asian ethnicity were more likely to be diagnosed with later-stage lung cancer and had a longer median time to treatment initiation. Therefore, ethnicity and stigma are considered to be relevant equality considerations for the Committee. Additionally, there are currently no targeted treatments available in the UK for patients with EGFR exon 20 insertion mutation-positive advanced NSCLC. The economic model therefore does not reflect the inequity in survival outcomes faced by patients with EGFR exon 20 insertion mutation-positive NSCLC versus patients with common EGFR

			mutated NSCLC, who are able to access targeted treatments for their disease via the NHS.
Based on Table 1 of CS¹ AE = adverse event; CS = company submission; DOR: duration of response; EGFR: epidermal growth factor receptor; EQ-5D-5L = EuroQol-5 Dimensions-5 Levels; HRQoL = health-related quality of life; IO = immuno-oncology; MHRA = Medicines and Healthcare products Regulatory Agency; NCRAS = National Cancer Registration and Analysis Service; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PD-L1 = programmed cell death ligand 1 PFS = progression-free survival; PSS = Personal Social Services; QALY = quality-adjusted life year; RWE = real-world evidence; SoC = standard of care; TKI = tyrosine kinase inhibitor; TTD = time to treatment discontinuation; TTSP = time to symptomatic progression; TTST = time to subsequent treatment; UK = United Kingdom			

2.1 Population

The population defined in the NICE final scope is:² *“Adults with untreated, locally advanced or metastatic NSCLC with an EGFR exon 20 insertion mutation.”* The population in the company submission (CS) decision problem (DP) is:¹ *“First-line treatment of adult patients with advanced NSCLC with activating EGFR Exon 20 insertion mutations.”* Therefore, the scope of the population in the DP in the CS is narrower than the population which was defined in the National Institute for Health and Care Excellence (NICE) final scope.

EAG comment: In the clarification letter the Evidence Assessment Group (EAG) pointed out that in terms of the rationale which was provided for not assessing subgroups of patients based on histology type, Table 1 of the CS stated that:³ *“The PAPILLON trial excludes squamous non-small cell lung cancer (NSCLC) and, since 99% of the trial population was of adenocarcinoma histology type, these subgroups could not be explored”*. However, the population defined in the NICE final scope was *“Adults with untreated, locally advanced or metastatic NSCLC with an epidermal growth factor receptor (EGFR) exon 20 insertion mutation.”*, which includes both squamous and non-squamous histology. The EAG therefore requested the company to provide further justification for the exclusion of squamous non-small cell lung cancer (NSCLC) in the CS, given that this was not specified in the NICE final scope.

In responding to the EAG’s request, the company made the following statement:⁴ *“The pivotal, Phase 3 PAPILLON clinical trial included patients with histologically or cytologically confirmed, locally advanced or metastatic, non-squamous NSCLC with documented primary EGFR Exon20 insertion activating mutations.2 The trial excluded patients with squamous histology as EGFR mutations are very rare in squamous-cell lung cancer.3 A European real-world study (assessing patients from 2015 to 2020) using data collected from the ESME database showed that, out of 19,759 patients screened, only 602 has squamous histology (3.05%). Non-squamous and adenocarcinoma of the lung are used interchangeably, and it is in this patient population where EGFR Exon20insertion mutations have been identified. Hence the PAPILLON trial only included patients with non-squamous histology. Johnson & Johnson have therefore aligned the CS to the population in the pivotal PAPILLON trial and as such, excluded patients with squamous histology.”* The company went on to state:⁴ *“Squamous histology is excluded from the decision problem as patients with squamous lung cancer were not included in the PAPILLON trial population. Johnson & Johnson can therefore confirm that the decision problem excludes patients with squamous histology, in line with the population within the CS.”*

It therefore appears to be the case that the DP should be updated to exclude squamous histology and therefore this is a key issue.

2.2 Intervention

The intervention defined in the NICE final scope is amivantamab in combination with carboplatin and pemetrexed. The intervention (amivantamab in combination with carboplatin and pemetrexed) addressed in the decision problem is in line with the NICE final scope.

EAG comment: The EAG considers that the intervention is in line with the NICE final scope.

2.3 Comparators

The description of the comparators in the NICE final scope is as follows:²

- “Chemotherapy such as docetaxel, gemcitabine, paclitaxel or vinorelbine in combination with a platinum drug (carboplatin or cisplatin), with or without pemetrexed maintenance treatment
- Pembrolizumab (monotherapy or in combination with chemotherapy according to PD-L1 expression)
- Atezolizumab
- TKIs (gefitinib, erlotinib, afatinib, dacomitinib, osimertinib and osimertinib with chemotherapy [subject to NICE appraisal])”

However, the DP lists the following comparators:

- Carboplatin with pemetrexed
- Pembrolizumab with carboplatin and pemetrexed
- Pembrolizumab monotherapy
- UK real-world evidence (RWE) (collected from the National Cancer Registration and Analysis Service [NCRAS] dataset) – as scenario.

EAG comment: In the request for clarification, the EAG stated that the DP (Table 1) lists pembrolizumab monotherapy as a comparator, but this is not included in the cost effectiveness analysis.³ Table 1 also includes carboplatin with pemetrexed, but excludes any other chemotherapy on the basis of clinical expert opinion. Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are also excluded on the basis of clinical expert opinion. However, the English data from the NECTAR study (Table 3 of the Study Report) showed 21.7% immuno-monotherapy and 8.7% TKI use, and three clinical expert opinions (included in the June 2023 advisory board) stated that atezolizumab, bevacizumab, carboplatin and paclitaxel (ABCP) combination therapy was used (10%-20%).⁵ On the basis that limited use is not the same as no use and that any treatment used in clinical practice should be a comparator, the company were asked to include pembrolizumab monotherapy and all forms of chemotherapy in clinical practice in all clinical and cost effectiveness analyses. In response, the company cited clinical expert opinion from three advisory boards, June 2023, May 2024 and August 2024 to support the exclusion of all forms of chemotherapy other than carboplatin plus pemetrexed. The company stated that ABCP could be excluded because it was only mentioned in the survey ahead of the first advisory board and apparently it was not discussed in the actual meeting. However, the EAG notes that only the report for the final advisory board reported the actual questions asked or individual clinical expert responses and none asked specifically about ABCP. It is also unclear what the degree of overlap is between the advisors who completed the survey for and attended the first meeting and those who attended the subsequent meetings.⁶⁻⁸ It does appear to the EAG that ABCP cannot be ruled out as a comparator on the basis of clinical expert opinion. The EAG considered that it should also not be excluded according to the NECTAR study, given that Table 3 of the report shows that 17.4% of patients in England received “Platinum+IO”.⁵ However, in the FAC the company explained that this category excluded anti-VEGF treatment and that there was no use of ABCP reported in the NECTAR study.⁹

In relation to pembrolizumab monotherapy, in response to the request for clarification the company argued that the NECTAR study data are too few and too old (diagnosis up to 2021) and so clinical expert opinion has to be used instead to guide choice of comparator.⁴ The EAG note that monotherapy was not listed in the survey for the first advisory board.⁸ In the second and third meeting reports it is stated respectively:^{6,7} “Advisors aligned on a consensus that IO monotherapy was not used in practice

and should not constitute a comparator to amivantamab.” and “The clinical experts agreed that prescribing IO monotherapy and epidermal growth factor receptor (EGFR) tyrosine-kinase inhibitors (TKIs) are not considered best practice...”. In the third meeting report it is also stated that: “However, some clinicians’ primary specialty is not lung cancer and thus these regimens may be prescribed due to a lack of knowledge of this specific mutation.” Nevertheless, the company conducted a cost effectiveness analysis with pembrolizumab monotherapy as comparator (see Section 4 of this report).

The EAG clinical expert completed a table that indicated the following treatments used in clinical practice to be carboplatin with pemetrexed (60%), carboplatin or cisplatin (10%) and pembrolizumab with carboplatin and pemetrexed (30%). This is consistent with the CS, other than the use of platinum therapy alone. In conclusion, given some uncertainty, the choice of comparators is included as a key issue, although, if ABCP is used in clinical practice then evidence as to its effectiveness will need to be sought. Also, there are almost no data on the effectiveness of platinum therapy with only one patient having been reported to have received it in the NECTAR study and only in the United States (US) part of the database.⁵

2.4 Outcomes

The NICE final scope lists the following outcome measures:²

- Overall survival (OS)
- Progression-free survival (PFS)
- Overall response rate (ORR)
- Time to subsequent treatment (TTST)
- Adverse effects of treatment
- Health-related quality of life (HRQoL).

The outcome measures included in the CS were consistent with those specified by the NICE final scope.¹

2.5 Other relevant factors

The CS included equality issues pertaining to stigma, ethnicity, along with the gap in treatment options and outcomes between patients with EGFR Exon20 mutations versus patients with common EGFR mutations. These are detailed within Sections A3, A.1.6, B.1.3.2.2 and B.1.4 of the CS.¹

3. Clinical effectiveness

3.1 Critique of the methods of review(s)

The company performed a systematic review (SR) to identify and summarise the available randomised controlled trial (RCT) and RWE relating to the efficacy and safety of amivantamab in combination with carboplatin and pemetrexed for the first-line treatment of adult patients with advanced NSCLC with activating EGFR exon 20 insertion mutations.

3.1.1 Searches

The following paragraphs contain summaries and critiques of the searches related to clinical effectiveness presented in the CS.¹ The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence-based checklist for the Peer Review of Electronic Search Strategies (PRESS) was used to inform this critique.¹⁰ The EAG has presented only the major limitations of each search strategy in the report.

Appendix D of the CS details the systematic literature review (SLR) conducted to identify relevant clinical evidence and safety outcomes in patients with advanced EGFR exon 20 insertion mutated NSCLC.¹¹ The searches were conducted in January 2021, and updated in September 2021, February 2022, September 2023, March 2024 and June 2024.

A summary of the sources searched is provided in Table 3.1.

Table 3.1: Data sources for the clinical effectiveness systematic review (as reported in CS)

Resource	Host/Source	Date Ranges	Date searched
Electronic databases			
MEDLINE (inc. In Process & Other Non-Indexed Citations and Daily)	Ovid	1946-25.6.24	January 2021 September 2021
Embase	Ovid	1974-25.6.24	February 2022
CENTRAL	Cochrane Library	to Issue 5/12 2024	September 2023 March 2024
CDSR	Cochrane Library	to Issue 6/12 2024	June 2024
DARE	CRD website	to Issue 2/4, March 2015	
Conferences			
AACR Annual Meeting	Internet	2018-2024	January 2021
ASCO Annual Meeting		2018-2024	September 2021
ESMO Congress		2018-2024	February 2022
ESMO Asia Congress		2018-2023	September 2023
IASLC WCLC		2018-2023	March 2024
ELCC		2018-2023	June 2024
ISPOR international meeting		2024	
Trials registries			
ClinicalTrials.gov	Internet	all years	January 2021 September 2021

Resource	Host/Source	Date Ranges	Date searched
			February 2022 September 2023 March 2024 June 2024
AACR = American Association for Cancer Research; ASCO = American Society of Clinical Oncology; CDSR = Cochrane Database of Systematic Reviews; CENTRAL = Cochrane Central Register of Controlled Trials; CRD = Centre for Reviews and Dissemination; CS = company submission; DARE = Database of Abstracts of Reviews of Effects; ELCC = European Lung Cancer Annual Congress; ESMO = European Society of Medical Oncology; IASLC WCLC = International Association for the Study of Lung Cancer World Conference on Lung Cancer; ISPOR = International Society for Pharmacoeconomics and Outcomes Research			

EAG comment:

- Searches were undertaken in January 2021, September 2021, February 2022, September 2023, March 2024 and June 2024 to identify clinical evidence and safety outcomes in patients with advanced EGFR exon 20 insertion mutated NSCLC. The CS, Appendix D and the company's response to the request for clarification provided sufficient details for the EAG to appraise the literature searches.^{3, 4, 11}
- A good range of bibliographic databases, conferences and trials registries were searched. Reference checking was conducted. The search documentation was clear and concise, and the searches were well structured, transparent and reproducible.
- The database searches for the clinical effectiveness SLR combined facets for EGFR+ NSCLC. In the Embase and MEDLINE searches, this was then combined with a study design filter for clinical trials. Referenced study design filters were used. From September 2023, exon 20 insertion specific terms were added to the disease area terms, to ensure all relevant publications were captured. Animal-only studies were excluded.
- Database searches were not limited by date or language of publication.
- Conference proceedings were handsearched for seven key international conferences from 2018 to date. Embase was also searched for conference proceedings published between 2018 and 2024.

3.1.2 Inclusion criteria

The company submission¹ states that an SLR was undertaken in January 2021 to identify relevant evidence on clinical efficacy and safety outcomes in patients with EGFR exon 20 insertion mutation-positive advanced NSCLC. The process for the identification and appraisal of the evidence base in this submission is summarised in this section. The SLR was subsequently updated in September 2021, February 2022, September 2023, March 2024, and June 2024 to ensure recently published relevant evidence has been identified.

The eligibility criteria used in the search strategy for randomised controlled trials (RCTs) and non-RCTs is presented in Table 3.2 below.

Screening of records at both title and abstract stage, and at full text stage was conducted by two independent reviewers with any disagreements resolved by consensus or the intervention of a third reviewer. This represents the optimal approach for reducing the likelihood of error or bias. The EAG asked the company to provide details on how the discrepancies between the two reviewers were resolved for quality assessment of the included studies. As the SLR updated overtime, EAG also request the company to confirm whether the process of study selection, data extraction and quality assessment were the same for each updated version of the systematic review.

Table 3.2: Eligibility criteria used in search strategy for RCT and non-RCT evidence

	Inclusion	Exclusion
Population	Adult (≥ 18 years old) patients with locally advanced or metastatic NSCLC with exon 20 insertion mutations who are not amenable to curative therapy including surgical resection or chemoradiation, specifically: • Patient populations where at least 85% of the cohort has adenocarcinoma^a Subgroups: Stratifications by treatment setting • 1L (PAPILLON and MARIPOSA-1 indications)^b ○ Studies where participants have not received any prior systemic treatment at any time for locally advanced Stage III or metastatic Stage IV disease (adjuvant or neoadjuvant therapy for Stage I or II disease is allowed, if administered more than 12 months prior to the development of locally advanced or metastatic disease) • 2L+ (CHRYSLIS indication) • 2L+ further stratified to include post-3G TKI (MARIPOSA-2 indication; e.g., C797S mutation) and acquired TKI resistance (e.g., T790M)	• Patients < 18 years old • Patients with lung cancer not otherwise specified • Patients with $< 85\%$ adenocarcinoma or NSCLC not otherwise defined • Patients without metastatic or unresectable NSCLC or studies where outcomes are not presented separately for the patients of interest • Patients with surgically resectable or early stage I/II disease
Interventions	Any therapeutic or palliative intervention administered within the healthcare system	Non-therapeutic or -palliative interventions
Comparator	• Placebo or SoC • Any comparator if also an intervention of interest	N/A

	Inclusion	Exclusion
Outcomes	Clinical efficacy outcomes, including: • OS; PFS; PFS2; DFS; RFS • ORR; DCR; CBR; DOR; CR; PR; SD • TTNT; TTP; TTSP; CNS outcomes Safety outcomes, including: • AEs; SAEs; WDAEs; AESIs; Grade 3+ AEs; mortality PROs, including HRQoL e.g., as measured by including not limited to: • NSCLC-SAQ; SF-36; PGIS; PGIC; EORTC QLQ C-30; PROMIS-PF; EQ-5D	• No relevant outcomes • Epidemiological outcomes, such as incidence/prevalence, natural history, co-morbidity, morbidity, and mortality • Economic outcomes such as cost effectiveness, direct costs, indirect costs, and resource utilisation
Study design	All treatment settings • RCTs (phase I, II, III, IV) 2L+ post-osimertinib (or any 3G TKI) setting or patients with ex20ins • Non-randomised interventional studies (including compassionate use programmes and post-hoc pooled analyses) • Observational studies e.g., cohort studies, case-control studies, chart reviews, case series • Real-world evidence	Any other study designs, including economic models and trial-based economic analyses
Publication type	• Original peer reviewed research • Conference abstracts published in or after 2020 • Letters if reporting primary research	• Any other publication type, including studies not reporting any original research and non-peer-reviewed (e.g., narrative reviews, case studies) • SLR/NMAs unless they present original research (N.B. will be included for hand-searching and a list of SLRs will be provided) • Congress abstracts published before 2020
Location	Any location, focused on OECD countries	N/A
Language restrictions	English language (abstract or full text)	Not in English language

	Inclusion	Exclusion
Based on Table 29 of the Appendices Amivantamab ¹¹		
^a For studies that did not clearly report whether patients had adenocarcinoma, this was inferred where possible, based on the context of the study (for example, the treatments received). If no information was provided, the study was included.		
^b Key eligibility criteria for PAPILLON and MARIPOSA are included in this table. The MARIPOSA indication refers to the first-line treatment of advanced NSCLC with common EGFR mutations.		
1L = first-line; AE = adverse event; AESI = adverse event of special interest; CBR = clinical benefit rate; CNS = central nervous system; CR = complete response; DCR = disease control rate; DFS = disease free survival; DOR = duration of response; EORTC QLQ C-30 = European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30; EQ-5D = EuroQol 5 Dimensions; HRQoL = health-related quality of life; N/A = not applicable; (N)MA = (network) meta-analysis; NSCLC = non-small cell lung cancer; NSCLC-SAQ = Non-Small Cell Lung Cancer Symptom Assessment Questionnaire; OECD = Organisation for Economic Co-operation and Development; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PFS2 = time to second progression; PGIC = Patient Global Impression of Change Scale; PGIS = Patient's Global Impression of Severity; PR = partial response; PRO = patient-reported outcome; PROMIS-PF = Patient-Reported Outcomes Measurement Information System – Physical Function; RCT = randomised controlled/clinical trial; RFS = relapse/recurrent-free survival; SAE = serious adverse event; SD = stable disease; SF-36 = 36-Item Short Form Survey; SLR = systematic literature review; SoC = standard of care; TKI = tyrosine kinase inhibitor; TTNT = time to next treatment; TTP = time to progression; TTSP = time to symptomatic progression; WDAE: withdrawals due to adverse event		

3.1.3 Critique of data extraction

According to the CS¹, the data extraction was performed in line with guidelines from the University of York Centre for Reviews and Dissemination (CRD). Data extraction was conducted by two independent analysts. Any disputes were resolved by consensus or by a third reviewer. This is an optimal method for data extraction and reduces likelihood of error or bias.

3.1.4 Quality assessment

Based on the Appendix D¹¹, the company stated that the quality of all included RCTs was assessed using the quality assessment tool developed by the University of York CRD, as recommended by NICE. The quality of included non-randomised interventional studies and observational studies was assessed using the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool. The quality assessment was completed by one individual and verified by a second individual. If necessary, a third individual arbitrated the final decision. In Appendix D¹¹, the quality appraisal results for three RCT studies using the York CRD quality assessment checklist and 58 included non-RCTs using the ROBINS-I tool were included.

3.1.5 Evidence synthesis

The CS states that pairwise meta-analysis was not undertaken because data from a direct comparison between amivantamab plus chemotherapy versus chemotherapy for the population of interest was only available from the PAPILLON RCT.¹ However, data from other real world databases associated with relevant comparators were combined with the data of the PAPILLON trial in an indirect treatment comparison (ITC) analysis. Further details are provided in Section 3.3 of this report.

3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Study retrieval

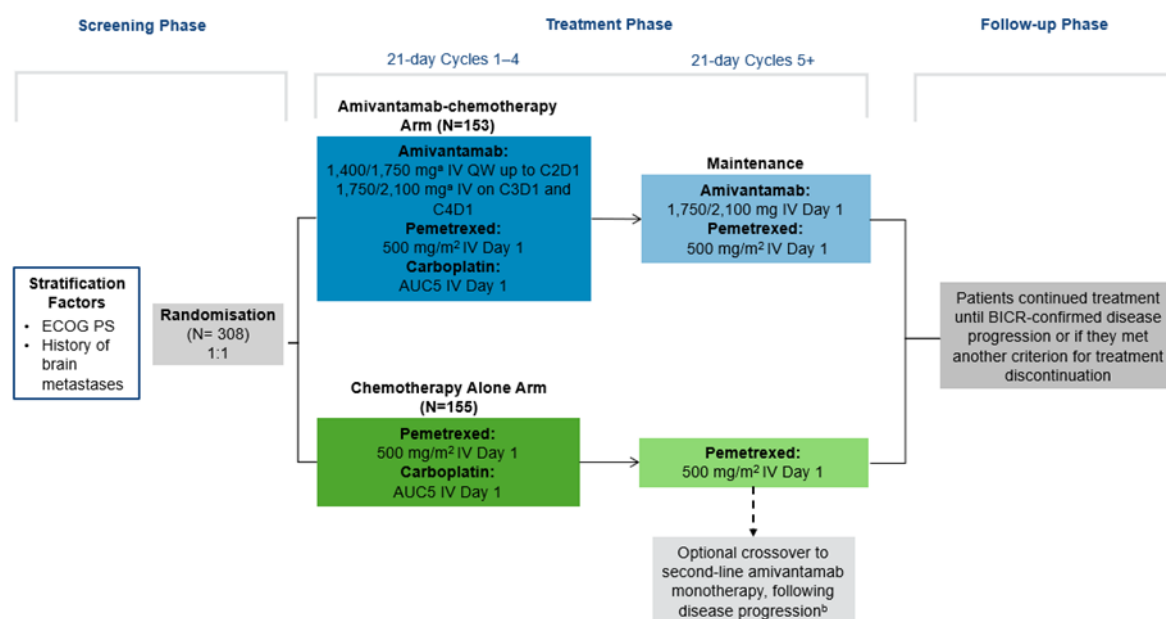
The flow of evidence identification and selection are presented in Appendix D¹¹, with the Preferred reporting items for systematic reviews and meta-analyses (PRISMA) diagram for the final SLR update only (June 2024).

In the original SLR of January 2021, a total of 9,811 records were retrieved by the electronic database searches, of which 2,927 were duplicates, resulting in 6,884 novel records that were screened at the title/abstract review stage against the eligibility criteria. Subsequently, 2,401 full publications were screened against the eligibility criteria at full text review. A total of 217 records were found to fulfil the eligibility criteria for the SLR. A further 52 records were considered identified and included in the SLR from the supplementary searches.

Across the original SLR and all SLR updates (the first SLR update (September 2021), second SLR update (February 2022), third SLR update (September 2023), fourth SLR update (March 2024) and fifth SLR update (June 2024)), a total of 257 publications reporting on 134 unique studies were included in the SLR. Of these studies, 91 publications reporting on 60 unique studies investigated treatment in the first-line setting for EGFR exon 20 insertion mutation-positive NSCLC.

3.2.2 Details of the PAPILLON trial

The CS¹ states that the PAPILLON trial is an “ongoing, randomised, open-label, multicentre, Phase 3 study which compares amivantamab in combination with carboplatin and pemetrexed (hereafter referred to as the amivantamab-chemotherapy arm) versus carboplatin with chemotherapy (the chemotherapy arm) for patients with treatment-naïve, locally advanced or metastatic EGFR Exon20 insertion mutation-positive NSCLC.” A computer-generated randomisation schedule was used to randomly assign patients in a 1:1 ratio to receive either amivantamab-chemotherapy or chemotherapy in 21-day cycles.

Figure 3.1: Design of the registrational PAPILLON trial (NCT04538664)

Based on Figure 7 of the CS¹

Source: Zhou et al. 2023¹²

^a Doses are shown by body weight (<80 kg/≥80 kg).

^b Treatment crossover was only permitted following confirmation of disease progression by BICR; dosing for second-line amivantamab monotherapy is the same as in the main treatment phase of the study.

AUC = area under the curve; BICR = blinded independent central review; C = Cycle; D = Day; ECOG = Eastern Cooperative Oncology Group; IV = intravenous; PS = performance status; QW = once a week

As illustrated in Figure 3.1, the PAPILLON trial was comprised of three phases – screening phase, treatment phase and follow-up phase. Screening occurred 28 days before randomisation where patients were stratified and randomly allocated to either the amivantamab-chemotherapy arm or chemotherapy arm.

The treatment phase commenced at cycle 1 day 1 and as stated in the CS “*continued in 21-day cycles until the ‘end of treatment’ visit*”, which was approximately 30 days after discontinuation of study treatment.¹ Patients could stop study treatment upon documented disease progression (based on Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 criteria and confirmed by an independent review). However, treatment could continue after disease progression with approval from the medical monitor, if the investigator believed the patient was still benefiting.

Patients who stopped their study treatment were monitored for subsequent therapy, disease status, survival, and symptomatic progression during the follow-up phase. This phase began after the end of treatment visit and continued until the study ended, the patient died, was lost to follow-up, or withdrew consent.

The CS stated that “*Patients were permitted to treatment switch to amivantamab monotherapy between [] and [] days after their last dose of chemotherapy.*” The switch phase was not randomised or controlled, but study assessments and procedures largely followed those of the randomised phase.

3.2.3 Trial methodology

The PAPILLON trial methodology is presented in Table 3.3.

Table 3.3: Summary of the PAPILLON trial methodology

Trial name	PAPILLON (NCT04538664)
Location	International: 131 sites across 25 countries, including three UK sites
Trial design	Phase 3, randomised, open-label, multicentre study
Population	Adult patients (aged ≥ 18 years) with treatment-naïve locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations
Eligibility criteria for patients	Key inclusion criteria: Adult patients (≥ 18 years of age) Histologically- or cytologically-confirmed locally advanced or metastatic, non-squamous NSCLC with documented primary EGFR exon 20 insertion mutations Must have measurable disease according to RECIST v1.1 An ECOG performance status of 0 or 1 Adequate organ and bone marrow function, as assessed by laboratory measurements of haemoglobin, absolute neutrophil count, platelets, alanine aminotransferase, aspartate aminotransferase, total bilirubin and serum creatine Key exclusion criteria: Have received prior systemic treatment for locally advanced or metastatic disease (with the exception of a few regimens outlined in the protocol) Evidence of synchronous NSCLC disease (as suggested by genetic characterisation or radiographic appearance) Untreated or active brain metastases History of leptomeningeal disease A history of spinal cord compression that has not been treated definitively with surgery or radiation Uncontrolled tumour-related pain Medical history of ILD, including drug-induced ILD, or radiation pneumonitis An active malignancy other than the disease being treated under the study A history of clinically significant cardiovascular disease Positive hepatitis B, C, or other clinically active infectious liver disease at screening Received an investigational drug (not including anti-cancer therapy) within six weeks before randomisation or had major surgery within four weeks of randomisation Uncontrolled inter-current illness The full list of inclusion and exclusion criteria are presented in the PAPILLON protocol.
Study intervention and administration	Amivantamab administered in combination with carboplatin and pemetrexed, with all components administered via IV infusion at the following doses: Amivantamab 1,400 mg (1,750 mg if body weight is ≥ 80 kg) by IV infusion once weekly from Weeks 1 to 4

	Week 1 – split infusion on Day 1 and Day 2 Weeks 2 to 4 – infusion on Day 1 1,750 mg (2,100 mg if body weight is ≥ 80 kg) every three weeks starting at Week 7 onwards Pemetrexed 500 mg/m² (with vitamin supplementation) on Day 1 of each 21-day cycle Given in combination with carboplatin for the first four cycles, and then as maintenance monotherapy until disease progression Carboplatin Carboplatin AUC5 on Day 1 of each 21-day cycle, for up to four cycles
Comparator(s)	Carboplatin and pemetrexed chemotherapy, administered as outlined above and as per clinical practice guidelines
Permitted and disallowed concomitant medication	Investigators were allowed to prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care, except for those listed as prohibited therapies (see below). Corticosteroids, folic acid and vitamin B12, were administered concomitantly with pemetrexed according to local prescribing information or per standard local practice. Further medications allowed or disallowed before and during the study are described below: Allowed: Symptomatic treatment of related toxicities Prophylactic medications Leucocyte-depleted blood transfusions at any time after randomisation Prohibited: Any chemotherapy, anti-cancer therapy, or experimental therapy (other than study treatments): Radiotherapy to tumour lesions being assessed for tumour response prior to radiographic progression Use of live attenuated vaccines Use of phenytoin or fosphenytoin with carboplatin For further detail on the permitted, prohibited, or restricted concomitant medication, refer to the PAPILLON protocol.
Primary outcome	PFS assessed by BICR
Secondary and exploratory outcomes	Secondary outcomes assessed in the PAPILLON trial were: ORR DOR OS TTST PFS2 TTSP EORTC QLQ-C30 PROMIS-PF The following exploratory outcomes were also assessed: TTD EQ-5D-5L A broad range of safety outcomes were analysed including: TEAEs TEAEs leading to death or discontinuation of any study treatment Serious adverse event (SAEs)

	Infusion-related reactions
Pre-specified subgroups	Age: <65 versus ≥65 years and <75 versus ≥75 years Sex: male versus female Race: people of Asian ethnicity versus non-Asian ethnicity (patients with unknown race were not included in this subgroup analysis) Weight: <80 kg and ≥80 kg History of brain metastasis: yes versus no Baseline ECOG performance status: 0 versus 1 History of smoking: yes versus no
Based on Table 4 of the CS ¹ AUC = area under the concentration-time curve; BICR = blinded independent central review; CS = company submission; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D-5L = EuroQol-5 Dimensions-5 Levels; ILD = interstitial lung disease; IV = intravenous; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PROMIS-PF = Patient-Reported Outcomes Measurement Information System – Physical Function; PFS = progression-free survival; PFS2 = progression-free survival after first subsequent therapy; RECIST = Response Evaluation Criteria in Solid Tumours; SAE = serious adverse event; TEAE = treatment-emergent adverse event; TTD = time to treatment discontinuation; TTSP = time to symptomatic progression; TTST = time to subsequent treatment; UK = United Kingdom Source: Johnson & Johnson PAPILLON CSR 2023. ¹³ Johnson & Johnson PAPILLON Clinical Trial Protocol. ¹⁴	

3.2.4 Analysis sets

At the 3 May 2023 data cut-off (DCO), 65 patients had switched from chemotherapy to amivantamab monotherapy after confirmed disease progression. By the 31 October 2023 DCO, this number had increased to 78 patients, representing ■ of those patients who experienced disease progression. All analysis sets are presented in Table 3.4.

Table 3.4: Primary trial populations used for the analysis of outcomes from the PAPILLON trial

Analysis set	Number analysed	Definition
Full analysis set	Amivantamab-chemotherapy: N=153 Chemotherapy: N=155	All randomised patients, classified according to their assigned treatment arm regardless of the actual treatment received
Safety analysis set	Amivantamab-chemotherapy: N=151 Chemotherapy: N=155	Randomised patients who received at least one dose of study treatment
Crossover analysis set	N=65 (3 May 2023 DCO) N=78 (31 October 2023 DCO)	Patients originally randomised to the chemotherapy arm who switched to receive at least one dose of amivantamab monotherapy following BICR-confirmed disease progression
Patient-reported outcomes analysis set	N/A ^a	Randomised patients who received at least one dose of study treatment and have at least one evaluable postbaseline patient-reported outcome measurement

Based on Table 5 of the CS¹

Source: Johnson & Johnson PAPILLON CSR 2023 (Page 4).¹³

Analysis set	Number analysed	Definition
^a Patient numbers for the patient-reported outcomes set are dependent on timepoint and specific endpoint explored in the PAPILLON trial. BICR = blinded independent central review; CS = company submission; DCO = data cut-off; N/A = not available		

3.2.5 Endpoint definitions

Table 3.5 outlines the definitions of the key primary, secondary, and exploratory endpoints from the PAPILLON trial presented in this submission.

Table 3.5: Summary of endpoint definitions from the PAPILLON trial

Endpoint	Definition
Primary endpoint	
PFS (assessed by BICR)	The time from randomisation until the date of objective disease progression (assessed by BICR [primary endpoint] and by the treating investigator) using RECIST v1.1 or death (by any cause in the absence of progression), whichever comes first
Secondary endpoints	
ORR	The percentage of patients with best response of complete response (CR) or partial response (PR), as defined by RECIST v1.1
DOR	The time from the date of first documented response (CR or PR) until the date of documented progression or death from any cause, whichever comes first
OS	The time from the date of randomisation until the date of death due to any cause
TTST^a	The time from the date of randomisation to the start date of the subsequent anti-cancer therapy following study treatment discontinuation or death, whichever comes first
PFS2	The time from randomisation to the earliest of the progression event subsequent to that used for the primary variable PFS or death after starting the next line of treatment
TTSP	The time from randomisation to documentation in the electronic case report form (eCRF) of any of the following (whichever occurs earlier): onset of new symptoms, or, symptom worsening, that is considered by the investigator to be related to lung cancer and requires either a change in anticancer treatment and/or clinical intervention to manage symptoms
EORTC QLQ-C30	Measurement of cancer patients' symptoms and functioning for all cancer types
PROMIS-PF	Assessment of physical function, including upper, central, and lower extremity functions and instrumental activities of daily living
Exploratory endpoints	
TTD	The time from randomisation to discontinuation of all study treatments for any reason

Endpoint	Definition
EQ-5D-5L	Measurement of health state and health utility
Based on Table 6 of the CS ¹ BICR = blinded independent central review; CR = complete response; CS = company submission; DOR = duration of response; eCRF = electronic case report form, EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D-5L = EuroQol-5 Dimensions-5 Levels; ORR = objective response rate; OS = overall survival; PROMIS-PF = Patient-Reported Outcomes Measurement Information System – Physical Function; PFS = progression-free survival; PFS2 = progression-free survival after first subsequent therapy; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumours; TTD = time to treatment discontinuation; TTSP = time to symptomatic progression; TTST = time to subsequent treatment	

3.2.6 Baseline characteristics

Baseline demographic and clinical characteristics of patients in the PAPILLON trial, comparing the amivantamab-chemotherapy and chemotherapy arms are presented in Table 3.6, Table 3.7 and Table 3.8, respectively. The characteristics between the two treatment arms were generally well-balanced in terms of age, sex, smoking history, and cancer stage at diagnosis. For instance, the median age was similar (61.0 and 62.0 years), and gender was nearly balanced, though there was a slightly higher percentage of females in the chemotherapy arm (60.0%) compared to the amivantamab-chemotherapy arm (55.6%).

Ethnic composition showed a higher representation of Asian patients in both treatment arms (64.2% in the amivantamab-chemotherapy arm and 58.6% in the chemotherapy arm). Both arms had a small percentage of patients with prior EGFR TKI treatment, which was eventually excluded as a stratification factor due to the low numbers. The majority of patients were diagnosed with adenocarcinoma (98.7%) and Stage IV disease (approximately 81.2% - 86.9% at initial diagnosis).

Comparisons were also made with UK RWE data, which identified 24 patients with similar characteristics to the trial patients. However, a significantly lower proportion of Asian patients was found in the UK cohort (■■■■), underscoring a key demographic difference.

Table 3.6: Summary of patient demographics and baseline characteristics; full analysis set (N=308)

Characteristic	Amivantamab-chemotherapy (N=153)	Chemotherapy (N=155)
Age, years		
Mean (SD)	59.3 (11.9)	60.0 (12.0)
Median (range)	61.0 (27–86)	62.0 (30–92)
<65, n (%)	97 (63.4)	92 (59.3)
65 to <75, n (%)	44 (28.8)	48 (31.0)
≥75, n (%)	12 (7.8)	15 (9.7)
Sex, n (%)		
Female	85 (55.6)	93 (60.0)
Male	68 (44.4)	62 (40.0)
Race, n (%)^a		
N	151	152

Characteristic	Amivantamab-chemotherapy (N=153)	Chemotherapy (N=155)
American Indian or Alaska Native	1 (0.7)	2 (1.3)
Asian	97 (64.2)	89 (58.6)
Black or African American	2 (1.3)	0
White	49 (32.5)	60 (39.5)
Multiple ^b	1 (0.7)	0
Unknown	1 (0.7)	1 (0.7)
Weight, kg		
Mean (SD)	63.8 (14.6)	67.7 (14.0)
Median (range)	61.8 (39–127)	66.5 (37–112)
<80, n (%)	132 (86.3)	128 (82.6)
≥80, n (%)	21 (13.7)	27 (17.4)
Body mass index, kg/m²		
Mean (SD)	23.6 (4.1)	25.0 (4.6)
Median (range)	23.4 (16–39)	24.2 (16–43)
History of smoking, n (%)		
Yes	65 (42.5)	64 (41.3)
No	88 (57.5)	91 (58.7)
Based on Table 7 of the CS ¹ Source: EMA. Rybrevant EPAR assessment report (Table 13). ¹⁵ Zhou et al. 2023 ¹² ^a Race or ethnic group was reported by the patients. In some regions, reporting of race was not required. ^b Multiple includes one patient who selected Black or African American and White. CS = company submission; SD = standard deviation		

Table 3.7: Summary of baseline patient clinical disease characteristics; full analysis set (N=308)

Characteristic	Amivantamab-chemotherapy (N=153)	Chemotherapy (N=155)
History of brain metastasis, n (%)		
N	153	155
No	118 (77.1)	119 (76.8)
Yes	35 (22.9)	36 (23.2)
Prior EGFR TKI use, n (%)		
No	152 (99.3)	152 (98.1)
Yes	1 (0.7)	3 (1.9)
ECOG performance status, n (%)		
N	153	155
0	54 (35.3)	55 (35.5)
1	99 (64.7)	100 (64.5)
Initial diagnosis NSCLC subtype, n (%)		
N	153	155

Characteristic	Amivantamab-chemotherapy (N=153)	Chemotherapy (N=155)
Adenocarcinoma	151 (98.7)	153 (98.7)
Large cell carcinoma	0	1 (0.6)
Squamous cell carcinoma	0	0
Other	2 (1.3)	1 (0.6)
Histology grade at initial diagnosis, n (%)^a		
n	146	142
Poorly differentiated	24 (16.4)	17 (12.0)
Moderately differentiated	27 (18.5)	27 (19.0)
Well differentiated	11 (7.5)	8 (5.6)
Other	84 (57.5)	90 (63.4)
Cancer stage at initial diagnosis, n (%)		
n	153	149
IA	2 (1.3)	4 (2.7)
IB	4 (2.6)	6 (4.0)
IIA	0	1 (0.7)
IIB	1 (0.7)	5 (3.4)
IIIA	5 (3.3)	5 (3.4)
IIIB	7 (4.6)	5 (3.4)
IIIC	1 (0.7)	2 (1.3)
IVA	62 (40.5)	54 (36.2)
IVB	71 (46.4)	67 (45.0)
Cancer stage at screening, n (%)		
N	153	155
IIIB	3 (2.0)	0
IIIC	1 (0.7)	0
IVA	67 (43.8)	70 (45.2)
IVB	82 (53.6)	85 (54.8)
Location of metastasis at screening, n (%)^b		
n	151	153
Bone	71 (47.0)	80 (52.3)
Liver	18 (11.9)	31 (20.3)
Brain	35 (23.2)	36 (23.5)
Lymph Node	102 (67.5)	114 (74.5)
Adrenal Gland	10 (6.6)	19 (12.4)
Lung	113 (74.8)	120 (78.4)
Other	71 (47.0)	64 (41.8)
Time since initial lung cancer diagnosis, months		
N	153	155

Characteristic	Amivantamab-chemotherapy (N=153)	Chemotherapy (N=155)
Mean (SD)	5.89 (14.5)	8.49 (18.1)
Median (range)	1.77 (0.5–80.8)	1.84 (0.6–95.9)
Time since metastatic disease diagnosis, months		
n	151	154
Mean (SD)	2.23 (3.799)	2.29 (3.088)
Median (range)	1.51 (0.2–40.0)	1.61 (0.3–30.7)
Based on Table 8 of the CS ¹ Source: EMA. Rybrevant EPAR assessment report (Table 13). ¹⁵ Zhou et al. (2023). ¹² ^a Other includes unknown histology grade. ^b Subjects can be counted in more than one category. CS =company submission; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; NSCLC = non-small cell lung cancer; SD = standard deviation; TKI = tyrosine kinase inhibitor		

Table 3.8: Prior therapies for lung cancer received by patients; safety analysis set (N=306)

Prior therapy, n (%)	Amivantamab-chemotherapy (N=151)	Chemotherapy (N=155)
Systemic therapy	8 (5.3)	14 (9.0)
Adjuvant	7 (4.5)	12 (7.9)
Neo-adjuvant	1 (0.6)	0
Palliative ^{a,c}	1 (0.6)	3 (2.0)
Radiotherapy	47 (31.1)	59 (38.1)
Cancer-related surgery ^b	151 (100.0)	155 (100.0)
EGFR TKI use	1 (0.7)	3 (1.9)
Based on Table 9 of the CS ¹ Source: EMA. Rybrevant EPAR assessment report (Table 13). ¹⁵ Zhou et al. 2023 ¹² ^a Palliative was defined as curative/palliative/any other intent. One patient received both adjuvant and palliative therapy. ^b Prior cancer-related surgery includes tumour biopsies performed for diagnosis. ^c One subject received both adjuvant and palliative therapy. CS = company submission; EGFR = epidermal growth factor receptor; TKI = tyrosine kinase inhibitor		

EAG comment: The overrepresentation of Asian patients (64.2% and 58.6% in the two arms) presents a significant limitation for external validity, especially in regions like England and Wales, where Asian ethnicity constitutes a much smaller percentage of the lung cancer population (██████ in the UK RWE data). This demographic difference may limit the generalisability of the trial's findings to Western populations, particularly in England and Wales. As treatment responses can vary across different ethnic groups due to genetic factors, this overrepresentation could skew the applicability of the results for populations with different ethnic compositions. Attempts were made in the CS¹ to validate trial findings by comparing them with UK RWE data, but the small sample size of only 24 patients in the UK cohort limits the strength of this comparison. Furthermore, the aforementioned clear ethnic disparity between the trial and the UK population weakens the conclusions drawn from this comparison. The lower proportion of Asian patients in the UK further highlights the demographic mismatch, raising concerns about the transferability of the trial outcomes to a UK setting, particularly England and Wales.

The low number of patients with prior EGFR TKI use (0.7% in the amivantamab-chemotherapy arm and 1.9% in the chemotherapy arm) reflects a strict inclusion criterion, which excluded most patients with prior targeted therapy. While this ensures the trial's internal validity for treatment-naïve patients, it limits its real-world applicability. In clinical practice, patients often receive multiple lines of therapy prior to the advanced setting before being treated with new agents like amivantamab, so the trial's exclusion of pre-treated patients may not accurately reflect real-world treatment pathways. Prior therapies were well-balanced between the arms, though the small number of patients receiving palliative or neoadjuvant therapy might affect the understanding of how prior treatments influence outcomes. Given that only a few patients had previously received EGFR TKIs, the trial cannot provide meaningful data on how amivantamab performs in a pre-treated population, which limits its relevance to many real-world patients who often undergo multiple therapies.

3.2.7 Baseline characteristics

The statistical methodologies used for the primary analysis of the PAPILLON trial are highlighted in Table 3.9.

Table 3.9: Statistical methods for the primary analysis of the PAPILLON trial

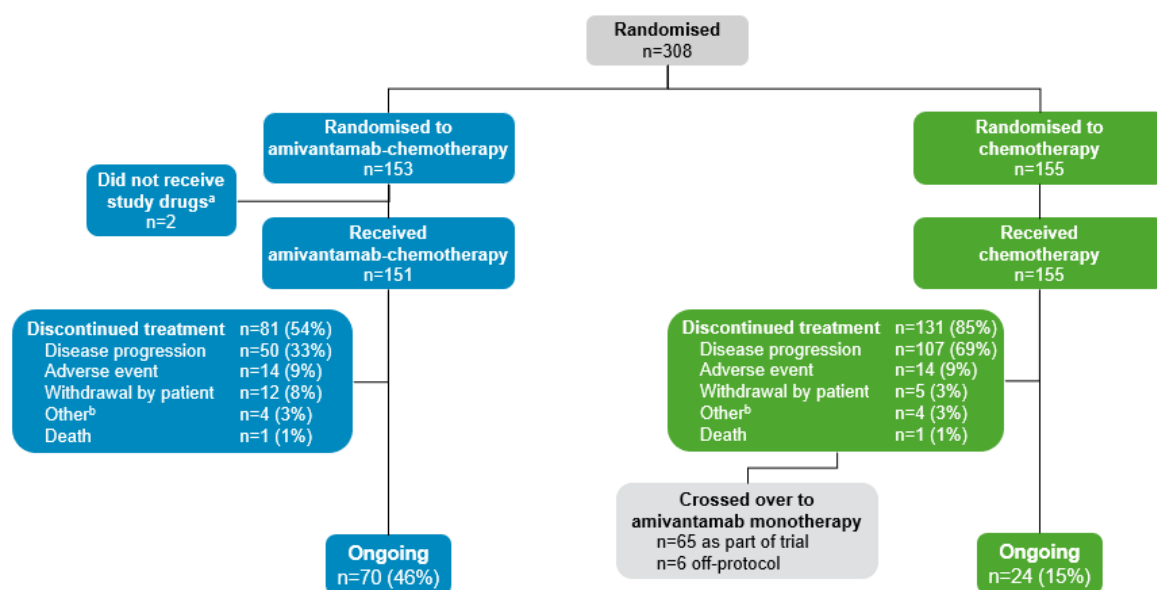
Hypothesis objective	The statistical hypothesis was that the addition of amivantamab to carboplatin and pemetrexed doublet chemotherapy would reduce the risk of either disease progression or death, as compared with carboplatin and pemetrexed, in patients with treatment-naïve, locally advanced or metastatic NSCLC characterised by EGFR exon 20 insertion mutations.
Statistical analysis	Primary endpoint analysis: PFS PFS was analysed using the full analysis set. The treatment effect of the amivantamab-chemotherapy arm was compared with the chemotherapy arm based on the log-rank test stratified by ECOG performance status (0 or 1) and history of brain metastases (yes or no), using the Breslow approach for handling ties. The p-value generated from the stratified log-rank test was used for the primary hypothesis testing. The HR and the corresponding 95% CI were estimated based on a stratified Cox's regression model, using the same stratification factors as for the log-rank test, with treatment as the sole explanatory variable. Patients who did not progress or die at the time of analysis were censored at the time of the latest date of their last evaluable RECIST v1.1 assessment. If the patient progressed or died after two or more consecutive missed disease assessments, the patient was censored at the time of the last evaluable RECIST v1.1 assessment. If the patient had no evaluable visits or did not have baseline data, they were censored at Day 1 unless they died within two visits of baseline. The median PFS with 95% CI was estimated using the Kaplan-Meier (KM) method. The KM PFS curve was plotted by treatment group. Additionally, PFS rates with 95% CI were estimated by the KM method at landmark timepoints (at 6-month, 12-month, and 18-month, etc.) and reported for each treatment group. The number and percentage of patients who had a PFS event or were censored were reported and reasons for PFS event and censoring were summarised. To control the overall type I error rate for the hypotheses testing of the primary and the secondary endpoints strongly at 5%, a sequential testing strategy was used. As per the protocol, if the testing for the primary endpoint of PFS was statistically significant, the key secondary endpoints of ORR and

	OS would be sequentially tested, each with an overall 2-sided alpha of 0.05. Additionally, the test for ORR was conducted before the test for OS. The primary PFS endpoint was assessed by BICR. Results for PFS assessed by the treating investigator are presented in Appendix M.1.2. Secondary endpoint analysis OS was analysed using a similar methodology and model as for the primary analysis of PFS for the full analysis set. Comparison between the two intervention groups was evaluated using the HR, with 95% CIs calculated from a Cox regression model in each subgroup. Any patient not known to have died at the time of analysis was censored based on the last recorded date on which the patient was known to be alive. ORR was analysed using a logistic regression model stratified by ECOG performance status (0 or 1) and history of brain metastases (yes or no). The results of the analysis were presented in terms of an odds ratio and associated 95% profile likelihood CIs and p-value. DOR was assessed by producing a KM plot and median DOR with 95% CI calculated from the KM estimate for each treatment group. TTST and TTSP were analysed using a similar method as the primary analysis of PFS in the full analysis set. PFS2 was analysed using a similar method to the primary analysis of PFS in the full analysis set. Statistical analyses used for PRO measures and tertiary endpoints in the PAPILLON trial are outlined in the statistical analysis plan (SAP) provided alongside this submission.
Sample size, power calculation	As per the SAP for the PAPILLON trial, a total of 200 PFS events provides approximately 90% power to detect an HR of 0.625, corresponding to at least three months improvement in median PFS (five months for chemotherapy and eight months for the combination of amivantamab with chemotherapy) with a log-rank test (two-sided alpha=0.05). Therefore, the total sample size needed for the study was approximately 300 patients (randomised to approximately 150 patients per treatment arm). The sample size calculation takes into consideration an annual dropout rate of 5%. Assuming a 15-month recruitment period, 200 PFS events were expected to occur approximately 18 months after the first patient was randomised
Based on Table 10 of the CS¹ Source: Johnson & Johnson PAPILLON SAP v2.¹⁶ BICR = blinded independent central review; CI = confidence interval; CS = company submission; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; HR = hazard ratio; KM = Kaplan-Meier; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PFS2 = progression-free survival after first subsequent therapy; PRO: patient-reported outcome; RECIST = Response Evaluation Criteria in Solid Tumours; SAP: statistical analysis plan; TTSP = time to symptomatic progression; TTST = time to subsequent treatment.	

EAG comment: The statistical methods appear to be satisfactory.

3.2.8 Patient flow in the PAPILLON trial

The Consolidated Standards of Reporting Trials (CONSORT) diagram for the PAPILLON trial is presented in Figure 3.2.

Figure 3.2: CONSORT diagram for the PAPILLON trial (3 May 2023 DCO)

Based on Figure 8 of the CS¹

Adapted from Zhou et al. 2023¹²

^a Both patients withdrew consent after randomisation.

^b Other includes non-compliance, other, and physician's decision ($n \leq 2$ for all).

CONSORT = Consolidated Standards of Reporting Trials; CS = company submission; DCO = data cut-off

At the 3 May 2023 DCO in the PAPILLON trial, 153 patients were randomised to the amivantamab-chemotherapy arm and 155 to the chemotherapy arm. A total of 306 patients received at least one dose of study treatment. At the DCO, 46.4% (70) of patients in the amivantamab-chemotherapy arm and 15.5% (24) in the chemotherapy arm remained on treatment. Disease progression was the most common reason for discontinuation, affecting 33.1% of the amivantamab-chemotherapy arm and 69.0% of the chemotherapy arm. Fourteen patients in each arm discontinued treatment due to adverse events (AEs). Additionally, 65 chemotherapy patients switched to amivantamab monotherapy after confirmed disease progression, with 6 switching outside the trial protocol.

3.2.9 Treatment switching in the PAPILLON trial

In the PAPILLON trial, patients randomised to the chemotherapy arm were allowed to switch to amivantamab monotherapy after disease progression confirmed by independent review. The dosing schedule for amivantamab was based on patient weight, with higher doses for those ≥ 80 kg. By the 3 May 2023 DCO, 65 patients had switched to amivantamab, increasing to 78 by 31 October 2023. Efficacy results for the chemotherapy arm were reported as a whole, including patients who switched to amivantamab after progression. This treatment switching was expected to confound the OS results, as shown in the CHRYSALIS trial, where amivantamab monotherapy extended survival in post-chemotherapy patients with EGFR exon 20 insertion mutations.¹⁷ As a result, the findings of OS in the PAPILLON trial were considered conservative in estimating the treatment effect of amivantamab-chemotherapy.

The company explained how amivantamab is not currently recommended by NICE for use after the failure of platinum-based therapy in patients with EGFR exon 20 insertion mutations, meaning it is not available through the National Health Service (NHS).¹⁸ Consequently, OS results for the chemotherapy

arm were adjusted to exclude the effects of treatment switching to reflect survival outcomes more accurately in both England and Wales clinical settings, as per NICE's guidance on adjusting clinical trial results to account for treatments not available in the NHS.

EAG comment: Despite the company acknowledging potential confounding of OS results, it should be emphasised that this could be a significant issue. Patients who switched to amivantamab, a drug proven to provide survival benefits in post-chemotherapy patients,¹⁷ are included in the chemotherapy arm's results. This obscures the true efficacy of chemotherapy alone, as the addition of amivantamab likely improved outcomes for patients who would otherwise have worse survival rates on chemotherapy alone. As a result, the overall OS results do not reflect the isolated effect of chemotherapy, making direct comparisons between treatment arms problematic.

Furthermore, despite the company claiming that the OS estimates are "conservative", this assertion lacks clarity. The impact of treatment switching could both understate or overstate the treatment effect, depending on various factors such as when the switch occurred and the extent of the survival benefit from amivantamab. A clearer separation of outcomes for patients who switched treatments would provide a more accurate assessment of the treatment effects in each arm.

Finally, the lack of availability of amivantamab in the NHS raises questions about the real-world applicability of the PAPILLON trial results to England and Wales settings. Despite the effort to adjust for treatment switching, the large number of patients who switched therapies (by 31 October 2023) further emphasises that the chemotherapy arm's outcomes may not fully represent the survival rates expected under NHS protocols, where amivantamab is not an option post-progression.

3.2.10 Adjustment of treatment switching in the PAPILLON trial

Given that there was treatment switching in the PAPILLON study, this issue would confound the OS results for chemotherapy, thereby resulting in an over-estimation of the survival compared to what would be expected in UK clinical practice.

At the October 2023 data cut-off (DCO), [REDACTED] % of patients in the chemotherapy arm who experienced blinded independent central review (BICR)-confirmed disease progression (78 out of [REDACTED]) received subsequent treatment with amivantamab monotherapy. The company stated that the large proportion of patients within the control arm (chemotherapy) who received amivantamab monotherapy as a subsequent therapy after disease progression was associated with the limited efficacy of first-line chemotherapy. The proportion of patients who switched to receive amivantamab monotherapy as a subsequent treatment could be attributed to BICR-confirmed disease progression.⁴

The company adjusted the OS results for chemotherapy to account for the observed treatment switching in the PAPILLON study by using the Inverse Probability of Censoring Weighting (IPCW) in the base-case. Following the adjustment of treatment switching, the results showed that there were consistencies between the OS hazard ratio (HR) for the IPCW-adjusted chemotherapy data ([REDACTED]) and the OS HR ([REDACTED]) for the average effect of the treated (ATT)-adjusted indirect comparison of chemotherapy data from the NECTAR study with amivantamab-chemotherapy data from PAPILLON (which did not include subsequent amivantamab monotherapy).⁴

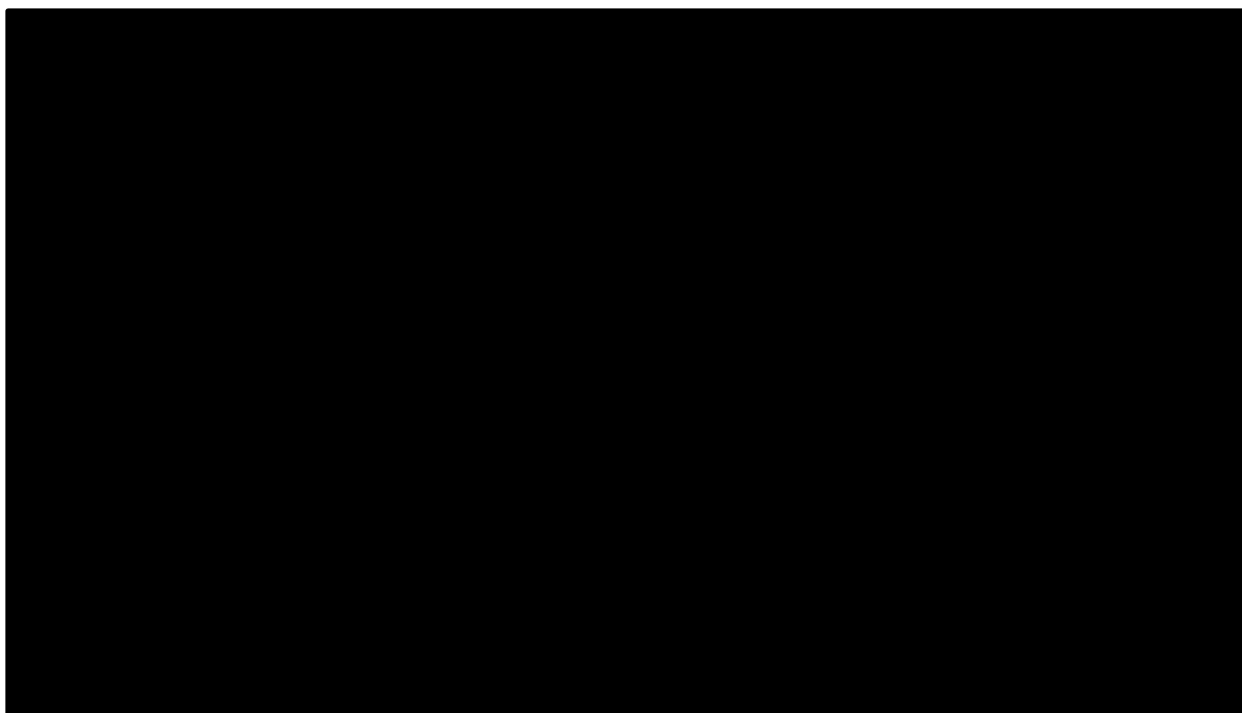
The comparative efficacy of amivantamab-chemotherapy versus chemotherapy for OS is presented in Table 3.10.

Table 3.10: Comparative efficacy of amivantamab-chemotherapy versus chemotherapy for OS

Method	Median OS (months)	OS HR (95% CI)	P-value	Setting
PAPILLON trial (ITT)	28.86	0.76 (0.50-1.14)	0.1825	No adjustment for switching
PAPILLON trial (IPCW)	████	████	████	Censor at time of switch and reweight; stabilised weight
RWE (NECTAR study) ^a	████	████	████	ATT-adjusted analysis Oct 23 data cut-off; n=230
Based on Table 6 of company clarification response⁴ ^an=70 subjects. Data leveraged from four RW datasets (NCRAS, ESME, US [ConcertAI and COTA]) between 2012 and 2023 ATT = average treatment effect for the treated; CI = confidence interval; ESME = Epidemiological Strategy and Medical Economics; HR = hazard ratio; IPCW = inverse probability of censoring weighting; ITT = intention to treat; NCRAS = National Cancer Registration and Analysis Service; OS = overall survival; RWE = real-world evidence				

Figure 3.3 shows the generalisability of the chemotherapy OS data after treatment switch adjustment via two methodologies (blue curve for two-stage estimation [TSE] and red curve for IPCW), and the limited generalisability of the chemotherapy OS data with no adjustment for treatment switching (green curve in the figure below) to RWE. The company made the following statement: “*This figure shows that, compared to chemotherapy with no treatment switch adjustment (green curve), the Kaplan-Meier (KM) curve for chemotherapy OS after adjustment for treatment switching (using two switching methodologies, the IPCW and TSE without recensoring, blue and red curves) better aligns with the KM curve for chemotherapy OS from the NECTAR study where no subsequent amivantamab monotherapy was observed (black curve) and the English-specific RWE from the NCRAS sample (black dotted curve)*”.⁴

Figure 3.3: Comparison of OS data for chemotherapy from the PAPILLON trial (with/without adjustment via IPCW and TSE without re-censoring) versus RWE sources



Based on Figure 2 of company clarification response⁴

ATT = average treatment effect for the treated; CP: carboplatin + pemetrexed; IPCW: inverse probability of censoring weighting; NCRAS: National Cancer Registration and Analysis Service; OS = overall survival; RWE = real-world evidence; TSE: two-stage estimation

EAG comment: The EAG considers that treatment-switching adjustment methods used by the company appear to be appropriate.

3.2.11 Critical appraisal of the relevant clinical effectiveness evidence

The CS¹ provided a quality assessment of the PAPILLON trial using the York CRD quality assessment checklist, which is designed for RCTs. According to this CS the company states that the PAPILLON trial was found to be a “*robust, high-quality trial, with minimal risk of bias*”.¹ Key aspects of the quality assessment included low risk of bias for randomisation, outcome assessor blinding, balanced groups, and the absence of unexpected discontinuations. However, there were areas of uncertainty, such as allocation concealment and the use of the intention-to-treat (ITT) principle. The trial also had a high risk of bias in terms of patient and care provider blinding. This is highlighted in Table 3.11.

Table 3.11: Quality assessment of the PAPILLON trial (NCT04538664)

Source of bias	Risk of bias
Randomisation	Low
Allocation concealment	Unclear
Patient/care provider blinding	High
Outcome assessor blinding	Low
Balanced groups	Low
Unexpected imbalance in discontinuations	Low
More outcomes measured than reported	Low
ITT used appropriately	Unclear
Based on Table 11 of the CS ¹ CS = company submission; ITT = intention-to-treat	

EAG comment: Given that patients in the PAPILLON trial were permitted to cross over from the chemotherapy group to the amivantamab monotherapy group after disease progression, the quality assessment provided by the company (Table 3.11) raises some important concerns about whether it fully reflects the complexities of the trial design.

The PAPILLON trial’s crossover design, where patients in the chemotherapy arm were allowed to switch to amivantamab monotherapy after disease progression, introduces significant concerns about bias and the integrity of the reported results. Crossover between treatment arms, particularly in a study designed to assess OS, can dilute the treatment effect of the original group and complicate the interpretation of efficacy. In such trials, the survival benefit attributed to one treatment may be confounded by the addition of a second therapy post-crossover. Without appropriate adjustments, the true efficacy of chemotherapy or amivantamab-chemotherapy could be misrepresented, weakening the reliability of the OS data.

The uncertainty surrounding the use of the ITT analysis is especially concerning given the crossover design. In trials with crossover, ITT is crucial to preserving the benefits of randomisation by ensuring that all patients are analysed in the groups to which they were originally assigned, regardless of whether they switched treatments. If the ITT analysis was not appropriately applied or adjusted for patients who switched treatments, the trial’s findings could be biased, as the effects of the original treatment arm

could be obscured by the subsequent therapy. Proper implementation of ITT would account for these crossovers and provide a clearer understanding of the comparative efficacy of each treatment. The lack of clarity in this area raises questions about the robustness of the reported outcomes.

The unclear status of allocation concealment further complicates the trial's validity, especially in the context of a crossover design. Allocation concealment ensures that neither researchers nor participants can predict group assignments, reducing the risk of selection bias. In the absence of adequate concealment, there is a risk that patients more likely to benefit from one treatment could have been systematically assigned to that group, potentially distorting the baseline characteristics of the treatment arms. This issue becomes even more problematic when patients switch treatments, as improper allocation concealment could exacerbate imbalances and confound the results.

The high risk of bias related to patient and care provider blinding in the PAPILLON trial is particularly problematic in a crossover study. When patients and caregivers are aware of the treatment being administered, their expectations and behaviours may influence subjective outcomes such as quality of life or symptom improvement. This lack of blinding could introduce placebo effects or biased reporting of subjective measures, skewing the overall results. The EAG rated the PAPILLON trial as being at moderate risk of bias. Given that this PAPILLON trial used crossover study design, the company used appropriate approaches to adjust for treatment switching in the analysis.

3.2.12 Efficacy results of the PAPILLON trial

The company presented efficacy results for the PAPILLON trial from the full analysis set, consisting of 153 patients in the amivantamab-chemotherapy arm and 155 patients in the chemotherapy arm.

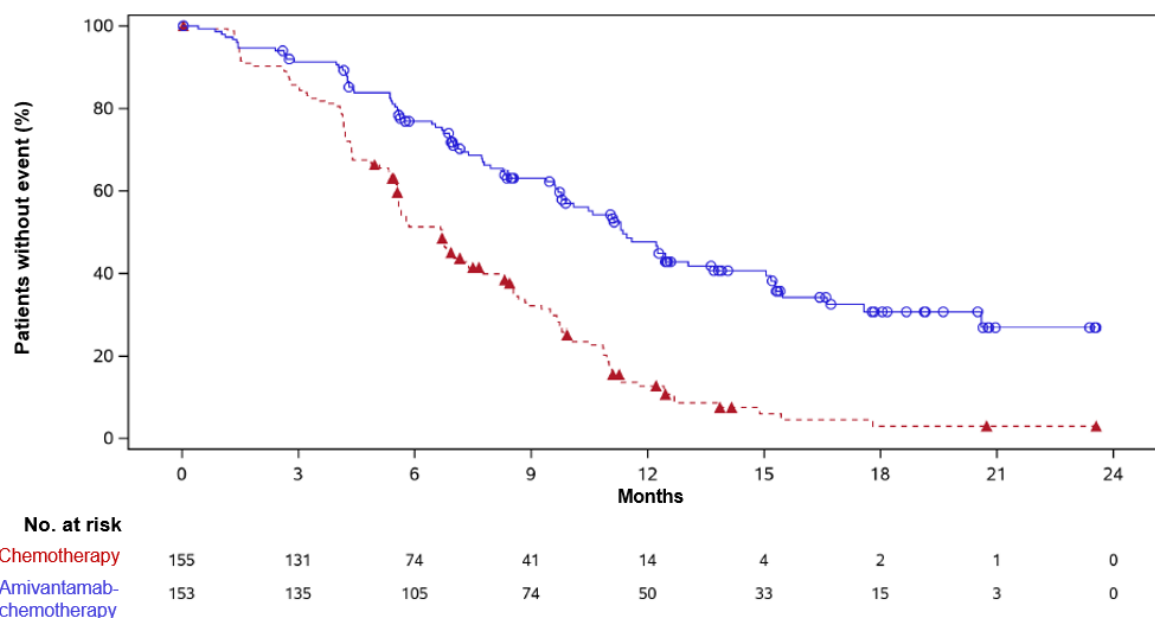
3.2.12.1 Progression-free survival by BICR

Section B.2.6.1 of the CS¹ included the following statements: *“The median BICR-assessed PFS was 11.37 months (95% CI: 9.79-13.70) in the amivantamab-chemotherapy arm and 6.70 months (95% CI: 5.59-7.33) in the chemotherapy arm. Additionally, 12- and 18-month event-free rates of 48% and 31% were observed for patients in the amivantamab-chemotherapy treatment arm, with rates of 13% and 3% observed for patients in the chemotherapy treatment arm.”* Further details are shown in Table 3.12 below.

The company further confirmed that, *“A KM plot for PFS in both treatment arms is presented in Figure 9. The plot shows a distinct early separation of the treatment arms, favouring treatment with amivantamab-chemotherapy, after the second disease assessment. This benefit continued throughout the maintenance phase as evidenced by the increased separation of the curves. By 15 months, the benefit from chemotherapy in the chemotherapy arm was no longer evident, while the amivantamab-chemotherapy curve appears to plateau, with disease control maintained in approximately one-third of patients in the amivantamab-chemotherapy arm.”*¹ The relevant details are shown in Figure 3.4 below.

Table 3.12: Summary of PFS assessed by BICR (3 May 2023 DCO; full analysis set)

	Amivantamab- chemotherapy (N=153)	Chemotherapy (N=155)
Event, n (%)	84 (54.9)	132 (85.2)
Censored, n (%)	69 (45.1)	23 (14.8)
Time to event (months)		
Median (95% CI)	11.37 (9.79-13.70)	6.70 (5.59-7.33)
25 th percentile (95% CI)	6.70 (5.39-7.72)	4.21 (3.48-4.40)
75 th percentile (95% CI)	NE (16.62-NE)	9.95 (8.87-11.01)
Range	0.0+, 23.6+	0.0+, 23.6+
6-month event-free rate (95% CI)	0.77 (0.69-0.83)	0.51 (0.43-0.59)
12-month event-free rate (95% CI)	0.48 (0.39-0.56)	0.13 (0.08-0.19)
18-month event-free rate (95% CI)	0.31 (0.22-0.40)	0.03 (0.01-0.09)
Treatment difference		
p-value ^a	<0.0001	
HR (95% CI) ^b	0.40 (0.30-0.53)	
Based on Table 13 of the CS ¹		
^a p-value is from a log-rank test stratified by ECOG PS (0 or 1) and history of brain metastases (yes or no).		
^b HR is from stratified proportional hazards model. HR <1 favours amivantamab-chemotherapy treatment.		
BICR = blinded independent central review; CI = confidence interval; CS = company submission; DCO = data cut-off; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; NE = not estimable; PFS = progression-free survival		

Figure 3.4: KM plot of PFS assessed by BICR (3 May 2023 DCO; full analysis set)Based on Figure 9 of the CS¹

BICR = blinded independent central review; CS = company submission; DCO = data cut-off; KM = Kaplan-Meier; PFS = progression-free survival

Table 3.14: Summary of DOR in confirmed responders based on patients with measurable disease at baseline by BICR (3 May 2023 DCO; full analysis set)

	Amivantamab- chemotherapy (N=153)	Chemotherapy (N=155)
Number of patients with measurable disease at baseline	152	152
Event, n (%)	52 (51.0)	45 (81.8)
Censored, n (%)	50 (49.0)	10 (18.2)
Time to event (months)		
Median (95% CI)	10.09 (8.48-13.90)	5.55 (4.44-6.93)
25 th percentile (95% CI)	6.54 (5.39-8.21)	4.17 (2.86-4.44)
75 th percentile (95% CI)	NE (15.21-NE)	8.94 (6.93-11.47)
Range	1.4+, 22.3+	1.3+, 22.4+
6-month event-free rate (95% CI)	0.77 (0.67-0.85)	0.44 (0.30-0.56)
12-month event-free rate (95% CI)	0.45 (0.34-0.55)	0.11 (0.03-0.23)
18-month event-free rate (95% CI)	0.35 (0.24-0.47)	0.05 (0.01-0.19)
Based on Table 15 of the CS ¹ + censored observation BICR = blinded independent central review; CI = confidence interval; CS = company submission; DCO = data cut-off; DOR = duration of response; NE = not estimable		

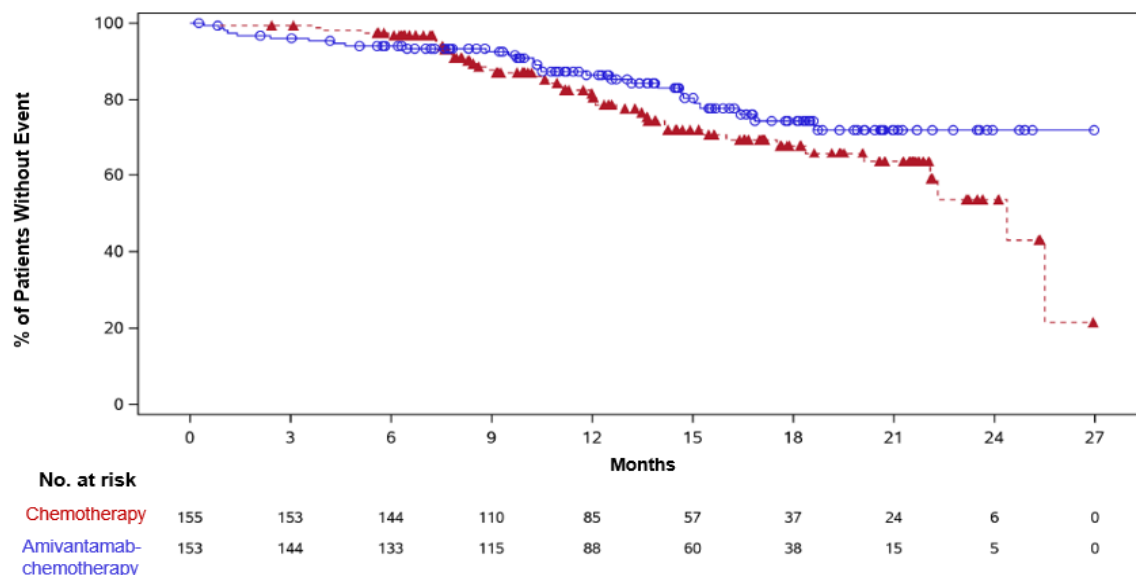
3.2.12.4 Overall survival

Section B.2.6.2.3 of the CS¹ included the following statements: “At the 3rd May DCO, there were 28 OS events in the amivantamab-chemotherapy arm and 42 in the chemotherapy arm. There was a strong trend towards improved survival in the amivantamab-chemotherapy arm, despite 65 patients in the chemotherapy arm receiving amivantamab monotherapy after BICR-confirmed disease progression (HR: 0.67 [95% CI: 0.42-1.09]; p=0.1056). The OS rate at 18 months and 24 months was 74% and 72%, respectively, for patients in the amivantamab-chemotherapy arm versus 68% and 54%, respectively for patients treated with chemotherapy.” The further details can be found as below in Table 3.15.

The company also added that, “The KM plot demonstrates a strong trend towards improved survival in the amivantamab-chemotherapy arm.” The further details can be found as below in Figure 3.5. The OS results at the 31 October DCO are presented in Table 3.16 and Figure 3.6.

Table 3.15: Summary of OS (3 May 2023 DCO; full analysis set)

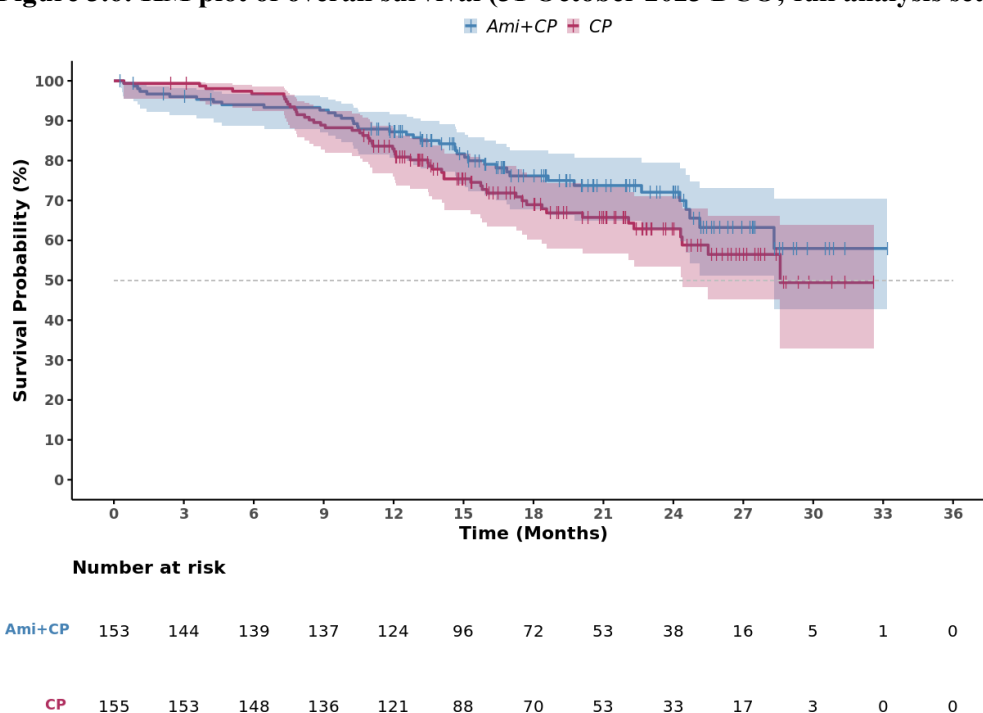
	Amivantamab- chemotherapy (N=153)	Chemotherapy (N=155)
Event, n (%)	28 (18.3)	42 (27.1)
Censored, n (%)	125 (81.7)	113 (72.9)
Time to event (months)		
Median (95% CI)	NE (NE-NE)	24.38 (22.08-NE)
25 th percentile (95% CI)	16.85 (13.96-NE)	13.67 (11.10-18.37)
75 th percentile (95% CI)	NE (NE-NE)	25.49 (24.38-NE)
Range	0.3+, 27.0+	0.4, 26.9+
6-month event-free rate (95% CI)	0.94 (0.89-0.97)	0.97 (0.92-0.99)
12-month event-free rate (95% CI)	0.86 (0.79-0.91)	0.82 (0.74-0.87)
18-month event-free rate (95% CI)	0.74 (0.64-0.82)	0.68 (0.58-0.76)
24-month event-free rate (95% CI)	0.72 (0.61-0.81)	0.54 (0.37-0.68)
Treatment difference		
p-value ^a	0.1056	
HR (95% CI) ^b	0.67 (0.42-1.09)	
Based on Table 16 of the CS ¹		
^a p-value is from a log-rank test.		
^b HR is from stratified proportional hazards model. HR <1 favours amivantamab-chemotherapy treatment.		
+ censored observation		
CI = confidence interval; CS = company submission; DCO = data cut-off; HR = hazard ratio; NE = not estimable; OS = overall survival		

Figure 3.5: KM plot of overall survival (3 May 2023 DCO; full analysis set)Based on Figure 10 of the CS¹

CS = company submission; DCO: data cut-off; KM: Kaplan-Meier

Table 3.16: Summary of OS (31 October 2023 DCO; full analysis set)

	Amivantamab- chemotherapy (N=153)	Chemotherapy (N=155)
Event, n (%)	40 (26.1)	52 (33.5)
Time to event (months)		
Median (95% CI)	NE (28.3-NE)	28.6 (24.4-NE)
Treatment difference		
p-value	0.1825	
HR (95% CI), p value	0.76 (0.50-1.14, p=0.1825)	
Based on Table 17 of the CS ¹ CI = confidence interval; CS = company submission; DCO = data cut-off; HR = hazard ratio; NE = not estimable; OS = overall survival		

Figure 3.6: KM plot of overall survival (31 October 2023 DCO; full analysis set)

Based on Figure 11 of the CS¹

ACP = amivantamab in combination with carboplatin and pemetrexed; CP = carboplatin and pemetrexed; CS = company submission; DCO = data cut-off; KM = Kaplan-Meier

3.2.12.5 Time to subsequent therapy

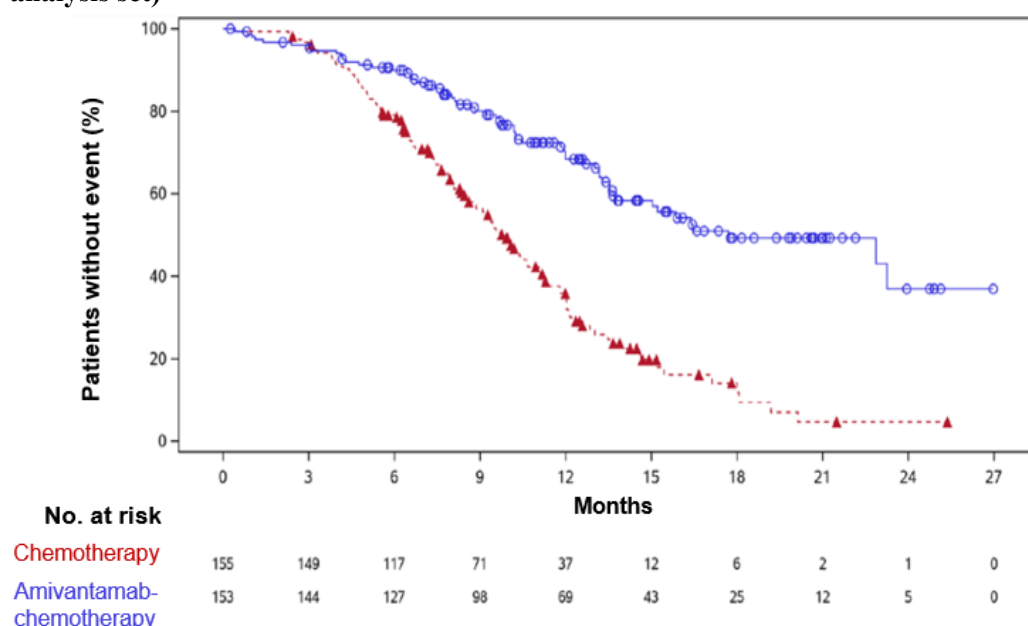
In Section B.2.6.2.4 of the CS¹ the company reported that, “A substantially higher proportion of patients in the amivantamab-chemotherapy arm had not initiated subsequent systemic therapy compared with the chemotherapy arm at the 3rd May 2023 DCO (62.1% versus 29.7%, respectively).” The further details can be found as below in Table 3.17.

This result also demonstrated the durability of clinical benefit offered by amivantamab-chemotherapy in prolonging time until patients require a subsequent therapy versus chemotherapy.

The associated KM plot also presented in Figure 3.7 as below.

Table 3.17: Summary of time to subsequent systemic anti-cancer therapy (3 May 2023 DCO; full analysis set)

	Amivantamab-chemotherapy (N=153)	Chemotherapy (N=155)
Event, n (%)	58 (37.9)	109 (70.3)
Censored, n (%)	95 (62.1)	46 (29.7)
Time to event (months)		
Median (95% CI)	17.71 (13.67-NE)	9.89 (8.57-11.07)
25 th percentile (95% CI)	10.18 (8.18-12.65)	6.34 (5.36-7.39)
75 th percentile (95% CI)	NE (23.26-NE)	13.47 (12.02-15.44)
Range	0.3+, 27.0+	0.4, 25.4+
6-month event-free rate (95% CI)	0.90 (0.84-0.94)	0.79 (0.72-0.85)
12-month event-free rate (95% CI)	0.68 (0.59-0.76)	0.36 (0.27-0.44)
18-month event-free rate (95% CI)	0.49 (0.39-0.59)	0.14 (0.07-0.23)
24-month event-free rate (95% CI)	0.37 (0.21-0.53)	0.05 (0.01-0.13)
Treatment difference		
Nominal p-value ^a	<0.0001	
HR (95% CI) ^b	0.35 (0.25-0.49)	
Based on Table 18 of the CS ¹		
^a p-value is from a log-rank test stratified by ECOG PS (0 or 1) and history of brain metastases (yes or no).		
^b HR is from stratified proportional hazards model. HR <1 favours amivantamab-chemotherapy treatment.		
+ censored observation		
CI = confidence interval; CS = company submission; DCO = data cut-off; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; NE = not estimable; PS = performance status		

Figure 3.7: KM plot of time to subsequent systemic anti-cancer therapy (3 May 2023 DCO; full analysis set)Based on Figure 12 of the CS¹

CS = company submission; DCO: data cut-off; KM: Kaplan-Meier

3.2.12.6 PFS after first subsequent therapy

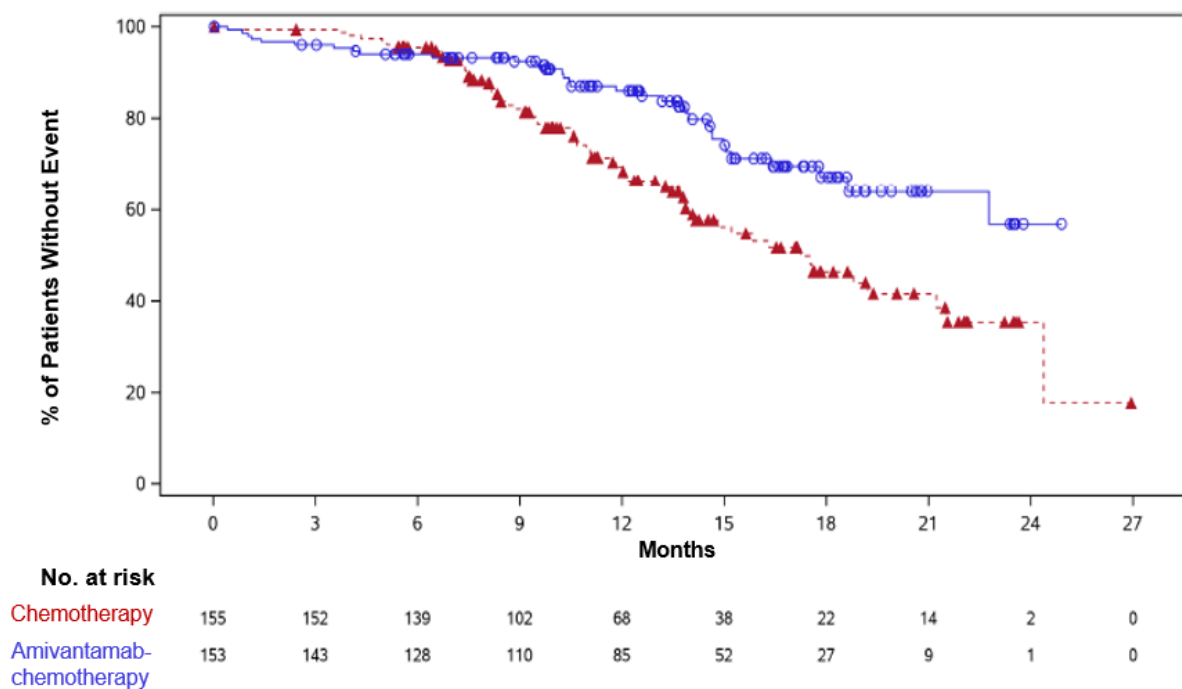
In Section B.2.6.2.5 of the CS¹ the company reported that, “At the 3rd May 2023 DCO, a higher proportion of patients had experienced progression after first subsequent therapy (PFS2) in the chemotherapy arm (39.4%) compared with amivantamab-chemotherapy arm (21.6%).”

The company also added that “Despite 65 patients in the chemotherapy arm treatment switching to receive amivantamab monotherapy as the first systemic subsequent therapy received at the 3rd May 2023 DCO, PFS2 analysis showed a 51% reduction in the risk of second disease progression or death in the amivantamab-chemotherapy arm compared with the chemotherapy arm (HR: 0.49 [95% CI: 0.32-0.76; nominal $p=0.0010$]).”¹ These results demonstrated that receipt of amivantamab-chemotherapy at first line also confers a benefit in delaying patients’ subsequent progression. Further details can be found below in Table 3.18.

The associated Kaplan-Meier plot for progression-free survival after first subsequent therapy (PFS2) is presented in Figure 3.8.

Table 3.18: Summary of PFS2 (3 May 2023 DCO; full analysis set)

	Amivantamab- chemotherapy (N=153)	Chemotherapy (N=155)
Event, n (%)	33 (21.6)	61 (39.4)
Censored, n (%)	120 (78.4)	94 (60.6)
Time to event (months)		
Median (95% CI)	NE (22.77-NE)	17.25 (13.96-21.52)
25 th percentile (95% CI)	14.98 (13.67-18.63)	10.68 (8.87-12.06)
75 th percentile (95% CI)	NE (NE-NE)	24.38 (21.52-NE)
Range	0.0+, 24.9+	0.0+, 26.9+
6-month event-free rate (95% CI)	0.94 (0.89-0.97)	0.95 (0.91-0.98)
12-month event-free rate (95% CI)	0.86 (0.79-0.91)	0.69 (0.60-0.77)
18-month event-free rate (95% CI)	0.67 (0.55-0.76)	0.46 (0.35-0.57)
24-month event-free rate (95% CI)	0.57 (0.39-0.72)	0.35 (0.23-0.48)
Treatment difference		
Nominal p-value ^a	0.0010	
HR (95% CI) ^b	0.49 (0.32-0.76)	
Based on Table 19 of the CS ¹		
^a p-value is from a log-rank test stratified by ECOG PS (0 or 1) and history of brain metastases (yes or no).		
^b HR is from stratified proportional hazards model. HR <1 favours amivantamab-chemotherapy treatment.		
+ censored observation		
CI = confidence interval; CS = company submission; DCO = data cut-off; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; NE = not estimable; PFS2 = progression-free survival after first subsequent therapy; PS = performance status		

Figure 3.8: KM plot of PFS2 (3 May 2023 DCO; full analysis set)

Based on Figure 13 of the CS¹

CS = company submission; DCO = data cut-off; KM = Kaplan-Meier; PFS2 = progression-free survival after first subsequent therapy

3.2.12.7 Time to treatment discontinuation

The company reported “At the 3rd May DCO, there was approximately three times as many patients in the amivantamab-chemotherapy arm who were continuing treatment compared with the chemotherapy arm (70 versus 24).” Further details are shown in Table 3.19 as below.

Table 3.19: Summary of TTD (3 May 2023 DCO; full analysis set)

	Amivantamab- chemotherapy (N=153)	Chemotherapy (N=155)
Event, n (%)	83 (54.2)	131 (84.5)
Censored, n (%)	70 (45.8)	24 (15.5)
Time to event (months)		
Median (95% CI)	13.17 (11.76-15.24)	7.46 (6.97-8.38)
25 th percentile (95% CI)	8.02 (6.28-9.56)	5.13 (4.27-5.85)
75 th percentile (95% CI)	22.34 (18.40-NE)	11.14 (9.99-12.29)
Range	0.3, 27.0+	0.4, 25.4+
6-month event-free rate (95% CI)	0.84 (0.77-0.89)	0.66 (0.58-0.73)
12-month event-free rate (95% CI)	0.58 (0.49-0.66)	0.21 (0.15-0.29)
18-month event-free rate (95% CI)	0.35 (0.26-0.45)	0.05 (0.02-0.11)
24-month event-free rate (95% CI)	0.23 (0.13-0.35)	0.03 (0.01-0.08)
Treatment difference		
p-value ^a	<0.0001	
HR (95% CI) ^b	0.38 (0.28-0.51)	
Based on Table 20 of the CS ¹		
^a p-value is from a log-rank test stratified by ECOG PS (0 or 1) and history of brain metastases (yes or no).		
^b HR is from stratified proportional hazards model. HR <1 favours amivantamab-chemotherapy treatment.		
+ censored observation		
CI = confidence interval; CS = company submission; DCO = data cut-off; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; NE = not estimable; PS = performance status; TTD = time to treatment discontinuation		

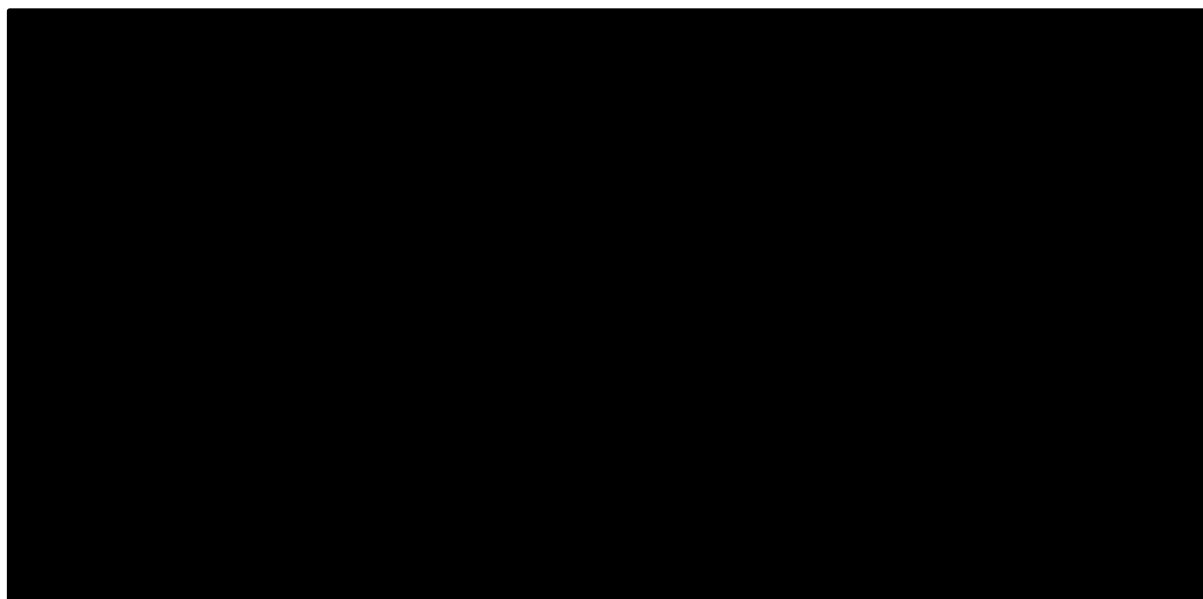
EAG comment: The survival data and other efficacy outcomes from the CS were not relatively mature. There was a lack of longer-term follow-up data from the PAPILLION trial.

3.2.12.8 EORTC QLQ-C30

The company reported that “EORTC-QLQ-C30 scores indicated that a larger proportion of patients in the amivantamab-chemotherapy arm had improved/stable global health status and physical functioning at 6- and 12-months versus patients in the chemotherapy arm, with 54% of patients in the amivantamab-chemotherapy arm reporting improved/stable global health status versus 43% in the chemotherapy arm at 6 months ($p = 0.064$), with this difference increasing at 12 months (36% versus 13% for amivantamab-chemotherapy versus chemotherapy, $P < 0.0001$). Additionally, a higher proportion of patients in the amivantamab-chemotherapy arm reported improved / stable physical functioning compared with the chemotherapy arm at 6-months (57% vs 42%, $P = 0.008$) and 12-months (28% vs 14%, $P = 0.014$).”¹ Changes in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) global health status scores from baseline across the two treatment arms at key trial timepoints are presented in Table 3.20 and Figure 3.9, with physical functioning scores presented in Table 3.20 and Figure 3.10.

Table 3.20: Analysis of EORTC QLQ-C30 global health status scores (3 May 2023 DCO; full analysis set)

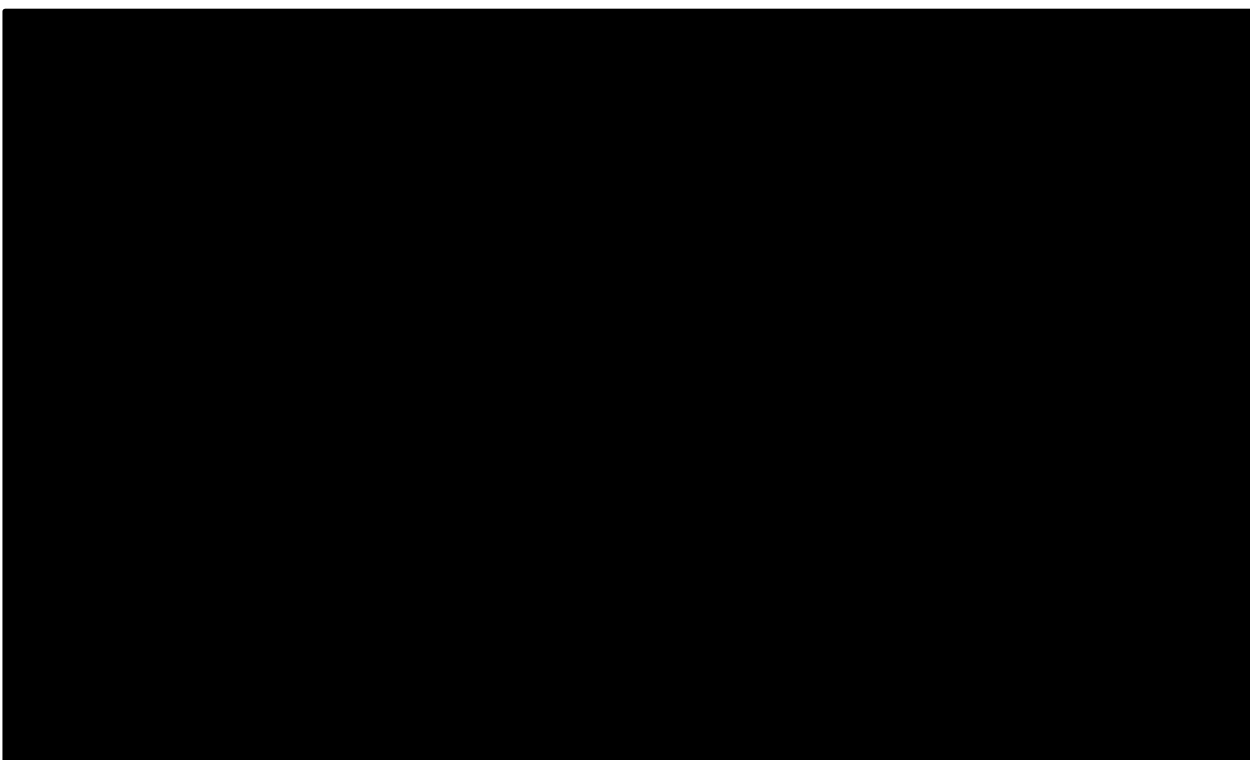
Global health status	Amivantamab- chemotherapy (N=153)	Chemotherapy (N=155)
Baseline		
n	████	████
Mean (SD)	████	████
Initiation of maintenance phase (Cycle 5 Day 1)		
n	████	████
Mean (SD)	████	████
Mean change from baseline	████	████
End of treatment		
n	████	████
Mean (SD)	████	████
Mean change from baseline	████	████
Based on Table 21 of the CS ¹ CS = company submission; DCO = data cut-off; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; SD = standard deviation		

Figure 3.9: Change from baseline of EORTC QLQ-C30 global health status/quality of life score over time (3 May 2023 DCO; full analysis set)Based on Figure 14 of the CS¹

C = cycle; CS = company submission; D = day; DCO = data cut-off; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; GHS = global health score; QoL = quality of life; SE = standard error

Table 3.21: Analysis of EORTC QLQ-C30 physical functioning scores (3 May 2023 DCO; full analysis set)

Physical functioning	Amivantamab- chemotherapy (N=153)	Chemotherapy (N=155)
Baseline		
n	████	████
Mean (SD)	████	████
Initiation of maintenance phase (Cycle 5 Day 1)		
n	████	████
Mean (SD)	████	████
Mean change from baseline	████	████
End of treatment		
n	████	████
Mean (SD)	████	████
Mean change from baseline	████	████
Based on Table 22 of the CS ¹ CS = company submission; DCO = data cut-off; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; SD = standard deviation		

Figure 3.10: Change from baseline of EORTC QLQ-C30 physical functioning score over time (3 May 2023 DCO; full analysis set)Based on Figure 15 of the CS¹

C = cycle; CS = company submission; D = day; DCO = data cut-off; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; SE = standard error

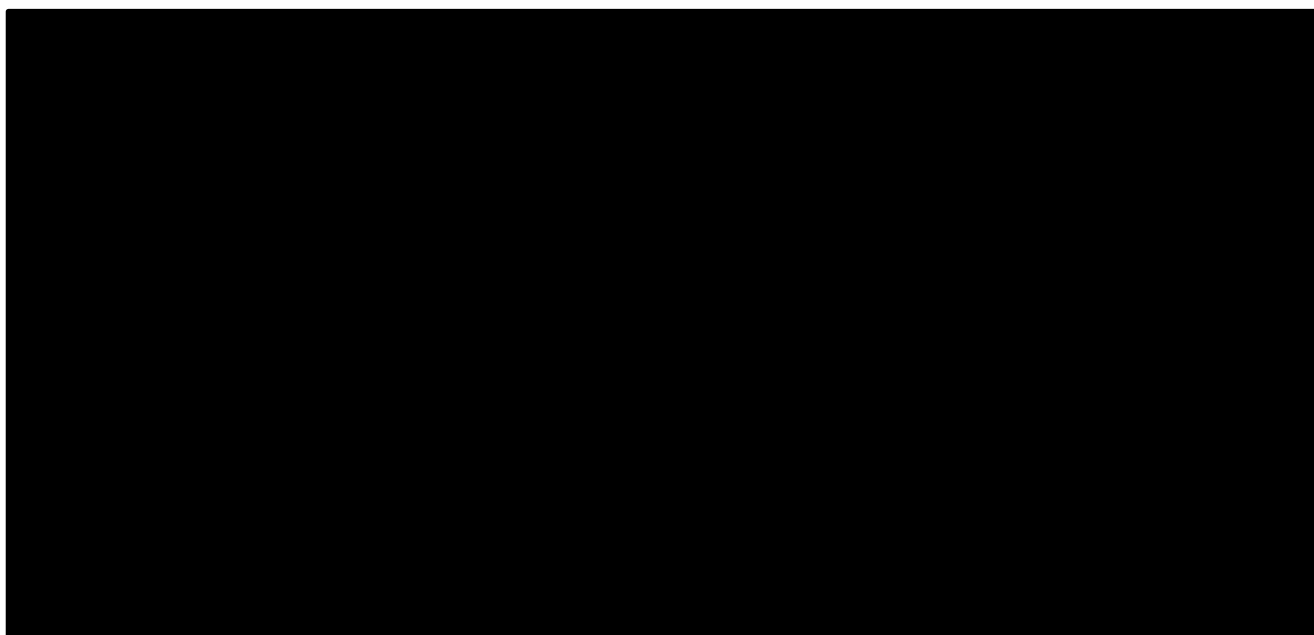
3.2.12.9 EQ-5D-5L

The company reported that “EQ-5D-5L utility scores were broadly consistent between the two treatment arms at each key timepoint in the trial (baseline, start of maintenance phase and end of treatment), further indicating that the addition of amivantamab does not negatively impact the HRQoL of patients.”¹ Changes in the European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L) utility scores from baseline across the two treatment arms are presented in Table 3.22 and Figure 3.11.

Table 3.22: Analysis of EQ-5D-5L utility scores (3 May 2023 DCO; full analysis set)

Utility score	Amivantamab- chemotherapy (N=153)	Chemotherapy (N=155)
Baseline		
n	████	████
Mean (SD) utility	████	████
Initiation of maintenance phase (Cycle 5 Day 1)		
n	████	████
Mean (SD) utility	████	████
Mean change from baseline	████	████
End of treatment		
n	████	████
Mean (SD) utility	████	████
Mean change from baseline	████	████
Based on Table 23 of the CS ¹ CS = company submission; DCO = data cut-off; EQ-5D-5L = EuroQol-5 Dimensions-5 Levels; SD = standard deviation		

Figure 3.11: Change from baseline of EQ-5D-5L utility score over time (3 May 2023 DCO; full analysis set)



Based on Figure 16 of the CS¹

C = cycle; CS = company submission; D = day; DCO = data cut-off; EQ-5D-5L = EuroQol-5 Dimensions-5 Levels; SE = standard error

EAG comment: It should be noted that only short-term data assessed by the EQ-5D-5L and other relevant HRQoL data from the PAPILLION trial were provided. There was a lack of long-term follow-up data relating to HRQoL outcomes from the PAPILLION trial.

3.2.12.10 Subgroup analysis

The company provided subgroup analyses of PFS assessed by BICR (see Figure 17 of the CS).¹

EAG comment: The 95% confidence interval (CI) of the HR was always below 1 except for those with a history of brain metastases where the upper limit was 1.06, which is also the subgroup with the highest point estimate (0.63 versus 0.40 for all randomised patients). The EAG requested that subgroup analyses also be presented for OS, but the company refused, citing several reasons:⁴

- Limited sample size “...in the subgroups specified within the NICE final scope (e.g., based on histology, disease stage, and type of EGFR Exon20 alteration).”
- Lack of stratification “...according to the suggested subgroups in the final scope.”, even though there was stratification based on ECOG PS (0 or 1), history of brain metastases (yes or no), and prior receipt of an EGFR tyrosine kinase inhibitor (yes or no).
- “OS data from the October 2023 DCO were not assessed by subgroup and these data are therefore not available.”

The EAG consider that these reasons are insufficient grounds for not performing any subgroup analysis for OS, especially given that subgroup analyses were performed regardless of stratification. However, low sample size does seem adequate justification for not performing subgroup analyses according to histology, disease stage and type of EGFR exon 20 alteration.

3.2.13 Adverse events (AEs)

3.2.13.1 Overall AEs

Overall AEs from the PAPILLON trial at the 3 May DCO are presented as Table 3.23.

Results are presented from the safety analysis set, defined as randomised patients who received at least one dose of study treatment; 151 patients in the amivantamab-chemotherapy arm and 155 patients in the chemotherapy arm.

In the amivantamab-chemotherapy arm, treatment-emergent AEs (TEAEs) were observed for all 151 participants. In the chemotherapy arm, 146 participants (94.2%) experienced TEAEs.

Seven AEs (4.6%) resulted in death in the amivantamab-chemotherapy arm (investigators considered one death to be related to amivantamab¹²), and four AEs (2.6%) resulted in death in the chemotherapy arm.

Serious AEs (SAEs) were reported for 56 (37.1%) participants in the amivantamab-chemotherapy arm, and 48 (31.0%) participants in the chemotherapy arm. Serious AEs deemed to be treatment-related by study investigators were 36 (23.8%) for amivantamab-chemotherapy, and 16 (10.3%) for chemotherapy.

Treatment-emergent AEs at Grade 3 and above were reported for 114 (75.5%) participants in the amivantamab-chemotherapy arm, and 83 (53.5%) participants in the chemotherapy arm.

Dose reduction occurred for 73 (48.3%) participants in the amivantamab-chemotherapy arm and 35 (22.6%) participants in the chemotherapy arm; 104 (68.9%) participants experienced a dose interruption for amivantamab-chemotherapy and 56 (36.1%) participants for chemotherapy; 36 (23.8%) participants discontinued treatment in the amivantamab-chemotherapy arm and 16 (10.3%) participants in the chemotherapy arm.

Considering amivantamab in isolation, dose reductions of amivantamab occurred for 54 (35.8%) participants, and dose interruptions occurred for 97 (64.2%) participants in the amivantamab-chemotherapy arm. Dose reductions of amivantamab occurred due to amivantamab-related AEs for 54 (35.8%) participants, and dose interruptions of amivantamab occurred due to amivantamab-related AEs for 63 (41.7%) participants. Amivantamab was discontinued in 17 (11.3%) participants, and discontinuation of treatment due to amivantamab-related AEs occurred in 10 (6.6%) participants.

Adverse events of special interest (AESIs) were predefined as rash, infusion-related reactions and pneumonitis/interstitial lung disease. 139 (92.1%) participants in the amivantamab-chemotherapy arm and 30 (19.4%) of patients in the chemotherapy arm experienced at least one AESI. No new AESIs were identified over the course of the study.

Table 3.23: Summary of adverse events

Category		Amivantamab-chemotherapy (N=151)	Chemotherapy (N=155)
Participants with any AEs		151 (100.0%)	152 (98.1%)
Participants with any TEAEs [§]		151 (100.0%)	146 (94.2%)
Participants with any AEs of CTCAE Grade 3 and above		114 (75.5%)	83 (53.5%)
Participants with any SAEs		56 (37.1%)	48 (31.0%)
Participants with any treatment-related SAEs [§]		36 (23.8%)	16 (10.3%)
Severity grade (Refer to NCI-CTCAE V 5.0) ^{&}	Mild (Grade 1)	██████	██████
	Moderate (Grade 2)	██████	██████
	Severe (Grade 3)	██████	██████
	Life Threatening (Grade 4)	██████	██████
	Death (Grade 5)	██████	██████
Participants with AEs leading to treatment discontinuation	Discontinuation of any study agent	36 (23.8%)	16 (10.3%)
	Discontinuation of amivantamab	17 (11.3%)	N/A
	Due to AEs related to amivantamab	10 (6.6%)	N/A
Participants with AEs leading to dose reduction	Reduction of any study agent	73 (48.3%)	35 (22.6%)
	Reduction of amivantamab	54 (35.8%)	N/A
	Due to AEs related to amivantamab	54 (35.8%)	N/A
Participants with AEs leading to dose interruption	Interruption of any study agent	104 (68.9%)	56 (36.1%)
	Interruption of amivantamab	97 (64.2%)	N/A
	Due to AEs related to amivantamab	63 (41.7%)	N/A
Based on Tables 34, 35 and 36 of the CS ¹ . Adverse events by maximum severity grade for subject level.			
[§] Assessed by the investigator as related to the study treatment.			
^{&} CTCAE v5.0			
AE =adverse event; CS = company submission; CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute; SAE = serious adverse event; TEAE = treatment-emergent adverse event			

3.2.13.2 Common TEAEs by preferred term

Treatment-emergent AEs are recorded in the CS as events with frequency $\geq 5\%$ in either treatment arm. The CS states that a number of the most common TEAEs experienced by participants in the amivantamab-chemotherapy arm were associated with the known activity of amivantamab: “Common TEAEs associated with the EGFR inhibition activity of amivantamab included rash and dermatitis acneiform (53.6%), paronychia (56.3%), stomatitis (25.2%) and diarrhoea (20.5%) and were more frequently observed in the amivantamab-chemotherapy arm compared with the chemotherapy arm. Common TEAEs associated with MET inhibition activity of amivantamab included hypoalbuminemia (41.1%) and peripheral oedema (29.8%), which were observed more frequently in the amivantamab-chemotherapy arm compared to the chemotherapy arm; 9.7% and 10.3%, respectively.”

All adverse events with frequency $\geq 5\%$ in either treatment are recorded in Table 3.24. Comparing TEAEs by system organ class, cases of injury, poisoning and procedural complications and skin, subcutaneous and tissue disorders are markedly higher in the amivantamab-chemotherapy arm compared to the chemotherapy arm (risk ratio 4.79; 95% CI 2.87 to 7.98 and 2.65; 95% CI 2.87 to 7.98, respectively). Looking at TEAEs individually, the larger proportion of skin, subcutaneous and tissue disorders correspond to a higher incidence of rash and dermatitis acneiform (as stated in the CS), as well as dry skin and ulcer in the amivantamab-chemotherapy arm (████ and █████, respectively) compared to the chemotherapy arm (████ and █████, respectively). The higher frequency of injury, poisoning and procedural complications in the amivantamab-chemotherapy arm can be attributed to 63 cases of infusion-related reactions (41.7%), versus two cases (1.3%) in the chemotherapy arm. Other notable differences between the arms include infections and infestations (risk ratio 1.90; 95% CI 1.55 to 2.32), where cases of paronychia (56.3% for amivantamab-chemotherapy versus 0% for chemotherapy) and COVID-19 (23.8% for amivantamab-chemotherapy versus 13.5% for chemotherapy) contribute most strongly to this difference. Additionally, within the metabolism and nutrition group (risk ratio 1.46; 95% CI 1.22 to 1.74) there is a higher proportion of events in the amivantamab-chemotherapy arm across all reported measures except hyperglycaemia (████ for amivantamab-chemotherapy, █████ for chemotherapy). There are few TEAEs reported where incidence in the chemotherapy group is decidedly higher than the amivantamab-chemotherapy group. The most marked difference is for hypertension; █████ for chemotherapy versus █████ for amivantamab-chemotherapy.

Table 3.24: Number of patients with TEAEs with a frequency of at least 5% in any treatment group by system organ class and preferred term (3 May 2023 DCO; safety analysis set)

Event, n (%)	Amivantamab-chemotherapy (N=151)	Chemotherapy (N=155)
Patients with 1 or more AEs	151 (100.0)	152 (98.1)
Skin and subcutaneous tissue disorders	████	████
Rash	81 (53.6)	12 (7.7)
Dermatitis acneiform	47 (31.1)	5 (3.2)
Dry skin	████	████
Alopecia	████	████
Pruritus	████	████
Skin ulcer	████	████

Event, n (%)	Amivantamab- chemotherapy (N=151)	Chemotherapy (N=155)
Erythema	████	████
Gastrointestinal disorders	████	████
Constipation	60 (39.7)	47 (30.3)
Nausea	55 (36.4)	65 (41.9)
Stomatitis	38 (25.2)	9 (5.8)
Vomiting	32 (21.2)	29 (18.7)
Diarrhoea	31 (20.5)	20 (12.9)
Haemorrhoids	████	████
Mouth ulceration	████	████
Abdominal pain	████	████
Gingival bleeding	████	████
Abdominal distension	████	████
Abdominal pain upper	████	████
Infections and infestations	████	████
Paronychia	85 (56.3)	0
COVID-19	36 (23.8)	21 (13.5)
Pneumonia	████	████
Conjunctivitis	████	████
Upper respiratory tract infection	████	████
Urinary tract infection	████	████
Metabolism and nutrition disorders	████	████
Hypoalbuminaemia	62 (41.1)	15 (9.7)
Decreased appetite	54 (35.8)	43 (27.7)
Hypokalaemia	32 (21.2)	13 (8.4)
Hypomagnesaemia	████	████
Hypocalcaemia	████	████
Hyponatraemia	████	████
Hypophosphataemia	████	████
Hypoproteinaemia	████	████
Hyperglycaemia	████	████
Hyperkalaemia	████	████
Blood and lymphatic system disorders	████	████
Neutropenia	89 (58.9)	70 (45.2)
Anaemia	76 (50.3)	85 (54.8)
Leukopenia	57 (37.7)	50 (32.3)
Thrombocytopenia	55 (36.4)	46 (29.7)
Lymphopenia	████	████

Event, n (%)	Amivantamab- chemotherapy (N=151)	Chemotherapy (N=155)
General disorders and administration site conditions		
Oedema peripheral	45 (29.8)	16 (10.3)
Asthenia	30 (19.9)	29 (18.7)
Pyrexia	24 (15.9)	9 (5.8)
Fatigue	23 (15.2)	32 (20.6)
Malaise		
Mucosal inflammation		
Oedema		
Investigations		
Alanine aminotransferase increased	50 (33.1)	56 (36.1)
Aspartate aminotransferase increased	47 (31.1)	51 (32.9)
Gamma-glutamyltransferase increased	21 (13.9)	26 (16.8)
Weight decreased		
Blood alkaline phosphatase increased		
Blood lactate dehydrogenase increased		
Blood creatinine increased		
Injury, poisoning and procedural complications		
Infusion related reaction	63 (41.7)	2 (1.3)
Respiratory, thoracic and mediastinal disorders		
Cough	21 (13.9)	24 (15.5)
Dyspnoea		
Pulmonary embolism		
Productive cough		
Pleural effusion		
Nervous system disorders		
Dizziness		
Dysgeusia		
Headache		
Musculoskeletal and connective tissue disorders		
Back pain		
Arthralgia		
Myalgia		
Eye disorders		
Lacrimation increased		

Event, n (%)	Amivantamab- chemotherapy (N=151)	Chemotherapy (N=155)
Vascular disorders	████	████
Deep vein thrombosis	████	████
Hypertension	████	████
Hepatobiliary disorders	████	████
Hyperbilirubinaemia	████	████
Psychiatric disorders	████	████
Insomnia	████	████
Based on Table 35 of CS ¹ CS = company submission; DCO = data cut-off; TEAE = treatment-emergent adverse event		

3.2.13.3 Serious adverse events

Serious AEs have been defined in the PAPILLON trial protocol as per the definition published by the International Council for Harmonization (ICH) and European Union Guidelines on Pharmacovigilance for Medicinal Products for Human Use. These are any untoward medical occurrences that, at any dose results in death, is life-threatening, requires inpatient hospitalisation (or prolongation of an existing hospitalisation), persistent or significant disability/incapacity, is a congenital anomaly/birth defect, is a suspected transmission of any infectious agent via a medicinal product, is medically important.

Serious AEs were reported in 56 participants (37.1%) in the amivantamab-chemotherapy arm and 48 participants (31.0%) in the chemotherapy arm. SAEs are reported in Table 3.25. The three most common types of SAE for the amivantamab-chemotherapy arm are infections and infestations (18 cases, 11.9%), gastrointestinal disorders (10 cases, 6.6%) and respiratory, thoracic and mediastinal disorders (eight cases, 5.3%). There were no notable differences between SAEs by organ class between either treatment arm.

Incidence of all individual SAEs was less than 5% in either arm. The most common SAEs for the amivantamab-chemotherapy arm are pneumonia (4%; 2.6% in chemotherapy arm), pneumonitis (2.6%; 0% in chemotherapy arm) and pulmonary embolism (2.6%; 2.6% in chemotherapy arm). No notable differences in the incidence of individual SAEs can be seen between either arm.

Table 3.25: Number of patients with treatment-emergent SAEs by system organ class and preferred term (3 May 2023 DCO; safety analysis set)

Event, n (%)	Amivantamab- chemotherapy (N=151)	Chemotherapy (N=155)
Patients with 1 or more SAEs	56 (37.1)	48 (31.0)
Infections and infestations	18 (11.9)	10 (6.5)
Pneumonia	6 (4.0)	4 (2.6)
COVID-19	3 (2.0)	1 (0.6)
Cellulitis	2 (1.3)	1 (0.6)
Rash pustular	2 (1.3)	0
Skin infection	2 (1.3)	0
COVID-19 pneumonia	1 (0.7)	0
Infection	1 (0.7)	0

Event, n (%)	Amivantamab- chemotherapy (N=151)	Chemotherapy (N=155)
Pneumonia viral	1 (0.7)	0
Postoperative wound infection	1 (0.7)	1 (0.6)
Sepsis	1 (0.7)	1 (0.6)
Appendicitis	0	1 (0.6)
Enterocolitis infectious	0	1 (0.6)
Gastrointestinal disorders	10 (6.6)	4 (2.6)
Vomiting	3 (2.0)	1 (0.6)
Diarrhoea	2 (1.3)	1 (0.6)
Abdominal pain	1 (0.7)	0
Cheilitis	1 (0.7)	0
Duodenitis	1 (0.7)	0
Enterocolitis	1 (0.7)	0
Lower gastrointestinal haemorrhage	1 (0.7)	0
Ascites	0	1 (0.6)
Gastrointestinal haemorrhage	0	1 (0.6)
Respiratory, thoracic and mediastinal disorders	8 (5.3)	14 (9.0)
Pneumonitis	4 (2.6)	0
Pulmonary embolism	4 (2.6)	4 (2.6)
Dyspnoea	1 (0.7)	5 (3.2)
Haemoptysis	1 (0.7)	1 (0.6)
Pleural effusion	1 (0.7)	5 (3.2)
Hypoxia	0	1 (0.6)
Metabolism and nutrition disorders	6 (4.0)	5 (3.2)
Hypokalaemia	3 (2.0)	1 (0.6)
Decreased appetite	1 (0.7)	0
Dehydration	1 (0.7)	0
Hypomagnesaemia	1 (0.7)	0
Hyponatraemia	1 (0.7)	1 (0.6)
Hypophagia	1 (0.7)	1 (0.6)
Hyperglycaemia	0	1 (0.6)
Malnutrition	0	1 (0.6)
Blood and lymphatic system disorders	5 (3.3)	11 (7.1)
Thrombocytopenia	3 (2.0)	5 (3.2)
Neutropenia	2 (1.3)	0
Anaemia	1 (0.7)	6 (3.9)
Febrile neutropenia	1 (0.7)	3 (1.9)
Leukopenia	1 (0.7)	0
Myelosuppression	0	1 (0.6)

Event, n (%)	Amivantamab- chemotherapy (N=151)	Chemotherapy (N=155)
Skin and subcutaneous tissue disorders	5 (3.3)	0
Dermatitis acneiform	2 (1.3)	0
Rash	2 (1.3)	0
Rash maculo-papular	1 (0.7)	0
Nervous system disorders	4 (2.6)	5 (3.2)
Cerebrovascular accident	1 (0.7)	0
Encephalopathy	1 (0.7)	0
Myoclonic epilepsy	1 (0.7)	0
Transient ischaemic attack	1 (0.7)	0
Depressed level of consciousness	0	1 (0.6)
Dysarthria	0	1 (0.6)
Headache	0	1 (0.6)
Lacunar infarction	0	1 (0.6)
Syncope	0	1 (0.6)
Vertebrobasilar insufficiency	0	1 (0.6)
General disorders and administration site conditions	3 (2.0)	6 (3.9)
Asthenia	2 (1.3)	1 (0.6)
Death	1 (0.7)	1 (0.6)
Fatigue	0	1 (0.6)
General physical health deterioration	0	1 (0.6)
Influenza like illness	0	1 (0.6)
Pain	0	1 (0.6)
Investigations	3 (2.0)	2 (1.3)
Alanine aminotransferase increased	1 (0.7)	1 (0.6)
Blood creatinine increased	1 (0.7)	1 (0.6)
C-reactive protein increased	1 (0.7)	0
Aspartate aminotransferase increased	0	1 (0.6)
Injury, poisoning and procedural complications	2 (1.3)	2 (1.3)
Infusion related reaction	1 (0.7)	0
Lumbar vertebral fracture	1 (0.7)	0
Femur fracture	0	1 (0.6)
Incisional hernia	0	1 (0.6)
Musculoskeletal and connective tissue disorders	2 (1.3)	4 (2.6)
Back pain	1 (0.7)	0
Myalgia	1 (0.7)	0
Arthralgia	0	1 (0.6)

Event, n (%)	Amivantamab- chemotherapy (N=151)	Chemotherapy (N=155)
Bone pain	0	1 (0.6)
Pain in extremity	0	1 (0.6)
Pathological fracture	0	1 (0.6)
Reproductive system and breast disorders	2 (1.3)	0
Endometrial thickening	1 (0.7)	0
Ovarian mass	1 (0.7)	0
Cardiac disorders	1 (0.7)	2 (1.3)
Cardio-respiratory arrest	1 (0.7)	0
Acute myocardial infarction	0	1 (0.6)
Pericardial effusion	0	1 (0.6)
Hepatobiliary disorders	1 (0.7)	1 (0.6)
Biliary obstruction	1 (0.7)	0
Cholecystitis acute	1 (0.7%)	0
Jaundice cholestatic	0	1 (0.6)
Immune system disorders	1 (0.7%)	0
Contrast media reaction	1 (0.7%)	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (0.7%)	1 (0.6)
Prostate cancer	1 (0.7%)	0
Cancer pain	0	1 (0.6)
Renal and urinary disorders	1 (0.7%)	0
Acute kidney injury	1 (0.7%)	0
Ear and labyrinth disorders	0	1 (0.6)
Hypoacusis	0	1 (0.6)
Based on Table 37 of CS ¹ CS = company submission; DCO = data cut-off; SAE = serious adverse event		

3.2.13.4 TEAEs $\geq$ CTCAE Grade 3

Treatment-emergent AEs at Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 and above were reported in 114 participants (75.5%) in the amivantamab-chemotherapy arm, and 83 patients (53.5%) in the chemotherapy arm. TEAEs $\geq$ CTCAE Grade 3 are presented in Table 3.26. Considering TEAEs by system organ class, a greater proportion of TEAEs in all reported groups were recorded in the amivantamab-chemotherapy arm than the chemotherapy arm.

Comparing individual TEAEs in both treatment arms, all TEAEs $\geq$ Grade 3 are reported at a markedly higher frequency in the amivantamab-chemotherapy arm compared to the chemotherapy arm, with the exception of anaemia (10.6% vs 12.3%, respectively) and thrombocytopaenia (9.9% and 10.3%, respectively).

Table 3.26: Number of patients with Grade ≥ 3 TEAEs with frequency of at least 5% in any treatment group by system organ class and preferred term (3 May 2023 DCO; safety analysis set)

Event, n (%)	Amivantamab-chemotherapy (N=151)	Chemotherapy (N=155)
Patients with 1 or more Grade ≥ 3 AEs	114 (75.5)	83 (53.5)
Blood and lymphatic system disorders	58 (38.4)	52 (33.5)
Neutropenia	50 (33.1)	35 (22.6)
Leukopenia	17 (11.3)	5 (3.2)
Anaemia	16 (10.6)	19 (12.3)
Thrombocytopenia	15 (9.9)	16 (10.3)
Infections and infestations	31 (20.5)	11 (7.1)
Paronychia	10 (6.6)	0
Skin and subcutaneous tissue disorders	28 (18.5)	0
Rash	17 (11.3)	0
Metabolism and nutrition disorders	23 (15.2)	7 (4.5)
Hypokalaemia	13 (8.6)	2 (1.3)
General disorders and administration site conditions	14 (9.3)	9 (5.8)
Asthenia	8 (5.3)	4 (2.6)
Based on Table 36 of CS ¹ AE = adverse event; CS = company submission; DCO = data cut-off; TEAE = treatment-emergent adverse event		

3.2.13.5 Deaths

All deaths occurring prior to the 3 May DCO were reported; this data is presented as Table 3.27. The vast majority of deaths during the PAPILLON trial were due to progressive disease: 20 deaths (13.1%) in the amivantamab-chemotherapy arm, and 30 deaths (19.4%) in the chemotherapy arm. In the amivantamab-chemotherapy arm, 7 deaths (4.6%) occurred due to adverse events during the study, compared to 4 deaths (2.6%) in the chemotherapy arm. A further 3 deaths (2%) occurred in the amivantamab-chemotherapy safety population due to AE, within 30 days of the last dose, compared to 4 deaths (2.6%) for the chemotherapy arm.

Adverse events causing death are presented as Table 3.28. The majority of AE-related deaths were due to infections and infestations (4 deaths (2.6%) for amivantamab-chemotherapy, 1 death (0.6%) for chemotherapy).

Table 3.27: Summary of death and cause of death (3 May 2023 DCO; full analysis set)

Event, n (%)	Amivantamab-chemotherapy (N=151)	Chemotherapy (N=155)
Deaths during study^a	28 (18.3)	42 (27.1)
Progressive disease	20 (13.1)	30 (19.4)
AE	4 (2.6)	9 (5.8)
Other	2 (1.3)	3 (1.9)
COVID-19	2 (1.3)	0

Event, n (%)	Amivantamab-chemotherapy (N=151)	Chemotherapy (N=155)
Deaths within 30 days of last dose^{a,b}	7 (4.6)	7 (4.5)
AE	3 (2.0)	4 (2.6)
Progressive disease	1 (0.7)	2 (1.3)
COVID-19	2 (1.3)	0
Other	1 (0.7)	1 (0.6)
Deaths within 30 days of last dose (main study)^{b,c}	7 (4.6)	4 (2.6)
AE	3 (2.0)	2 (1.3)
COVID-19	2 (1.3)	0
Other	1 (0.7)	1 (0.6)
Progressive disease	1 (0.7)	1 (0.6)
Based on Table 38 of CS ¹ ^a Subjects who died during the treatment switch phase are included; ^b Subjects who died within 30 days will be counted in deaths during study as well; ^c Subjects who died during the treatment switch phase are excluded. AE = adverse event; CS = company submission; DCO = data cut-off		

Table 3.28: Number of patients with TEAEs leading to death by system organ class and preferred term (3 May 2023 DCO; safety analysis set)

Event, n (%)	Amivantamab-chemotherapy (N=151)	Chemotherapy (N=155)
Patients with 1 or more AEs leading to death	7 (4.6)	4 (2.6)
Infections and infestations	4 (2.6)	1 (0.6)
COVID-19	1 (0.7)	0
COVID-19 pneumonia	1 (0.7)	0
Pneumonia	1 (0.7)	0
Sepsis	1 (0.7)	1 (0.6)
Cardiac disorders	1 (0.7)	1 (0.6)
Cardio-respiratory arrest	1 (0.7)	0
Acute myocardial infarction	0	1 (0.6)
General disorders and administration site conditions	1 (0.7)	1 (0.6)
Death	1 (0.7)	1 (0.6)
Nervous system disorders	1 (0.7)	0
Cerebrovascular accident	1 (0.7)	0
Respiratory, thoracic and mediastinal disorders	0	1 (0.6)
Dyspnoea	0	1 (0.6)
Based on Table 39 of CS ¹ Patients were counted only once for any given event, regardless of the number of times they actually experienced the event. AEs were coded using MedDRA Version 25.0. AE = adverse event; CS = company submission; DCO = data cut-off; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event		

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

Indirect treatment comparison (ITC) was conducted by the company because there were no direct comparative data for amivantamab plus chemotherapy versus relevant comparators (pembrolizumab plus chemotherapy).

One RCT (PAPILLON trial) and four RWE databases in the NECTAR were identified via the SR and the data from these studies were used in the ITC analysis. Four RWE databases were used in the ITC: NCRAS, Epidemiological Strategy and Medical Economics (ESME), COTA and ConcertAI. The company made the following statements:

- “NCRAS is a population-based cancer registry covering England, which contains detailed and quality assured diagnostic and pathologic data for all people living in England diagnosed with malignant and pre-malignant neoplasms since 1971. This database is linked to sources such as the Somatic Molecular Dataset (SMD), Systemic Anti-Cancer Therapy dataset (SACT), Cancer Outcomes and Services Dataset (COSD) and Hospital Episode Statistics (HES) datasets. Overall, the database covers around 500,000 patients per year.
- ESME is a multicentre, real-world database using a retrospective data collection process from medical centres in France. The ESME dataset contains three data platforms, one of which is in metastatic NSCLC and is therefore relevant to this submission: The French Epidemio-Strategy and Medical Economics Advanced or Metastatic Lung Cancer Data Platform (ESME-LC). This is a longitudinal database derived from routine care electronic health records for advanced and metastatic lung cancer patients treated at 36 participating centres across France. The ESME-LC database includes around 26,000 advanced and metastatic lung cancer patients.
- The COTA and ConcertAI databases are both US datasets. The COTA database provides detailed real-world oncology patient data, including patients with NSCLC and confirmed EGFR exon 20 insertion mutations from five unique sites of care across the US. Additionally, the ConcertAI database sources clinical data from multiple partnerships spanning a broad range of US geographies. Inclusion of patients from the US databases was considered suitable as there were no notable differences in observed demographics and baseline characteristics between patients included in the US databases versus the European databases, with inclusion of the US data enriching this real-world evidence source”.¹

Table 3.29 presents the evidence sources used in the ITC. While the PAPILLON trial has median follow-up of 14.6 months for PFS and 20.9 months for OS, the median follow-up duration for RWE databases ranged from 27.2 months to 51.5 months.

Table 3.29: Evidence sources used in the ITC

Data Source	Country	Design	Period (years)	Median follow-up (months)	Data available
PAPILLON	Multi-centre	RCT	████████	14.6 (PFS) ^a , 20.9 (OS) ^b	IPD
NCRAS	UK	RWE	2016–2022	27.2	IPD
ESME	France	RWE	████████	████	IPD; indirectly accessible
COTA	US	RWE	██	████	IPD
ConcertAI	US	RWE	████████	████	IPD

Data Source	Country	Design	Period (years)	Median follow-up (months)	Data available
Based on Table 25 of CS ¹ ^a Median follow-up (months) for amivantamab-chemotherapy at the 3 May 2023 DCO. ^b Median follow-up (months) at the 31 October 2023 DCO. CS = company submission; DCO = data cut-off; ESME = Epidemiological Strategy and Medical Economics; IPD = individual participant data; ITC = indirect treatment comparison; N/A = not available; NCRAS = National Cancer Registration and Analysis Service; OS = overall survival; PFS = progression-free survival; RCT = randomised controlled trial; RWE = real-world evidence; UK = United Kingdom; US = United States					

3.3.1 Eligibility criteria

The PAPILLON trial had a predefined eligibility criteria and this trial recruited patients with EGFR exon 20 insertion mutation-positive advanced NSCLC. In order to closely align the pooled patient population from the RWE databases with the population of the PAPILLON trial, additional eligibility criteria were applied to each RWE data source. The eligibility criteria for the RWE data sources are presented in Table 3.30. Following the application of this eligibility criteria, N= [REDACTED] patients were included from the pooled RWE sources.¹

Table 3.30: Eligibility criteria for RWE data sources

Eligibility criteria for patients in the RWE data sources	Adult patients (≥18 years of age) Histologic confirmation of non-squamous advanced NSCLC ^a EGFR exon 20 insertion mutation diagnosis before 30 days after the start of first-line treatment No record of other malignancy in the 24 months before advanced NSCLC diagnosis Received first-line treatment, following advanced NSCLC diagnosis Record of ECOG performance status of 0 or 1 at the time of first-line treatment in the advanced NSCLC phase, with patients with missing ECOG performance status included
Based on Table 26 of CS ¹ ^a Includes patients diagnosed with Stage IIIB, IIIC, IV, IV-A, or IV-B NSCLC, or diagnosed with early-stage NSCLC and subsequently developed recurrent or progressive disease CS = company submission; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; NSCLC = non-small cell lung cancer; RWE = real-world evidence	

3.3.2 Patient characteristics

The baseline patient characteristics from the PAPILLON trial and each of the RWE databases are presented in Table 3.31. These patients' baseline data from the RWE databases are presented alongside baseline characteristics of the amivantamab-chemotherapy arm of the PAPILLON trial for means of comparison. The baseline characteristics are summarised for the total pooled population of RWE databases (N= [REDACTED]).¹

Table 3.31: Demographics and baseline patients characteristics from the PAPILLON trial and RWE databases

Characteristic, n (%)	PAPILLON (ACP)	Overall RWE	ESME	NCRAS	ConcertAI	COTA
N	153	[REDACTED]	[REDACTED]	23	[REDACTED]	[REDACTED]
Sex						
Female	85 (55.6)	[REDACTED]	[REDACTED]	16 (69.6)	[REDACTED]	[REDACTED]

Characteristic, n (%)	PAPILLON (ACP)	Overall RWE	ESME	NCRAS	ConcertAI	COTA
Male	68 (44.4)	****	****	7 (30.4)	****	****
ECOG performance status^a						
0	54 (35.3)	****	****	10 (43.5)	****	****
1	99 (64.7)	****	****	13 (56.5)	****	****
Missing	0 (0.0)	****	****	-	****	****
Smoking status						
Current or prior smoker	65 (42.5)	****	****	0 (0.0)	****	****
No smoking history	88 (57.5)	****	****	0 (0.0)	****	****
Missing	0 (0.0)	****	****	23 (100)	****	****
Metastatic site						
Adrenal glands						
No	NR	****	****	21 (91.3)	****	****
Yes	****	****	****	2 (8.7)	****	****
Bone						
No	NR	****	****	19 (82.6)	****	****
Yes	****	****	****	4 (17.4)	****	****
Brain						
No	****	****	****	23 (100)	****	****
Yes	****	****	****	0	****	****
Liver						
No	135 (88.2)	****	****	19 (82.6)	****	****
Yes	****	****	****	4 (17.4)	****	****
Lymph nodes						
No	NR	****	****	12 (52.2)	****	****
Yes	****	****	****	11 (47.8)	****	****
Number of metastatic locations (CT)						
0	NR	****	****	0	****	****
1	NR	****	****	5 (21.7)	****	****
2	NR	****	****	10 (43.5)	****	****
3	NR	****	****	5 (21.7)	****	****
4	NR	****	****	1 (4.3)	****	****
5	NR	****	****	2 (8.7)	****	****
6	NR	****	****	0 (0.0)	****	****
7	NR	****	****	0 (0.0)	****	****
Based on Table 27 of CS ¹ ACP = amivantamab chemotherapy; CS = company submission; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; ESME = Epidemiological Strategy and Medical						

Characteristic, n (%)	PAPILLON (ACP)	Overall RWE	ESME	NCRAS	ConcertAI	COTA
Economics; NCRAS = National Cancer Registration and Analysis Service; NR = not reported; RWE: real-world evidence						

3.3.3 Patient populations included in the analysis

The individual participant data (IPD) for all patients in the amivantamab-chemotherapy arm of the PAPILLON trial (N=153) were used in the ITC analysis. The index date for patients in the PAPILLON trial was the date that patients received the first dose of amivantamab.

Furthermore, IPD data from the RWE sources were pooled for the comparison of patients' baseline characteristics, first-line treatments as well as outcomes. The pooled dataset was stratified by first-line treatment received by patients. There were [REDACTED] patients who received pembrolizumab plus chemotherapy in the dataset. The index date for the RWE dataset was the date of initiation of first-line treatment for patients with advanced NSCLC with a confirmed EGFR exon 20 insertion mutation.¹

The last date of follow up for both the PAPILLON trial and the RWE data was the last contact date, last enrolment date, or continuous enrolment end date (if applicable), or the DCO date, whichever took place the earliest.¹

3.4 Critique of the indirect comparison and/or multiple treatment comparison

3.4.1 Identification and adjustment of prognostic variables

Patients who received pembrolizumab-chemotherapy in the first-line setting from the pooled RWE data were re-weighted to provide a similar distribution of confounders compared with the amivantamab-chemotherapy arm of the PAPILLON trial.

These potential prognostic factors for patients with advanced NSCLC were identified and ranked on the basis of an SR and expert validation being conducted in 2021. The full list of prognostic factors considered for adjustment in the analysis (in rank order) was:¹

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

The company stated that a 'missing' category was included for variables if needed. The variables with high numbers of missing values or those variables which led to lack of convergence of the propensity score model were not included in the adjustment of prognostic variables. The company further stated that an advisory board consisting of clinical experts in NSCLC and EGFR exon 20 insertion mutations concluded that these selected variables were sufficient for adjustment.¹

The EAG requested the company to clarify which baseline characteristics were used to estimate the PS. The EAG also requested the company to provide a table showing which baseline characteristics were included from the SR, which by clinical experts and which were available in the IPD for the ITC.

In responding to the EAG's request, the company made the following statement: *"Most prognostic variables identified as clinically important were available in the external data sources and were therefore adjusted for in the analyses. However, adjusting for available, clinically important, prognostic variables cannot entirely exclude bias due to residual confounding, as with any non-randomised comparison. The set of potential confounders was pre-specified following recommendations from the systematic literature review (SLR) and further validated through feedback from clinical experts. The individual participant data (IPD) received from participating sites were limited to these pre-specified variables, as detailed in the table below. All variables identified in the SLR that were commonly available across databases were included in the analysis. Consequently, a sensitivity analysis was deemed unnecessary."*⁴

Table 3.32: Comparison of baseline characteristics within the analysis

Baseline characteristics (SLR and clinical experts)	US	NCRAS	ESME	Included in the analysis	Reason for exclusion
Functional status ECOG at baseline					
Presence of brain metastases					
Presence of liver metastases					
Any other metastatic locations					
Age at baseline					
Asian ethnicity					
Smoking history					
Gender					
Based on Table 8 of company clarification response ⁴ ECOG = Eastern Cooperative Oncology Group; ESME = Epidemiological Strategy and Medical Economics; NCRAS = National Cancer Registration and Analysis Service; SLR = systematic literature review; US = United States					

3.4.2 Propensity score weighting

Propensity scores were used to adjust for prognostic factors in the ITC analysis between the patient populations being compared because an imbalance in these prognostic factors may have an impact on patient outcomes.¹ Propensity scores are defined as the probability of each patient receiving a particular treatment depending on their baseline covariates. When propensity scores are derived for each patient, patients between the patient populations being compared can then be matched or weighted or matched on the basis of their propensity scores.¹

Propensity scores were estimated by using logistic regression models where a binary treatment variable was used as the dependent variable which was the variable being predicted.¹ In the logistic regression models, these identified prognostic factors were used as explanatory variables, which were factors being used to predict the dependent variable. Relevant covariates were included in the logistic regression models in order of the ranking (which was described in the Section 3.3.1). It should be noted that adding these covariates into the logistic regression model was also based on data availability and the level of missing data from the data sources.¹

The estimated propensity scores were used to derive the weights for each patient. The propensity scores were then converted to ATT inverse probability weights. The company stated that this approach was selected as IPD data were available from the RWE data sources.¹

By using this approach, the company further stated that patients in the amivantamab-chemotherapy arm of the PAPILLON trial received a weight of 1 (i.e., remained unchanged), while patients in the comparator arm were re-weighted by a factor of $PS/(1-PS)$ which estimated the treatment effect in the amivantamab-chemotherapy arm.¹

The company also stated that in order to maintain the original sample size for both of the adjusted populations and to reflect the associated uncertainty, ATT weights were multiplied by the ratio of the original sample size versus the sum of the ATT weights, which would make the sum of these recalculated weights equal to the original sample size.¹

3.4.3 Estimating treatment effect

Treatment effect was then estimated by using a multivariable model where all of the relevant prognostic variables (which were listed above) were included as covariates together with the treatment indicator.¹ The multivariable regression analyses were then performed by using the prognostic variables as covariates in the regression model (Cox regression models for time to event endpoints).¹ Each prognostic factor was assessed separately as well as including all covariates in a multivariable model to assess the outcomes. The same set of covariates which were considered for propensity score methods were adjusted for in the outcome regression modelling after evaluating the impact of missing values in the prognostic factors. The company also stated that the time-to-event endpoints included in these ITCs were summarised for amivantamab-chemotherapy and pembrolizumab-chemotherapy treatment arms by using the total number and percentage of patients experiencing events (time to next treatment [TTNT] and OS) and the number and percentage of censored patients.¹

The KM estimates were produced with presenting summary statistics such as the median time to event with corresponding 95% CI (when estimable). The hazard ratios (HRs) with corresponding 95% CIs were estimated by using a weighted Cox proportional hazards model with treatment as the only covariate.¹

3.4.4 Adjustment of baseline characteristics

Because there were indirectly accessible IPD data from the ESME trial, the amivantamab-chemotherapy arm and the pembrolizumab-chemotherapy indirectly accessible population (ESME) were re-weighted separately to the pembrolizumab-chemotherapy directly accessible population (NCRAS, COTA and ConcertAI). The outcomes were then pooled between the two separate analyses.¹

The unadjusted and ATT-adjusted baseline characteristics for the amivantamab-chemotherapy arm of the PAPILLON trial and the pembrolizumab-chemotherapy directly accessible population (NCRAS, COTA and ConcertAI) are presented in Table 3.33. With adjustment, all variables were broadly aligned between the two treatment groups.

The unadjusted and ATT-adjusted baseline characteristics for the amivantamab-chemotherapy arm of the PAPILLON trial and the pembrolizumab-chemotherapy indirectly accessible population (ESME) are presented in Table 3.34. With adjustment, all variables were generally aligned between the two treatment groups.

Table 3.33: Unadjusted and ATT-adjusted baseline characteristics for patients in the amivantamab-chemotherapy arm and directly accessible pembrolizumab-chemotherapy population (NCRAS, ConcertAI and COTA)

Variable, n (%)	PC-IO Unadjusted	ACP Unadjusted	SMD Unadjusted	PC-IO Adjusted	ACP Adjusted	SMD Adjusted
Total, n	████	████		████	████	
ECOG performance status						
0	████	████	████	████	████	████
1	████	████		████	████	
Missing	████	████		████	████	
Metastatic site brain						
No	████	████	████	████	████	████
Yes	████	████		████	████	
Metastatic site liver						
No	████	████	████	████	████	████
Yes	████	████		████	████	
Age groups (cut-off = 65 years)						
≤65 years	████	████	████	████	████	████
>65 years	████	████		████	████	
Based on Table 28 of CS ¹ ACP = amivantamab-chemotherapy; ATT = average treatment effect for the treated; CS = company submission; ECOG = Eastern Cooperative Oncology Group; NCRAS = National Cancer Registration and Analysis Service; PC-IO = platinum chemotherapy-immune-oncology; SMD = standardised mean difference						

Table 3.34: Unadjusted and ATT-adjusted baseline characteristics for patients in the amivantamab-chemotherapy arm and indirectly accessible pembrolizumab-chemotherapy population (ESME)

Variable, n (%)	PC-IO Unadjusted	ACP Unadjusted	SMD Unadjusted	PC-IO Adjusted	ACP Adjusted	SMD Adjusted
Total, n	████	████	████	████	████	████
ECOG performance status						
0	████	████	████	████	████	████
1	████	████		████	████	
Missing	████	████		████	████	
Metastatic site brain						
No	████	████	████	████	████	████
Yes	████	████		████	████	
Metastatic site liver						
No	████	████	████	████	████	████
Yes	████	████		████	████	

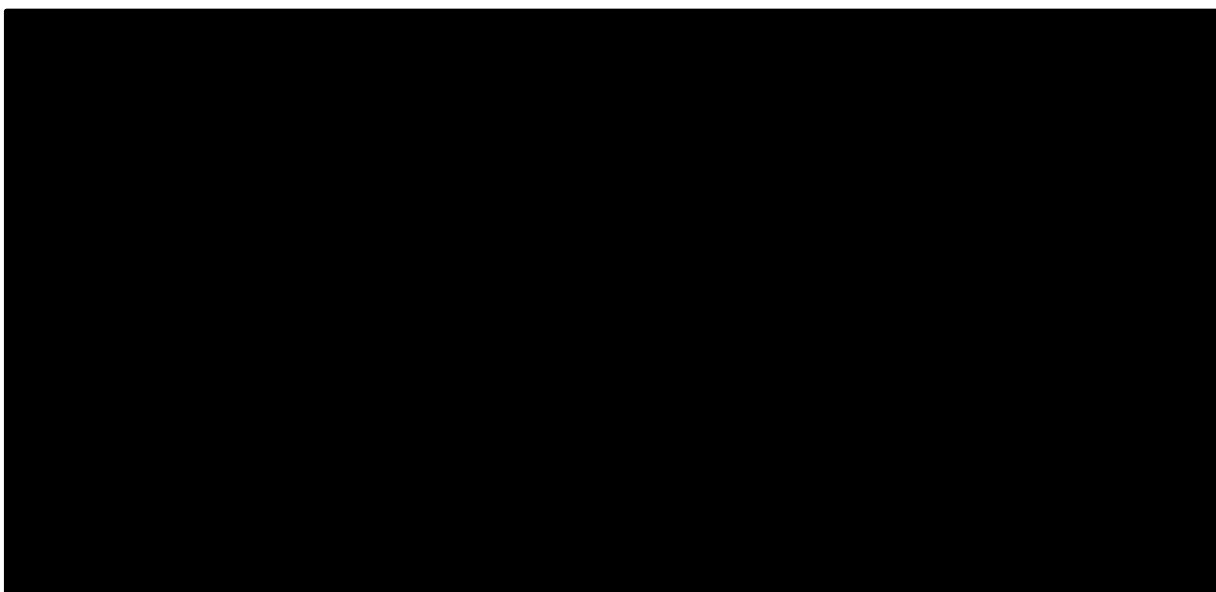
Variable, n (%)	PC-IO Unadjusted	ACP Unadjusted	SMD Unadjusted	PC-IO Adjusted	ACP Adjusted	SMD Adjusted
Age groups (cut-off=65 years)						
≤65 years	████	████	████	████	████	████
>65 years	████	████		████	████	
Based on Table 29 of CS ¹ ACP = amivantamab-chemotherapy; ATT = average treatment effect for the treated; CS = company submission; ECOG = Eastern Cooperative Oncology Group; ESME = Epidemiological Strategy and Medical Economics; PC-IO = platinum chemotherapy-immune-oncology; SMD = standardised mean difference						

3.4.5 Results of time to next treatment

The adjusted analysis demonstrated that amivantamab-chemotherapy was associated with a █████ % in the risk of initiating next treatment versus pembrolizumab-chemotherapy (adjusted time to next treatment [TTNT] HR: █████ [95% CI: █████; Wald p-value < █████). Furthermore, amivantamab-chemotherapy was associated with substantially longer median TTNT (████ months, 95% CI: █████) compared with pembrolizumab-chemotherapy (████ months, 95% CI: █████).¹

The unadjusted and ATT-adjusted TTNT Kaplan-Meier (KM) curves for amivantamab-chemotherapy and the pooled pembrolizumab-chemotherapy population (NCRAS, ESME, COTA, ConcertAI) are presented in Figure 3.12.

Figure 3.12: Unweighted and ATT-weighted TTNT KM curves for amivantamab-chemotherapy versus pembrolizumab-chemotherapy (pooled RWE)



Based on Figure 20 of CS¹

ACP = amivantamab-chemotherapy; ATT = average treatment effect for the treated; CI = confidence interval; CS = company submission; HR = hazard ratio; IO = immunotherapy; KM = Kaplan-Meier; NA = not applicable; RWE = real-world evidence; TTNT: time to next treatment.

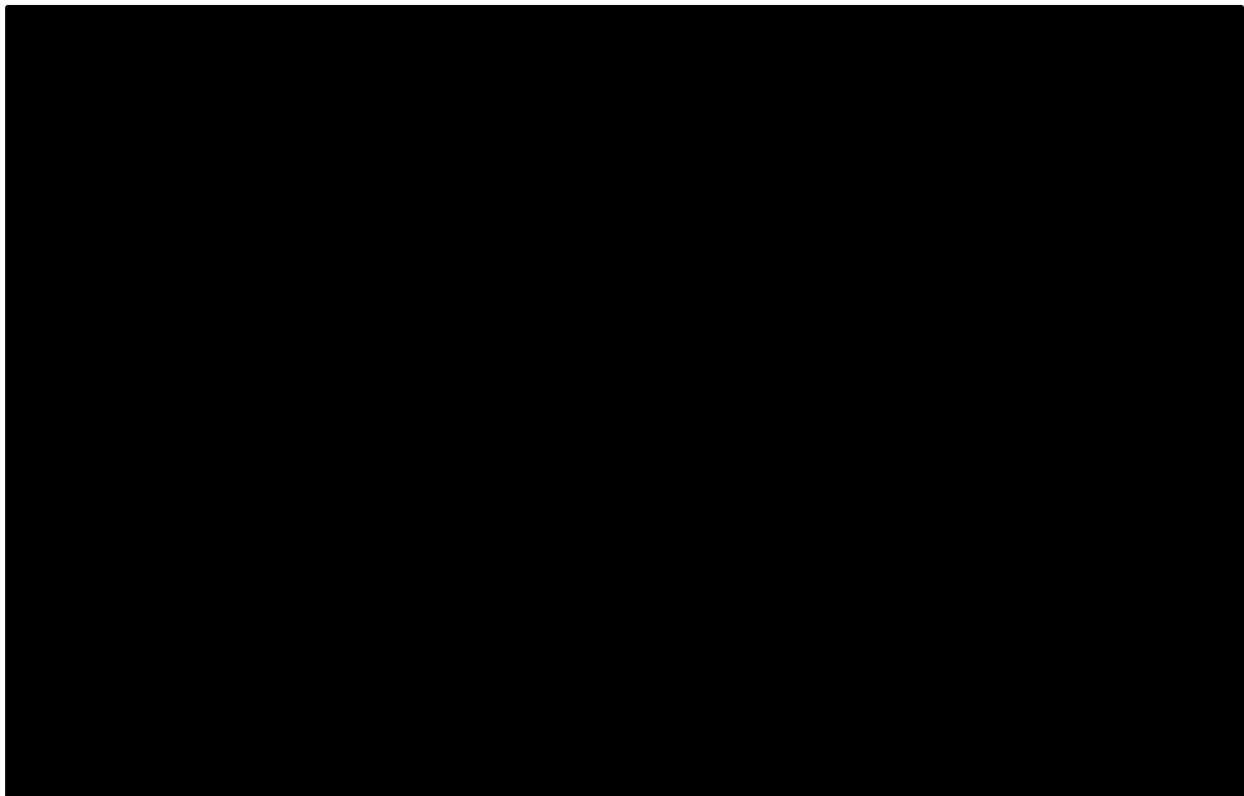
3.4.6 Results of overall survival

The OS data for amivantamab was informed by the most recent 31 October 2023 DCO of the PAPILLON trial. The ITC results showed that amivantamab-chemotherapy was associated with a

statistically significant reduction (█████ %) in the risk of death versus pembrolizumab-chemotherapy (ATT-adjusted HR: █████ [95% CI: █████ -█████]; Wald p-value=█████). Based on the adjusted analysis, the median OS for patients who received amivantamab-chemotherapy was █████ (95% CI: █████ -█████). However, the median OS █████ for patients who received pembrolizumab-chemotherapy █████ months, 95% CI: █████).¹

The unadjusted and ATT-adjusted OS KM curves for amivantamab-chemotherapy and the pooled pembrolizumab-chemotherapy population (NCRAS, ESME, COTA, ConcertAI) are presented in Figure 3.13.

Figure 3.13: Unweighted and ATT-weighted OS KM curves for amivantamab-chemotherapy versus pembrolizumab-chemotherapy (pooled RWE)



Based on Figure 21 of CS¹

ACP = amivantamab-chemotherapy; ATT = average treatment effect in the treated; CI = confidence interval; CS = company submission; HR: hazard ratio; IO: immunotherapy; KM = Kaplan-Meier; NA: not applicable; OS: overall survival; RWE = real-world evidence

Table 3.35 presents a summary of unadjusted and ATT-weighted efficacy outcomes for amivantamab plus chemotherapy versus pembrolizumab plus chemotherapy. These results demonstrated that amivantamab plus chemotherapy was associated with a statistically significant improvement for adjusted TTNT and OS compared to pembrolizumab plus chemotherapy.

Table 3.35: Summary of ITC results for amivantamab-chemotherapy versus pembrolizumab-chemotherapy

Outcome	Unadjusted analysis	ATT-adjusted analysis

	Median, months (95% CI)	HR (95% CI)	Wald p- value	Median, months (95% CI)	HR (95% CI)	Wald p- value
TTNT						
Amivantamab- chemotherapy	████████	████████	████████	████████	████████	████████
Pembrolizumab- chemotherapy	████████			████████		
OS						
Amivantamab- chemotherapy	████████	████████	████████	████████	████████	████████
Pembrolizumab- chemotherapy	████████			████████		
Based on Table 30 of CS ¹ ATT: average treatment effect in the treated; CI: confidence interval; CS = company submission; HR: hazard ratio; ITC: indirect treatment comparison; NE = not estimable; OS: overall survival; TTNT: time to next treatment						

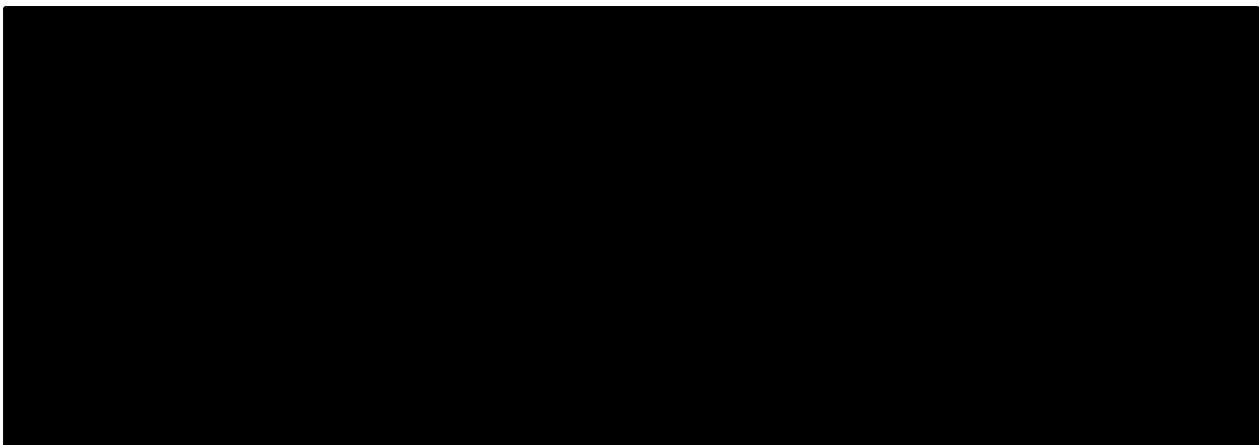
3.4.7 Sensitivity analysis

The EAG requested the company to conduct sensitivity analyses such as using regression adjustment and/or a doubly robust method. In responding to the EAG's request, the company provided the following statement:

- “Covariate adjustment and doubly robust regression require centralized pooling of all individual participant data (IPD). Due to the remote access setup of the IPD in ESME, these analyses could not be performed on the pooled NECTAR data. However, these methods can be applied using the UK data independently with results for both methods shown in the plot below.
- Using only the UK data, an analysis for a specific treatment class is not feasible due to a limited patient sample (4 patients for pembrolizumab + IO) class. However, it was feasible when taking into account all available UK RW data (RWCP) from 23 patients (i.e., the full NCRAS dataset included within the NECTAR study)”.⁴

The EAG also requested the company to conduct sensitivity analysis by using UK data only. In responding to the EAG's request, the company conducted sensitivity analysis by using UK data only.⁴ Figure 3.14 presents the sensitivity analysis of overall survival outcome for UK data only by considering full NCRAS sample (n=23).

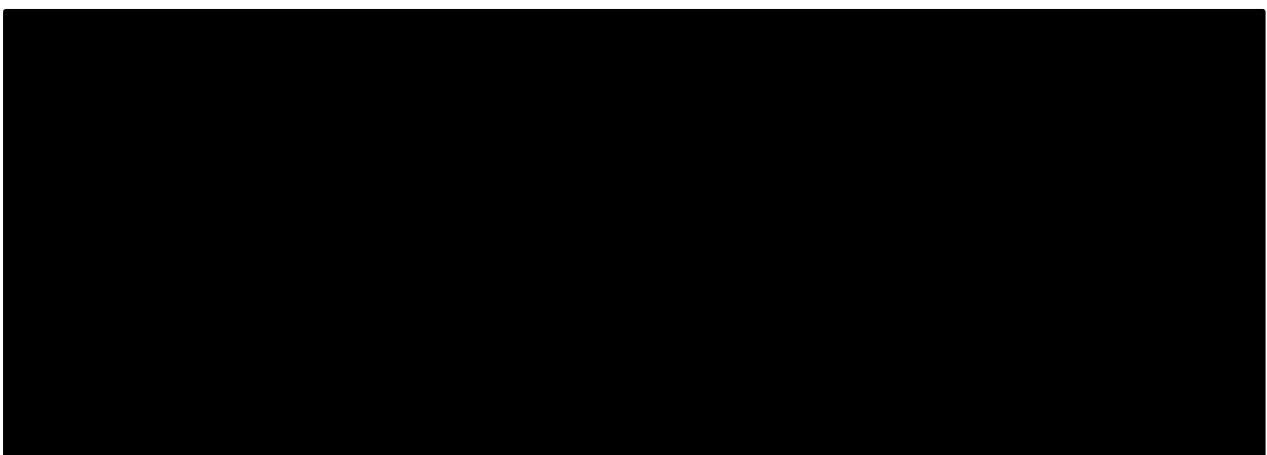
Figure 3.14: Overall survival (UK data only, considering full NCRAS sample, n=23)



Based on Figure 4 of company response clarification⁴

ACP = amivantamab in combination with carboplatin and pemetrexed; ATC = average treatment effect in the control; ATT = average treatment effect of the treated; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group HR = hazard ratio; NCRAS = National Cancer Registration and Analysis Service; RW = real-world; UK = United Kingdom

Figure 3.15: Time to next treatment (UK data only, considering full NCRAS sample, n=23)



Based on Figure 5 of company response clarification⁴

ACP = amivantamab in combination with carboplatin and pemetrexed; ATC = average treatment effect in the control; ATT = average treatment effect of the treated; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group HR = hazard ratio; NCRAS = National Cancer Registration and Analysis Service; RW = real-world; UK = United Kingdom

The results of ATT analysis by using the UK data only were consistent with the results of the ATT analysis. It should also be noted that based on UK data only, there were consistencies between the results of ATT analysis and those results of average treatment effect in the control (ATC) analysis, covariate adjustment analysis and doubly robust analysis.

3.4.8 Additional analysis

The EAG requested the company to present the ITC results for comparisons with all relevant comparators. In responding to the EAG's request, the company provided the ITC results for the comparison of amivantamab with chemotherapy versus immunotherapy (IO) alone as a comparator. The company stated that because of a small number of patients within the immunotherapy alone

treatment class, ATT-adjustment was not possible. Therefore, only unadjusted results were presented. The company made further statement that “results for the IO alone treatment class from the NECTAR study are expected to be representative of patients receiving pembrolizumab monotherapy given 75% (15/20) of patients within the IO alone treatment class were receiving pembrolizumab monotherapy”.⁴

3.4.8.1 Results of overall survival

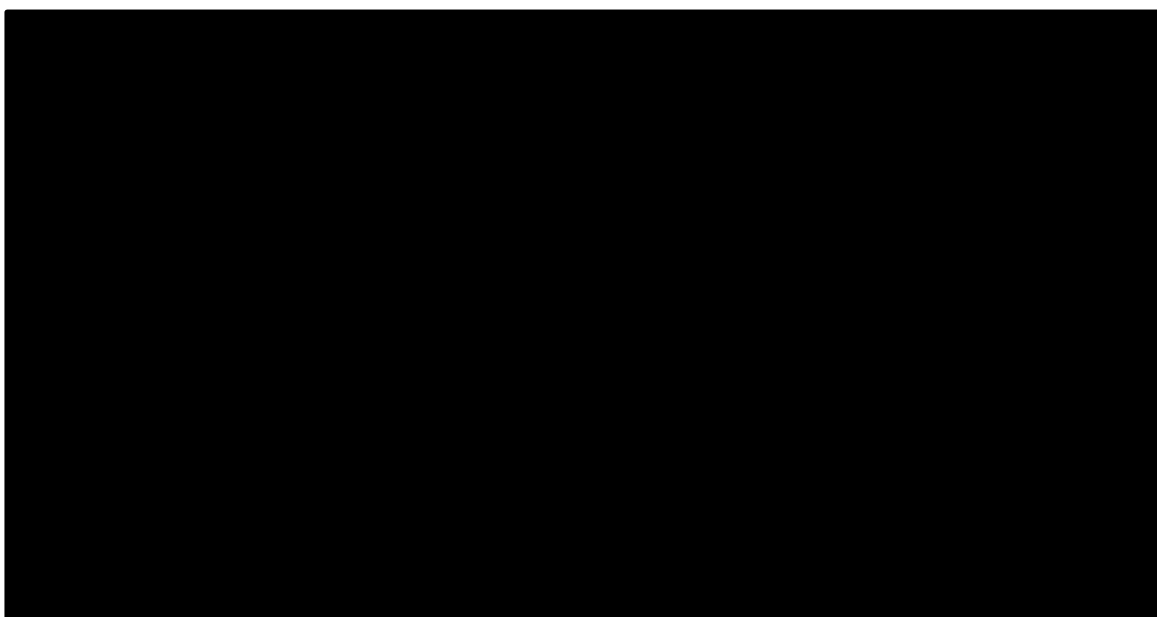
On the basis of unadjusted HR estimates of OS, amivantamab with chemotherapy was associated with statistically significant improvement in OS compared with IO alone [REDACTED] 95% CI [REDACTED]; Wald p-value = [REDACTED]. The unadjusted median OS for patients receiving IO alone was [REDACTED] months (95% CI: [REDACTED] however, the median OS was [REDACTED] for patients receiving amivantamab with chemotherapy.⁴

These results are presented in Table 3.36 and Figure 3.16.

Table 3.36: Unadjusted HR estimates of OS: ACP versus IO alone treatment class (Oct 2023 OS data)

OS	Unadjusted Analysis			
	N	Median, months (95% CI)	HR (95% CI)	Wald-p-value
ACP vs:	153	NE (28.32, NE)		
IO	20			
Based on Table 9 of company clarification response ⁴ ACP = amivantamab with carboplatin plus pemetrexed (PAPILLON active arm); CI = confidence interval; HR = hazard ratio; IO = immunotherapy; NE = not estimable; OS = overall survival				

Figure 3.16: Kaplan-Meier curve of OS for ACP versus RWD IO alone – unadjusted results (Oct 2023)



Based on Figure 6 of company clarification response⁴

RWD datasets were ENG-NCRAS, FR-ESME, US-ConcertAI, and US-COTA.

ACP = amivantamab with carboplatin plus pemetrexed (PAPILLON active arm); CI = confidence interval; ENG = England; ESME = Epidemiological Strategy and Medical Economics; FR = France; HR = hazard ratio; IO =

immunotherapy; NA = not applicable; NCRAS = National Cancer Registration and Analysis Service; OS = overall survival; RWD = real-world data; US = United States

3.4.8.2 Results of TTNT

Based on the unadjusted HR analysis of TTNT, amivantamab-chemotherapy was associated with statistically significant improvement in TTNT compared with IO alone (HR: [REDACTED] (95% CI: [REDACTED]; Wald p-value [REDACTED]). The unadjusted median TTNT for patients receiving IO alone was [REDACTED] months (95% CI: [REDACTED]) while the median TTNT was [REDACTED] months (95% CI: [REDACTED]) for patients receiving amivantamab-chemotherapy.⁴ These results are presented in Table 3.37 and Figure 3.17.

Table 3.37: Unadjusted and ATT-Adjusted HR Estimates of TTNT: ACP Versus Pooled RWD Treatments and Classes (Mar 2023)

TTNT	Unadjusted analysis			
	N	Median, months (95% CI)	HR (95% CI)	Wald-p-value
ACP versus:	153	17.7 (13.67, NE)	██████	██████
IO	20	██████		
Based on Table 10 of company clarification response ⁴ ACP = amivantamab with carboplatin plus pemetrexed (PAPILLON active arm); ATT = average treatment effect of the treated; CI = confidence interval; HR = hazard ratio; IO = immunotherapy; NE = not estimable; RWD = real-world data; TTNT: time to next treatment				

Figure 3.17: Kaplan-Meier Curve of TTNT for ACP Versus RWD IO Alone –Unadjusted Results (Mar 2023)



Based on Figure 7 of company clarification response⁴

ATT adjustment was not performed due to small sample size. RWD datasets were ENG-NCRAS, FR-ESME, US-ConcertAI, and US-COTA.

ACP = amivantamab with carboplatin plus pemetrexed (PAPILLON active arm); CI = confidence interval; ENG = England; ESME = Epidemiological Strategy and Medical Economics; FR = France; HR = hazard ratio; IO = immunotherapy; NA = not applicable; NCRAS = National Cancer Registration and Analysis Service; RWD = real-world data; US = United States

Furthermore, the company stated that the efficacy data for pembrolizumab-chemotherapy were informed by the pooled RWE databases from the NECTAR study. However, there was a lack of details on the methodology on the pooling of the data. The EAG requested the company to provide clarification on how the NECTAR data were pooled and whether this was conducted in a methodologically correct way by considering the multi-level structure of the data due to the multiple countries/sources of data. In responding to EAG's request, the company stated that *"a multilevel approach was not used in this analysis to address the potential clustering of patients within data sources. Multilevel modelling incorporates cluster-specific random effects to account for the homogeneity of outcomes within clusters. Including random effects in the Cox proportional hazards model yields a database-specific (conditional) interpretation, which indicates an increased or decreased hazard for each database"*.⁴

The company presented the results by taking into account the correlation within patient due to weights and the correlation within data source. A comparison between the unadjusted and inverse probability weighting (IPW)-ATT-adjusted TTNT and OS data is provided in Table 3.38.

Table 3.38: Comparison between unadjusted and IPW-ATT-adjusted TTNT and OS data

	TTNT		OS	
	Unadjusted	IPW-ATT	Unadjusted	IPW-ATT
Pembrolizumab + IO				
Accounting for correlation within patient due to weights	██████	██████	██████	██████
Accounting for correlation within data source	██████	██████	██████	██████
Platinum-based chemotherapy				
Accounting for correlation within patient due to weights	██████	██████	██████	██████
Accounting for correlation within data source	██████	██████	██████	██████
Based on Table 7 of company clarification response ⁴ ATT = average treatment effect of the treated; IO = immunotherapy; IPW = inverse probability weighting; OS = overall survival; TTNT = time to next treatment				

EAG comment:

- The ITC analysis was based on the data from one RCT (PAPILLON trial) and four RWE databases in the NECTAR. The four RWE databases used in the ITC were NCRAS, ESME, COTA and ConcertAI. The company stated that the efficacy data for pembrolizumab plus chemotherapy were informed by the pooled RWE databases from the NECTAR study. However, there was a lack of details on the methodology on the pooling of the data. The EAG requested the company to provide clarification on how the NECTAR data were pooled and whether this was conducted in a methodologically correct way by considering the multi-level structure of the data due to the multiple countries/sources of data.
- In responding to EAG's request, the company stated that *"a multilevel approach was not used in this analysis to address the potential clustering of patients within data sources. Multilevel modelling incorporates cluster-specific random effects to account for the homogeneity of outcomes within clusters."* The company presented the results by taking into account the correlation within patient due to weights and the correlation within data source. However, the company did not conduct the analysis by considering the multi-level structure of the data due to the multiple countries/sources of data.
- The EAG considers that given that the company performed the analyses with a lack of consideration of the multi-level structure of the data due to the multiple countries/sources of data, this may have introduced the limitations in the analysis.
- The ITC used propensity score weighting (PSW) to estimate the ATT in the comparison of amivantamab plus chemotherapy versus pembrolizumab plus chemotherapy. Eight baseline characteristics were listed for consideration in estimating the PS, but summary data were only provided for four baseline characteristics. The EAG requested the company to clarify which

baseline characteristics were used to estimate the PS. The EAG also requested the company to provide a table showing which baseline characteristics were included from the SR, which by clinical experts and which were available in the IPD for the ITC. In responding to the EAG's request, the company provided details of baseline characteristics that were used to estimate the PS. The company also provided reasons (e.g., not available across databases) for excluding some baseline characteristics to estimate the PS.

- The EAG considers that there was a lack of adjustment for some important prognostic variables in the ATT analyses due to limited availability of these variables across RWE databases. It should be noted that the prognostic variables of any other metastatic locations, Asian ethnicity and smoking history were not adjusted for in the ATT analyses due to the limited availability of these variables across RWE databases. Therefore, this limitation may have introduced the uncertainty in the results of ITC analysis.
- For the ITC analysis, the EAG requested the company to follow Decision Support Unit (DSU) Technical Support Document (TSD) 17 in showing all tests of validity of the IPD analysis. In responding to the EAG's request, the company stated that the balance in covariates across both treatment cohorts (before and after IPW adjustment) was assessed by computing the standardised mean differences (SMD) for each covariate. The company further stated that the SMDs together with the distribution of propensity scores (PS) confirmed that the ATT weighted real-world cohort was well balanced across all baseline characteristics versus the observed amivantamab plus chemotherapy cohort.
- The EAG considers that, while SMDs together with the distribution of PS scores showed that the ATT weighted real-world cohort was well balanced across all baseline characteristics versus the observed amivantamab plus chemotherapy cohort for five adjusted baseline characteristics, it was unclear whether some important prognostic variables at baseline (e.g. any other metastatic locations, smoking history and Asian ethnicity) were balanced between the two treatment cohorts due to the lack of adjustment on these important prognostic variables at baseline.
- The EAG requested the company to conduct sensitivity analyses by using the UK data only. In responding to the EAG's request, the company provided the results of sensitivity analyses by using the UK data only. It should be noted that the results of ATT adjusted analysis by using the UK data only were consistent with the results of the base-case ATT adjusted analysis.
- Furthermore, the EAG requested the company to conduct sensitivity analyses to estimate the average treatment effect by adjust to better match the UK real-world data (i.e. UK real-world data receive a PS of 1). In responding to the EAG's request, the company also conducted a sensitivity analysis by using the average treatment in the control (ATC) approach based on the UK data only. The results showed that by using the ATC-adjusted approach as sensitivity analysis, there were consistencies between the results of ATT-adjusted analysis and those results of ATC-adjusted analysis on the basis on the UK data only.
- The EAG requested the company to conduct sensitivity analyses as recommended in TSD 17, such as using regression adjustment and/or a doubly robust method. In responding the EAG's request, the company stated that regression covariate adjustment and doubly robust method required centralized pooling of all IPD. Due to the remote access setup of the IPD in ESME, these analyses could not be performed on the pooled NECTAR data. The company further stated that these methods can be only applied using the UK data independently.
Therefore, the company used alternative adjustment methods such as regression covariate adjustment method and a doubly robust method as sensitivity analyses based on the UK data only. It should be noted that based on UK data only, there were consistencies between the results of ATT adjusted analysis and those results of covariate adjustment analysis and a doubly robust analysis

- The EAG considers that, given that the sensitivity analysis by using alternative adjustment methods such as using regression adjustment and a doubly robust method were not conducted for the data of the base-case ATT adjusted analyses, it was unclear whether the results of base-case ATT adjusted analyses were robust.
- The company also presented the additional ITC results for the comparison of amivantamab plus chemotherapy versus immunotherapy alone during the clarification response stage in responding to the EAG's request. However, these analyses were not conducted by using the ATT adjustment method and/or alternative adjustment methods such as regression adjustment and a doubly robust method because of a small number of patients who received immunotherapy alone. Due to this issue, there were considerable uncertainties on these results of ITC analysis.

3.5 Additional work on clinical effectiveness undertaken by the EAG

Not applicable.

3.6 Conclusions of the clinical effectiveness section

The CS¹ and response to the request for clarification⁴ provided sufficient details for the EAG to appraise the literature searches conducted to identify clinical evidence and safety outcomes in patients with advanced EGFR exon 20 insertion mutated NSCLC. Searches were conducted in January 2021, and updated in September 2021, February 2022, September 2023, March 2024 and June 2024. Searches were transparent and reproducible, and comprehensive strategies were used. Bibliographic databases, conference proceedings and trials registers were searched. Overall, the EAG has no major concerns about the literature searches conducted.

The study selection criteria for participants, interventions, comparators and outcomes in the SR of clinical effectiveness generally encompassed those specified by the NICE final scope.² The data extraction process was satisfactory and in line with recommended good practice in SRs. The process for the assessment of risk of bias in the included studies was satisfactory. The process of assessing risk of bias and the number of reviewers involved were described. The number of studies retrieved, screened and included was clear based on the PRISMA flow chart. The use of the CRD quality assessment checklist for the assessment of risk of bias was appropriate

One unique RCT was identified as being relevant to the SR: one RCT (PAPILLION) provided the main source of evidence. The PAPILLION trial was an international, phase III, double-blinded RCT that assessed the efficacy and safety of amivantamab in combination with carboplatin and pemetrexed for the treatment of adult patients with advanced NSCLC with activating EGFR exon 20 insertion mutations. The EAG rated the PAPILLION trial as being at moderate risk of bias. Given that this PAPILLION trial used crossover study design, the company used appropriate approaches to adjust for treatment switching in the analysis.

At the data cut-off date for primary analysis of PFS (3 May 2023), BICR-assessed PFS was more favourable for amivantamab plus chemotherapy compared with chemotherapy in the population of PAPILLION trial. At the data cut-off date (3 May 2023), there was a strong trend towards improved survival in the amivantamab plus chemotherapy arm compared with the chemotherapy arm of the PAPILLION trial. There were no notable differences in the incidence of SAEs between the amivantamab plus chemotherapy arm and the chemotherapy arm of PAPILLION trial.

The ITC analysis was based on the data from one RCT (PAPILLION trial) and four real-world evidence (RWE) databases in the NECTAR. The four RWE database used in the ITC were NCRAS,

Epidemiological Strategy and Medical Economics (ESME), COTA and ConcertAI. The company stated that the efficacy data for pembrolizumab-chemotherapy were informed by the pooled RWE databases from the NECTAR study. However, there was a lack of details on the methodology on the pooling of the data. The EAG requested the company to provide clarification on how the NECTAR data were pooled and whether this was conducted in a methodologically correct way by considering the multi-level structure of the data due to the multiple countries/sources of data. The company presented the results by taking into account the correlation within patient due to weights and the correlation within data source. However, the company did not conduct the analysis by considering the multi-level structure of the data due to the multiple countries/sources of data. The EAG considers that as the company performed the analyses with lack of consideration of the multi-level structure of the data due to the multiple countries/sources of data, this may have introduced the limitations in the analysis.

The indirect treatment comparison (ITC) uses propensity score weighting (PSW) to estimate the average treatment effect for the treated (ATT) in the comparison of amivantamab plus chemotherapy versus pembrolizumab plus chemotherapy. Eight baseline characteristics were listed for consideration in estimating the PS, but summary data were only provided for four baseline characteristics. The EAG requested the company to clarify which baseline characteristics were used to estimate the PS. In responding to EAG's request, the company provided details of baseline characteristics that were used to estimate the PS.

The EAG considers that there was a lack of adjustment for some important prognostic variables in the ATT analyses due to limited availability of these variables across RWE databases. It should be noted that the prognostic variables of any other metastatic locations, Asian ethnicity and smoking history were not adjusted for in the ATT analyses due to the limited availability of these variables across RWE databases. Therefore, this limitation may have introduced the uncertainty in the results of ITC analysis.

For the ITC analysis, the EAG requested the company to show all tests of validity of the IPD analysis. In responding to the EAG's request, the company stated that the balance in covariates across both treatment cohorts (before and after IPW adjustment) was assessed by computing the standardised mean differences (SMD) for each covariate. The company further stated that the SMDs together with the distribution of PS scores confirmed that the ATT weighted real-world cohort was well balanced across all baseline characteristics versus the observed amivantamab plus chemotherapy cohort.

The EAG considers that, while SMDs together with the distribution of PS scores showed that the ATT weighted real-world cohort was well balanced across versus the observed amivantamab plus chemotherapy cohort for four adjusted baseline characteristics, it was unclear whether some important prognostic variables at baseline (e.g., smoking history, any other metastatic locations and Asian ethnicity) were balanced between the two treatment cohorts due to the lack of adjustment on these important prognostic variables at baseline.

The EAG requested the company to conduct sensitivity analyses by using the UK data only. In responding to the EAG's request, the company provided the results of sensitivity analyses by using the UK data only. It should be noted that the results of ATT analysis by using the UK data only were consistent with the results of the base-case ATT analysis.

The EAG requested the company to conduct sensitivity analyses such as using regression adjustment and/or a doubly robust method. In responding to the EAG's request, the company stated that covariate adjustment and doubly robust regression require centralised pooling of all individual participant data. Due to the remote access setup of the IPD in one RWE dataset (ESME), these analyses could not be performed on the pooled NECTAR data. The company further stated that these methods can be only

applied using the UK data independently. Therefore, the company used alternative adjustment methods such as regression covariate adjustment method and a doubly robust method as sensitivity analyses based on the UK data only. It should be noted that based on UK data only, there were consistencies between the results of ATT analysis and those results of regression covariate adjustment analysis and doubly robust analysis.

The EAG further requested the company to conduct sensitivity analyses to estimate the average treatment effect by adjust to better match the UK real-world data (i.e., UK real-world data receive a PS of 1). In responding to the EAG's request, the company also conducted a sensitivity analysis by using the average treatment in the control (ATC) approach based on the UK data only. Therefore, there were consistencies between the results of ATT analysis and those results of ATC analysis on the basis on the UK data only. The results of ATT analysis based on the UK data only are generalisable to the UK setting.

The EAG considers that, given that the sensitivity analysis by using alternative adjustment methods such as regression adjustment and doubly robust method were not conducted for the data of the base-case ATT analyses, it was unclear whether the results of base-case ATT analyses were robust.

The company further presented additional ITC results for the comparison of amivantamab plus chemotherapy versus immunotherapy alone during the clarification response stage in responding to the EAG's request. However, these analyses were not conducted by using the ATT adjustment method and/or alternative adjustment methods such as regression adjustment and a doubly robust method because of a small number of patients who received immunotherapy alone. Due to this issue, there were considerable uncertainties on these results of ITC analysis.

4. Cost effectiveness

4.1 EAG comment on company's review of cost effectiveness evidence

This section pertains mainly to the review of cost effectiveness analysis studies. However, the search section (4.1.1) also contains summaries and critiques of other searches related to cost effectiveness presented in the company submission. Therefore, the following section includes searches for the cost effectiveness analysis review, measurement and evaluation of health effects as well as for cost and healthcare resource identification, measurement and valuation.

4.1.1 Searches performed for cost effectiveness section

The following paragraphs contain summaries and critiques of all searches related to cost effectiveness, HRQoL and resource use identification presented in the CS.¹ The CADTH evidence-based checklist for the PRESS, was used to inform this critique.¹⁰ The EAG has presented only the major limitations of each search strategy in the report.

Appendices G, H and I of the CS provide details of an SLR conducted to identify relevant studies on cost effectiveness, utilities and HRQoL, and cost/health care resource use in the treatment of patients with advanced NSCLC.¹¹ The searches were conducted in May 2020 and updated in August 2022, October 2023, March 2024 and July 2024.

A summary of the sources searched is provided in Table 4.1.

Table 4.1: Data sources searched for economic evaluations, HRQoL and cost/resource use (as reported in CS)

Resource	Host/Source	Date Ranges	Date searched
Electronic databases			
MEDLINE (inc. In Process & Other Non-Indexed Citations and Daily)	Ovid	1946-1.7.24	4.5.20 2.8.22 4.10.23
Embase	Ovid	1974-1.7.24	12.3.24 1.7.24
Additional resources			
NHS EED	CRD website	to Iss 2/4 Apr 2015	4.5.20
HTA Database		to Iss 4/4 Oct 2016	
International HTA Database	Internet	to 1.7.24	4.5.20 2.8.22 4.10.23 12.3.24 1.7.24
HERC Database of Mapping Studies	Internet	All years	4.5.20 2.8.22
CEA Registry	Internet		4.10.23
EQ-5D Publications Database	Internet		12.3.24
ScHARRHUD	Internet		1.7.24
Conferences			
AACR Annual Meeting	Internet	2018-2024	May 2020

Resource	Host/Source	Date Ranges	Date searched
ELCC		2018-2024	July 2020 March 2024 July 2024
ESMO Congress		2018-2023	
ESMO Asia Congress		2020-2023	
ASCO Annual Meeting		2018-2024	
IASLC WCLC		2020-2023	
ISPOR Europe and international meetings		2018-2024	
AACR = American Association for Cancer Research; ASCO = American Society of Clinical Oncology; CEA Registry = Cost-Effectiveness Analysis Registry; CRD = Centre for Reviews and Dissemination; CS = company submission; ELCC = European Lung Cancer Annual Congress; EQ-5D = EuroQol 5 Dimensions; ESMO = European Society of Medical Oncology; HERC = Health Economics Research Centre; HRQoL = health-related quality of life; HTA = Health Technology Assessment; IASLC WCLC = International Association for the Study of Lung Cancer World Conference on Lung Cancer; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; NHS EED = National Health Service Economic Evaluation Database; SchARRHUD = University of Sheffield Health Utilities Database			

EAG comment:

- A single set of searches was undertaken in May 2020 and updated in August 2022, October 2023, March 2024 and July 2024 to identify relevant studies on cost effectiveness, HRQoL and cost/health care resource use in the treatment of patients with advanced NSCLC. The CS, Appendices G, H and I, and the company's response to the request for clarification provided sufficient details for the EAG to appraise the literature searches.^{1, 4, 11}
- In addition to bibliographic database searches, 15 HTA organisation websites, grey literature resources and seven conference proceedings were searched. Reference checking was conducted. The search documentation was clear and concise, and the searches were well structured, transparent and reproducible.
- The cost effectiveness searches contained a population facet for metastatic NSCLC. This was then combined with study design filters containing terms for economic evaluations, utilities and HRQoL, and cost and resource use. Referenced study design filters were used.
- Database searches were limited to cost/resource use references published since 2015. No date limits were applied to the economic evaluation or HRQoL searches. Searches were not limited by language of publication.
- Conference proceedings were hand-searched for seven key international conferences from 2018-date. Embase was also searched for conference proceedings published between 2018-2024.

4.1.2 Inclusion/exclusion criteria

Inclusion and exclusion criteria for the review on cost effectiveness studies are presented in CS Appendix Table 48. For inclusion and exclusion criteria used for the identification of HRQoL studies and costs and resource use studies, see CS Appendix Tables 54 and 55.

EAG comment: The EAG agrees that the eligibility criteria are suitable to fulfil the company's objective to identify cost effectiveness studies. The rationales for excluding cost effectiveness (CE) studies after full paper reviewing are considered appropriate given the defined in- and exclusion criteria.

4.1.3 Conclusions of the cost effectiveness review

The CS provides an overview of the included cost effectiveness (CS Appendix G), HRQoL (CS Appendix H) and resource use and costs (CS Appendix I) studies. Regarding cost effectiveness studies, a total of 52 unique studies were included (CS Appendix Figure 4). Out of the 52 studies, only two studies included patients with advanced or metastatic NSCLC with activating exon 20 insertion mutations (CS Appendix Table 49). The remaining 50 studies were deprioritised for extraction as they did not include patients with activating exon 20 insertion mutations. The HRQoL SLR did not identify any study for the exon 20 insertion mutation-positive population (CS Appendix Figure 5). The SLR for resource use and costs identified 133 unique studies (CS Appendix Figure 6), out of these only six reported included patients with advanced or metastatic NSCLC with activating exon 20 insertion mutations (CS Appendix Table 56). The remaining studies were deprioritised for extraction as they did not include patients with activating exon 20 insertion mutations.

Eligibility criteria seemed suitable for the SLR performed. However, the EAG would like to ask clarification from the company regarding tables 48, 54, and 55, from CS Appendices. There seems to be a formatting issue which combined part of the two columns of the inclusion and exclusion criteria in the population and publication type rows of the Tables. The EAG would like the company to clarify whether those merged cells should be written as inclusion or exclusion criteria.

4.2 Summary and critique of company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 4.2: NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on CS
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Consistent with NICE reference case
Perspective on costs	NHS and PSS	Consistent with NICE reference case
Type of economic evaluation	Cost utility analysis with fully incremental analysis	Partly consistent with NICE reference case
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Consistent with NICE reference case
Synthesis of evidence on health effects	Based on systematic review	Consistent with NICE reference case
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Consistent with NICE reference case
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Consistent with NICE reference case

Element of health technology assessment	Reference case	EAG comment on CS
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Unclear (from CS chapter 4) whether the UK tariff was used.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Consistent with NICE reference case
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Consistent with NICE reference case
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Consistent with NICE reference case
CS = company submission; EAG = Evidence Assessment Group; EQ-5D = EuroQol 5 Dimensions; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PSS = Personal Social Services; QALY = quality-adjusted life year; UK = United Kingdom		

4.2.2 Model structure

The company developed a de novo partitioned survival model (PSM) with three health states (pre-progression, post-progression, and death) and a one-week cycle length with a lifetime time horizon (i.e., 30 years), programmed in Microsoft® Excel. All patients started in the pre-progression health state. Once progressed, patients cannot return to the progression-free state; they are assumed to continue living with progressed disease or transition to the ‘dead’ state, an absorbing health state.

EAG comment: The main comment of the EAG relates to the use of a PSM approach. In response to the request for clarification question B5 the company argues that PSM remains the most frequently adopted structure choice in oncology models and was deemed suitable by prior NICE Committees for decision-making in applicable advanced NSCLC (including EGFR exon 20 insertion mutations) evaluations. Although the company did not provide the results of a state transition modelling approach to assist in verifying the plausibility of the PSM extrapolations and to address uncertainties in the extrapolation period (NICE DSU TSD 19, recommendation 11), the EAG believes that the use of the PSM approach is reasonable. Notably, the company argued that “*neither use of a PSM nor an STM is able to resolve uncertainty associated with immature trial data. Indeed, the immaturity of the PAPILLON trial does not provide sufficiently mature data to populate model transitions beyond progression*”, underscoring the uncertainty related to long-term effectiveness.

4.2.3 Population

Consistent with the NICE scope, the marketing authorisation for amivantamab and the population in the PAPILLON trial, the population considered in the CS (CS Table 1) was adult patients with advanced NSCLC with activating EGFR exon 20 insertion mutations in the first-line setting.

The key baseline patient characteristics to inform the company’s base-case in the economic model were based on the PAPILLON trial. The key baseline patient characteristics from PAPILLON, NECTAR and the NCRAS subset are listed in Table 4.3.

Table 4.3: Key baseline patient characteristics used in the economic model

Characteristic	PAPILLON* (mean (SD))	NECTAR (mean (SD))	NCRAS (mean (SD))
Age			65 (6.7)
Female, %	57.8		69.6%
Weight, kg			66.9 (17.2)
BSA, m ²			N/A
Patients <80 kg, %	84.4		80
*used to inform the company's base-case in the economic model Based on CS Table 42 and clarification response Table 11 BSA = body surface area; CS = company submission; N/A = not available; NCRAS = National Cancer Registration and Analysis Service; SD = standard deviation			

EAG comment: The main concerns of the EAG relate to: a) generalisability of the modelled baseline patient characteristics to UK clinical practice and b) the lack of considering subgroups listed in the final NICE scope.

- a) The company used the PAPILLON trial to inform baseline patient characteristics in its economic model. However, in the 2024 advisory board report it was stated that,

[REDACTED]

[REDACTED]. The EAG's clinical expert further suggested that, compared to the baseline patient characteristics from PAPILLON, a typical UK population is likely to be slightly older and the ethnic composition is likely to have fewer Asian and more white patients. In response to the request for clarification, the company provided a scenario analysis using UK population characteristics based on NCRAS (n=23), in which the mean age and percentage females was higher and the percentage patients below 80 kilograms was lower compared to PAPILLON. The EAG also requested a scenario analysis based on population characteristics from NECTAR, which was not provided by the company due to the lack of access to the ESME database after the NECTAR study was closed. The company's scenario analysis based on NCRAS (including a slightly higher age as suggested by the EAG clinical expert) had a minor impact on the cost effectiveness results. Based on this scenario and the fact that ethnicity is not a key baseline patient characteristic in the economic model, the EAG considers this issue likely not to be a model driver.

- b) The final NICE scope listed disease stage, histology and type of exon 20 alteration present and presence of co-mutations as subgroups to be considered. These subgroups, however, were not included in the company's base-case. In response to the request for clarification, the company stated that subgroups based on histology, disease stage and type of EGFR20 alterations or co-mutations were not feasible as 99% of the PAPILLON trial population had adenocarcinomas, efficacy data stratified by disease stage were not available, and subgroups based on mutation alteration had too small sample sizes. The EAG considers the company's justification for not providing subgroup analyses to be reasonable.

4.2.4 Interventions and comparators

The intervention considered in the CS was amivantamab in combination with carboplatin and pemetrexed (amivantamab-chemotherapy). The dosing for amivantamab (1,400 mg weekly from weeks 1 to 4 and 1,750 mg every three weeks from week 7 onwards for patients less than 80 kg, 1,750 mg weekly from weeks 1 to 4 and 2,100 mg every three weeks from week 7 onwards for patients equal to or heavier than 80 kg) was in line with the PAPILLON trial and the summary of product characteristics (SmPC) for amivantamab.^{14, 19} Carboplatin (area under the curve (AUC) 5 mg/mL per minute on day 1 of each 21-day cycle, for up to 4 cycles) and pemetrexed (500 mg/m² on day 1 of each 21-day cycle, given in combination with carboplatin for the first four cycles, and then as maintenance monotherapy until disease progression) were also modelled in line with the recommended dosing regimens included in the SmPC for these two treatments.

Based on three advisory boards and RWE collected from the NECTAR study, the company identified platinum-based chemotherapy (carboplatin with pemetrexed, informed by the PAPILLON trial) with or without IO (pembrolizumab [200 mg dose every three weeks until disease progression or a maximum of 2 years], informed by the NECTAR study) as the most relevant first-line comparator therapies. The company stated that, based on the three advisory board meetings, IO monotherapy and EGFR TKIs are not relevant comparators due to a lack of efficacy in this population.

The company modelled the weighted aggregated total costs and quality-adjusted life years (QALYs) to obtain the results for a blended comparator combining chemotherapy and pembrolizumab-chemotherapy. This blended approach was justified by the lack of an established treatment pathway and no relevant NICE guidelines for patients with untreated EGFR exon 20 insertion mutation-positive advanced NSCLC. The distribution of the blended comparator (70% platinum chemotherapy, 30% pembrolizumab-chemotherapy) was informed by clinical expert opinion and was similar to the ratio between these treatments in the NCRAS dataset (excluding TKIs and IO monotherapy). The company explored different distributions (i.e., higher usage of pembrolizumab-chemotherapy) in scenario analyses.

EAG comment: The main concerns of the EAG relate to: a) the use of a blended comparator, and b) lack of modelling comparators that were mentioned in the NICE scope.

- a) The company modelled a blended comparator comprising carboplatin and pemetrexed (70%) and pembrolizumab plus carboplatin and pemetrexed (30%) in its base-case. The EAG is concerned that the use of a blended comparator approach hides important differences in estimated cost-effectiveness: the probabilistic results of the updated economic model post clarification show that the incremental cost-effectiveness ratio (ICER) versus the blended comparator is £28,853 per QALY gained, while pairwise comparisons versus carboplatin plus pemetrexed and carboplatin plus pemetrexed plus pembrolizumab result in an ICER of £41,241 per QALY gained and amivantamab being dominant respectively. Additionally, the company's 2023 advisory board report highlighted that the weighing of treatments within the blended comparator varied considerably (e.g., for pembrolizumab in combination with carboplatin and pemetrexed the proportion within the blended comparator varied between 10%-80%). The company addressed these variations in scenario analyses, which had a substantial impact on the cost effectiveness results. In response to the request for clarification, the company's main arguments for modelling a blended comparator were the lack of a NICE treatment pathway for patients with EGFR exon 20 insertion mutation-positive advanced NSCLC and the lack of a single dominant comparator within this population. The EAG considers these arguments inadequate to justify a blended comparator approach and requested the company to provide all

results presented in CS sections B.3.10 and B.3.11 for the treatment options within the blended comparator separately. Despite the request, the company did not provide these results. Overall, the EAG considers the company's blended comparator approach not in line with best practices and prefers to report the EAG's base-case results for all relevant comparators separately.

- b) The company's considered carboplatin with pemetrexed, and pembrolizumab plus carboplatin with pemetrexed as the relevant comparators in its submission. The company also mentioned pembrolizumab monotherapy as a relevant comparator in Table 1 of the CS, but initially did not include this comparator in its economic model. It was included in their updated economic model after response to the request for clarification (without detailed supporting evidence for the modelling approach for this comparator), but the company stated that it was not considered a relevant comparator and hence results versus pembrolizumab monotherapy were not provided. Furthermore, other comparators mentioned in the final scope issued by NICE, including other chemotherapy combinations, atezolizumab and TKIs, were also not included in the company's economic model. Further details on the EAG comments regarding the omission of these comparators can be found in Section 2.3 of this report.

4.2.5 *Perspective, time horizon and discounting*

The analysis is performed from the NHS and Personal Social Services (PSS) perspective. Discount rates of 3.5% are applied to both costs and benefits. The model cycle length is one week with a lifetime time horizon (30 years) and a half-cycle correction is applied.

EAG comment: The approach is in concordance with the NICE reference case.

4.2.6 *Treatment effectiveness and extrapolation*

The main sources of evidence on treatment effectiveness used for amivantamab-chemotherapy and chemotherapy were informed by the phase 3 PAPILLON trial. Specifically, the May 2023 (PFS and time to treatment discontinuation or death (TTDD)) and the October 2023 (OS) data cut-offs were used. Moreover, for pembrolizumab-chemotherapy the pooled RWE databases from the NECTAR study were used as main evidence source for treatment effectiveness.

The key effectiveness inputs in the model were PFS, OS and TTDD. TTDD data were used to inform time on treatment and hence inform acquisition costs of treatment; TTDD data do not impact the efficacy of each treatment in the model as pre-progression QALYs are derived from the PFS data. Moreover, TTDD for each component of amivantamab-chemotherapy (amivantamab and carboplatin + pemetrexed) was modelled separately, given amivantamab and chemotherapy would be expected to have different treatment durations.

The estimation of the key effectiveness inputs involved adjusting for treatment switching for OS after chemotherapy (Section 4.2.6.1), estimation of parametric survival models (Section 4.2.6.2) and additional assumptions specifically for pembrolizumab-chemotherapy (Section 4.2.6.3). Finally, CS base-case assumptions related treatment waning assumptions are reported (Section 4.2.6.4).

4.2.6.1 *Adjusting for treatment switching for overall survival after chemotherapy*

At the October 2023 DCO of the PAPILLON trial, [REDACTED] patients in the chemotherapy arm underwent treatment switching to receive amivantamab monotherapy following BICR-confirmed disease progression. This is [REDACTED] of patients who experienced progression and [REDACTED] of all patients in the chemotherapy arm.

Amivantamab monotherapy is not currently recommended by NICE for adult patients with advanced NSCLC with activating EGFR exon 20 insertion mutations, after failure of platinum-based therapy. Therefore, the chemotherapy OS data were adjusted to account for treatment switching. The company explored three approaches for this treatment switching adjustment, in line with guidance provided by NICE DSU TSD 24:²⁰

- two-stage estimation (TSE);
- rank preserving structural failure time (RPSFT) and;
- inverse probability of censoring weight (IPCW) were explored.

The three approaches (outlined in CS Table 43) were assessed based on:

- the appropriateness of the core assumptions adopted by each method
- the clinical plausibility of the resulting survival estimates.

The assessment related to adjusting for treatment switching, was guided by feedback received from health economist experts as part of the August 2024 advisory board (see Section 3.2 of this report, summarised in Table 4.3 below). In short, the RPSFT was considered inappropriate given that the common treatment effect assumption was not deemed clinically plausible. Moreover, the TSE method was considered suboptimal due to its core assumption of the absence of time-dependent confounding between the time of disease progression and the start of the next treatment, as the time from progression to treatment switch ranged from [REDACTED] days, indicating considerable variability. Additionally, OS reported in CS Figure 26 indicated that chemotherapy OS after treatment switching adjustment, for both TSE without re-censoring and IPCW, aligned with OS observed in NECTAR (did not include patients who received subsequent amivantamab), indicating face validity/clinical plausibility of the results. However, the IPCW-adjusted chemotherapy data ([REDACTED]) is best aligned to the OS HR ([REDACTED]) for the ATT-adjusted indirect (unanchored) comparison of chemotherapy data from the NECTAR study with amivantamab-chemotherapy data from PAPILLON (CS Table 44). The TSE approach with and without re-censoring yielded OS HRs of [REDACTED] respectively. Due to the above reasons, regarding the appropriateness of core assumptions adopted by each method and clinical plausibility, the company adopted the IPCW method for treatment switching adjustment to inform the CS base-case.

Table 4.4: Treatment switching adjustment methods for chemotherapy OS

	TSE ^{a,b}	RPSFT	IPCW ^a
Description	Disease progression is considered as the secondary baseline under the assumption that all patients are at a similar stage of disease at the point of disease progression. Effectiveness of subsequent therapy (amivantamab monotherapy) estimated by comparing post-progression survival for switchers and non-switchers.	Adjusts OS after subsequent therapies using an acceleration factor. Effectiveness of subsequent therapy (amivantamab monotherapy) is estimated assuming equal acceleration factor as the initial treatment (i.e. ACP).	Artificially censors patients at the time of receipt of subsequent therapy and then weights remaining non-censored patients using information on baseline and time-dependent covariates.

	TSE ^{a,b}	RPSFT	IPCW ^a
Core assumptions	No unmeasured confounders at secondary baseline No time-dependent confounding between disease progression and treatment switch	Common treatment effect between patients who receive the intervention of interest at randomisation or at the time of treatment switching	No unmeasured confounders relating to the baseline and time-varying patient characteristics
Appropriateness of core assumptions	For patients in the chemotherapy treatment arm who switched to receive amivantamab monotherapy in the PAPILLON trial, the time from progression to treatment switch ranged from [REDACTED] indicating considerable variability. This was validated by the health economist experts in the August 2024 advisory board, highlighting a key limitation with one of the core assumptions of the TSE approach.	Not clinically plausible to assume the survival benefit (acceleration factor) of amivantamab monotherapy received in the second-line setting, following disease progression, is equal to that of amivantamab-chemotherapy in the first-line setting.	Most appropriate compared with TSE and RPSFT
Clinical plausibility of results^c	CS Figure 25 The adjusted HR for amivantamab-chemotherapy versus chemotherapy was [REDACTED] without re-censoring and [REDACTED] with re-censoring. ^d OS for CP after treatment switching adjustment (without re-censoring) aligned with OS observed in NECTAR (did not include patients who received subsequent amivantamab), indicating face validity/clinical plausibility of the results (CS Figure 26).	Not applicable, RPSFT not considered appropriate	CS Figure 24 The adjusted HR for amivantamab-chemotherapy versus chemotherapy was [REDACTED]. OS for CP after treatment switching adjustment aligned with OS observed in NECTAR (did not include patients who received subsequent amivantamab), indicating face validity/clinical plausibility of the results (CS Figure 26).
^a Prognostic variables considered for treatment switch adjustment: [REDACTED]			

4.2.6.2 Estimation of parametric survival models

1. Assessment of the proportional hazards (PH) assumption (for amivantamab-chemotherapy versus chemotherapy only)
2. Assessment of (smoothed) hazard functions
3. Visual assessment of fit based on the Kaplan-Meier curve
4. Goodness-of-fit statistics based on Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC)
5. Clinical plausibility of long-term projections

Table 4.5: Selection of approach to estimate and extrapolate OS, PFS and TTDD

	OS (CS B.3.3.2.4)	PFS (CS B.3.3.2.3) ^a	TTDD (CS B.3.3.2.5) ^a
Assessment of (smoothed) hazard functions	ACP CS Figure 36 CP CS Figure 38 PCP CS Figure 40	ACP Alignment of the hazard function with the log-logistic and lognormal models (CS Figure 28). CP Alignment of the hazard function with the gamma and generalized gamma models (CS Figure 30). PCP Alignment of the hazard function with the log-logistic and gamma models (CS Figure 32 for TTNT).	ACP CS Figures 42, 43 CP CS Figure 46 aligns well with the gamma, Weibull, and Generalised gamma up to around 12 months. PCP See PFS
Fit to the observed data based on visual comparison with the Kaplan-Meier curves	ACP CS Figure 37 CP CS Figure 39 PCP CS Figure 41	ACP CS Figure 29 CP CS Figure 31 PCP CS Figure 33 for TTNT	ACP CS Figures 44, 45 CP CS Figure 47 PCP See PFS (for TTNT)
Fit to the observed data based on AIC and BIC	ACP The Gompertz (AIC) and Exponential (BIC) had the best statistical fit while the other distributions except the lognormal where within roughly two AIC points (CS Table 51). CP The log-logistic had the best statistical fit while the Weibull and gamma were within roughly two AIC/BIC points (CS Table 53). PCP The log-logistic had the best statistical fit while the lognormal was within roughly two AIC/BIC points (CS Table 55).	ACP The log-logistic had the best statistical fit while the Weibull and gamma were within roughly two AIC/BIC points (CS Table 45). CP The gamma had the best statistical fit while the Weibull was within roughly two AIC/BIC points (CS Table 47). PCP The log-logistic had the best statistical (CS Table 49 for TTNT).	ACP Amivantamab: the Gompertz had the best statistical fit while the Weibull and generalized gamma were within roughly two AIC points (CS Table 57). CP the Weibull had the best statistical fit while the Gompertz and generalized gamma were within roughly two AIC points (CS Table 58). PCP the Gamma had the best statistical fit while the Weibull, log-logistic and generalized gamma were within roughly two AIC points (CS Table 57). PCP See PFS
Clinical plausibility of the extrapolation based on	ACP EO: 5- and 10-year OS was stated to be around 27.5% (25.0%-30.0%)-	ACP EO: 5-year PFS was stated to be over 5%. This aligned with the gamma distribution.	ACP Amivantamab: EO: 3-, 4- and 5-year TTDD were 35.0% (15.0%-55.0%),

	OS (CS B.3.3.2.4)	PFS (CS B.3.3.2.3) ^a	TTDD (CS B.3.3.2.5) ^a
clinical expert opinion	and 7.5% (5.0%-10.0%). According to the CS, this aligned with the Weibull distribution (██████████) at 5- and 10-year respectively). CP EO: 5- and 10-year OS was stated to be around 10.0% (5.0%-15.0%) and 1.0% (0.0%-2.0%). According to the CS, this was most aligned with the gamma distribution (██████████) at 5- and 10-year respectively). PCP EO: 5- and 10-year OS was stated to be around 13.0% (1.0%-25.0%) and 5.0% (0.0%-10.0%). For the log-logistic distribution this was ██████████ at 5- and 10-year respectively.	CP EO for PFS were not elicited PCP Not provided in CS section B.3.3.2.3	13.5% (2.0%-25.0%) and 5.0% (0.0%-10.0%) respectively. According to the CS, the Gompertz and generalised gamma extrapolations were overly pessimistic and hence the Weibull distribution was preferred/ CP: EO: 3-, 4- and 5-year TTDD were 10.5% (1.0%-20.0%), 5.0% (0.0%-10.0%) and 2.5% (0.0-5.0%) respectively. According to the CS the Weibull or gamma extrapolations were most plausible. CP EO: 3-, 4- and 5-year TTD were 8.5% (2.0%-15.0%), 5.0% (0.0%-10.0%) and 2.5% (0.0-5.0%) respectively. Clinical opinion indicated all distributions were acceptable given the low TTDD predicted at 5 years. PCP EO: 3-, 4- and 5-year TTD were 5.0% (0.0%-10.0%), 2.5% (0.0%-5.0%) and 1.0% (0.0%-2.0%) respectively. No interpretation provided.
Base-case approach	ACP The Weibull distribution was selected based on clinical plausibility of the extrapolation. CP The Gamma distribution was selected based on clinical plausibility of the extrapolation and fit to the observed data. OS for CP was adjusted for treatment switching using the IPCW method. PCP The log-logistic distribution was selected based on fit to the observed data.	ACP The gamma distribution was selected based on clinical plausibility of the extrapolation. CP The gamma distribution was selected based on fit to the observed data. PCP The TTNT estimated for pembrolizumab-chemotherapy (log-logistic distribution) was adjusted by applying the per cycle HR of TTNT vs PFS (based on amivantamab-chemotherapy in the PAPILLON trial) to provide an approximation for	ACP The Weibull distribution was selected for amivantamab based on clinical plausibility of the extrapolation. The Weibull distribution was selected for CP based on clinical plausibility of the extrapolation and fit to the observed data. CP The gamma distribution was selected based on fit to the observed data. PCP The PFS estimated for pembrolizumab-chemotherapy (log-logistic distribution) was adjusted by

	OS (CS B.3.3.2.4)	PFS (CS B.3.3.2.3) ^a	TTDD (CS B.3.3.2.5) ^a
		PFS for pembrolizumab-chemotherapy. See CS Figure 34 for the resulting curve.	applying the per cycle HR of PFS vs TTDD (based on amivantamab-chemotherapy in the PAPILLON trial) to provide an approximation for TTDD for pembrolizumab-chemotherapy. See CS Figure 48 for the resulting curve.
^a For pembrolizumab with carboplatin and pemetrexed, this was based on TTNT, with an adjustment (see next section) ACP = amivantamab with carboplatin and pemetrexed; AIC = Akaike information criterion; BIC = Bayesian information criterion; CP = carboplatin and pemetrexed; CS = company submission; EO = expert opinion; HR = hazard ratio; OS = overall survival; PCP = pembrolizumab with carboplatin and pemetrexed; PFS = progression-free survival; PH = proportional hazard; TTD = time to treatment discontinuation; TTDD = time to treatment discontinuation or death; PCP = pembrolizumab with carboplatin and pemetrexed; TTNT = time to next treatment			

4.2.6.3 Assumptions for pembrolizumab-chemotherapy

The NECTAR study, used to inform the effectiveness of pembrolizumab-chemotherapy, did not provide “complete details on the exact date of disease progression” and as a result, an alternative approach to estimating PFS was required. Therefore, TTNT was used for pembrolizumab-chemotherapy. However, according to the CS, using TTNT as a proxy for PFS would not reflect clinical practice as there is anticipated to be a gap between progression and initiation of subsequent treatment. Therefore, the TTNT estimated for pembrolizumab-chemotherapy was adjusted by applying the per cycle HR of TTNT versus PFS (based on amivantamab-chemotherapy in the PAPILLON trial) to provide an approximation for PFS for pembrolizumab-chemotherapy.

Similarly, TTDD was not available in the RWE for pembrolizumab-chemotherapy. Therefore, the PFS estimated for pembrolizumab-chemotherapy (as described above) was adjusted by applying the per cycle HR of PFS versus TTDD (based on amivantamab-chemotherapy in the PAPILLON trial) to provide an approximation for TTDD for pembrolizumab-chemotherapy.

In addition to assumptions related to the approximations of PFS and TTDD, the NECTAR data were weighted to have similar baseline characteristics to the amivantamab-chemotherapy treatment arm in the PAPILLON trial using an average treatment effect on the treated (ATT)-weighted approach (see Section 3.4 for further details).

4.2.6.4 Treatment waning

No explicit assumptions regarding waning of the relative treatment effect were discussed in the CS.

EAG comment: The main concerns of the EAG relate to: a) the estimation of OS that is not aligned with clinical opinion, b) the estimation of TTDD for amivantamab with chemotherapy and chemotherapy only that is not aligned with clinical opinion, c) the estimation of PFS for amivantamab with chemotherapy and chemotherapy only, d) the estimation of PFS for pembrolizumab with chemotherapy, e) the estimation of TTNT for pembrolizumab with chemotherapy, f) treatment effect waning and, g) ATT-weighting for pembrolizumab with chemotherapy.

- 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 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. 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. Finally, the OS estimated for pembrolizumab with chemotherapy in the CS base-case did align with clinical opinion presented to the EAG.

- b) According to the CS, the gamma distribution for TTDD was selected based on fit to the observed data for chemotherapy only stating that all extrapolations of TTDD were seen as appropriate as they all predicted similar outcomes (response to the request for clarification question B10). For chemotherapy only, the EAG can confirm that indeed the selected distribution for TTDD is not influential in terms of impact on the ICER. For amivantamab with chemotherapy the Weibull distribution was selected (both for the amivantamab as well as chemotherapy component) based on clinical plausibility of the extrapolation and fit to the observed data. However, based on the company's advisory board report as well as clinical opinion obtained by the EAG, the estimated TTDD in the CS base-case for both amivantamab and chemotherapy is substantially underestimated (see Table 4.4). Therefore, the EAG selected the log-logistic distribution for amivantamab and the exponential distribution for chemotherapy as these were more in line with the company's advisory board report as well as clinical opinion obtained by the EAG.
- c) The company selected the PFS distribution based on fit to the observed data only. The company stated in response to the request for clarification question B12 that "*clinical expert opinion was not used to inform the PFS extrapolations given that a different modelling approach (assuming TTNT was a proxy for PFS) was used at the time of the August 2024 advisory board*". In addition, the company provided the requested scenarios using alternative parametric survival distributions for amivantamab with chemotherapy and chemotherapy only. Here the company stated that "*in all scenarios, choosing the best or second best-fitting curve for the intervention and both components of the weighted comparator has a minimal impact on the ICER*". However, it should be noted that this statement is applicable to amivantamab with chemotherapy and chemotherapy only and is not necessarily also applicable to pembrolizumab with chemotherapy given that PFS for the latter is used to approximate TTDD.
- d) The TTNT estimated for pembrolizumab-chemotherapy was adjusted by applying the per cycle HR of TTNT versus PFS (based on amivantamab-chemotherapy in the PAPILLON trial) to provide an approximation for PFS for pembrolizumab-chemotherapy. The approach the company used to approximate PFS for pembrolizumab with chemotherapy was suboptimal as it relied on the assumption that the ratio between TTNT and PFS for pembrolizumab with chemotherapy is identical to that for amivantamab with chemotherapy. It was difficult to assess the appropriateness of this assumption by the EAG. However, the scenario analyses provided by the company in response to the request for clarification question B6 indicated that overall, the results (Tables 14 and 15) show that there is little variation in the ICER when the approach to estimating the PFS of pembrolizumab with chemotherapy is changed (i.e., exploring alternative assumptions). Although the impact of this assumption on the ICER seems modest, this was based on the blended comparator (consisting only for 30% out of pembrolizumab with chemotherapy). The impact of the assumptions of the CS approach to estimate PFS for pembrolizumab with chemotherapy when considering pembrolizumab with chemotherapy as a separate comparator would be more pronounced. Nevertheless, the impact is still likely to be modest and the EAG believes the CS approach to estimate PFS for pembrolizumab with chemotherapy to be reasonable.

- e) The PFS estimated for pembrolizumab-chemotherapy was adjusted by applying the per cycle HR of PFS versus TTDD (based on amivantamab-chemotherapy in the PAPILLON trial) to provide an approximation for TTDD for pembrolizumab-chemotherapy. The approach the company used to approximate TTDD for pembrolizumab with chemotherapy was suboptimal as it relied on the assumptions i) that the ratio between TTNT and PFS for pembrolizumab with chemotherapy is identical to that for amivantamab with chemotherapy (to estimate PFS based on TTNT, as mentioned above) and ii) that the ratio between PFS and TTDD for pembrolizumab with chemotherapy is identical to that for amivantamab with chemotherapy (to estimate TTDD based on PFS). It was difficult to assess the appropriateness of this assumption by the EAG. Although not explored by the company in response to the request for clarification question B7, the impact of the assumptions made to estimate PFS for pembrolizumab with chemotherapy are likely more pronounced than for PFS. As illustrated by CS Figure 52, [REDACTED]. To explore an alternative estimation of PFS and TTDD for pembrolizumab with chemotherapy, the EAG used the Gompertz distribution for TTNT (used to approximate both PFS and TTDD for pembrolizumab with chemotherapy) in a scenario analysis. According to CS Table 50, the 1-, 3- and 5-year TTNT estimates for the Gompertz distribution [REDACTED] log-logistic distribution.
- f) The company did not provide scenario analyses exploring alternative assumptions related to treatment effect waning. In response to the request for clarification question B11 it was stated that “*patients receiving amivantamab with chemotherapy are unlikely to experience treatment effect waning within their lifespan*”. 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.
- g) ATT-weighting was used for pembrolizumab with chemotherapy to attempt to generate a comparator that has similar baseline characteristics to the amivantamab-chemotherapy treatment arm in the PAPILLON trial. According to the EAG the validity of this ATT-adjustment is questionable for two main reasons i) whether the adjustment to the PAPILLON trial is most appropriate given that the NECTAR study might potentially be more similar to the population in UK clinical practice and; ii) the direction of the ATT-adjustment (when comparing unadjusted and adjusted analyses) might be different than expected (see also Section 3.4 of this report). To assess the impact of the ATT-adjustment on the cost effectiveness, the EAG requested (clarification question B8) to provide the results without the ATT-adjustment for pembrolizumab with chemotherapy. This was unfortunately not provided by the company, nor were the sensitivity analyses requested in clarification question A10 provided. This hampers the EAG to assess the implications of the ATT-adjustment (see Section 3.4).

4.2.7 Adverse events

Grade 3 or 4 AEs that had occurred in at least 5% of patients in either treatment arm of PAPILLON or the pembrolizumab-chemotherapy arm of KEYNOTE-189 were included in the company’s economic model (CS Table 64). The average duration of AEs (CS Table 65) with known end dates was used for imputation where AE durations had missing end dates (i.e., mean imputation).

EAG comment: The main comments of the EAG relate to: a) the modelling of pembrolizumab-chemotherapy AE incidence data based on KEYNOTE-189, and b) applying disutilities and costs using a one-off approach in the economic model.

- a) Due to the lack of a trial assessing pembrolizumab-chemotherapy in adult patients with EGFR exon 20 insertion mutated advanced NSCLC in the first-line setting, the company modelled the pembrolizumab-chemotherapy AE incidence data using KEYNOTE-189. This trial assessed pembrolizumab-chemotherapy in adult patients with previously untreated advanced NSCLC with no sensitising EGFR mutations, which the company considered a generalisable source to inform AE incidence data. In response to the request for clarification, the company further justified the use of KEYNOTE-189 by stating that it provided AE data for the treatment of interest (i.e., pembrolizumab in combination with carboplatin and pemetrexed) within patients with untreated advanced NSCLC. The EAG requested scenario analyses informing AE incidences based on NECTAR and other KEYNOTE trials. The company did not provide these scenario analyses and responded that AE incidence data were not available from NECTAR. The company further argued that the KEYNOTE-024 and KEYNOTE-042 included pembrolizumab monotherapy rather than in combination with chemotherapy, and these trials were therefore deemed less suitable to inform pembrolizumab-chemotherapy AE incidences in the economic model. The EAG agrees with the company that, in absence of a trial assessing pembrolizumab-chemotherapy in NSCLC patients with an EGFR exon 20 insertion mutation and AE incidence data from NECTAR, the KEYNOTE-189 trial is the most suitable source to inform AE incidence rates for pembrolizumab-chemotherapy in the economic model.
- b) In the economic model, AE disutilities and costs were applied using a one-off approach upon entry to the progression-free health state. In response to the request for clarification, the company further elaborated on their approach by stating that AEs are usually observed shortly after initiation of treatment in clinical practice and that it was therefore considered appropriate to apply AE disutilities and costs to the first model cycle (i.e., upon starting treatment). The cumulative incidence plots provided by the company in Figures 62 and 63 of the clarification response confirm that the majority of treatment emergent grade 3+ AEs in both arms of the PAPILLON trial occurred within the first year since randomisation. However, the daily rate plot in Figure 64 shows that AEs occurred for up to two years since randomisation for amivantamab with chemotherapy. The EAG requested a scenario analysis using a per-cycle approach to model the impact of AEs, but this was not provided by the company stating that the expected impact would be minimal. Although the requested scenario analysis would have been reassuring for the EAG, it agrees that this issue is unlikely to be a cost effectiveness driver.

4.2.8 Health-related quality of life

EQ-5D-5L data from the PAPILLON trial were mapped to EQ-5D-3L scores (method reported by Hernández Alava et al. 2017)²¹ to estimate progression free (PF) and progressed disease (PD) health state utility values.

4.2.8.1 Health-related quality of life data identified in the literature review

According to the CS, the SLR identified 58 studies reporting on utility values. Out of these, the company stated that no utility studies were identified that reported outcomes in a patient population with EGFR exon 20 insertion mutation-positive NSCLC.

4.2.8.2 Health state utility values

For the PF health state utility, a separate mixed-model repeated measures (MMRM) was fit for each EQ-5D-5L collection time point using information only from patients who stayed progression free until that time point, including visit as a categorical predictor to get time specific utility estimates. Then, the least squares mean estimate of the last time point was used from each of these MMRMs as the utility estimate for that time point. These PF estimates over time were combined to estimate the mean PF utility in the economic model. The PD health state utility was estimated based on patients who progressed in the PAPILLON trial, using a single MMRM. Health state utilities in the company's base-case were age-adjusted based on the methods of Ara and Brazier 2010.²²

A summary of the health state utility values used in the cost effectiveness analysis is provided in Table 4.6.

Table 4.6: Health state utility values

Health state	Utility value (SE)	Reference
Progression-free		PAPILLON trial ²³
Progressed disease		
Based on CS Table 66 CS = company submission; SE = standard error		

4.2.8.3 Disutility values

Adverse event disutilities were considered for first-line treatments and were sourced from the published literature (CS Table 65). For each AE, the disutility was multiplied by the corresponding AE incidence and mean duration (all derived from the PAPILLON trial) and then applied as a one-time utility decrement upon entry to the progression-free health state.

EAG comment: The main concerns of the EAG relate to: a) the proportion of patients with missing HRQoL data and assumption regarding handling for these data, b) different approaches for the estimation of PF and PD health state utilities, and c) the relatively high PF utility.

- a) In response to the request for clarification question B15, the company provided an overview of the EQ-5D data from PAPILLON that were used to inform health state utilities in the economic model. For the estimation of the PF utility, the average number of patients with missing data across treatment cycles was ██████████, of which the company stated that missingness would have little impact on the overall mean. The company further stated that the proportion of missing data was similar in both arms and that there was no clear pattern of missingness over time. However, from Table 26 in the clarification response it appears that the percentage missingness was generally larger in the amivantamab plus chemotherapy arm compared to the chemotherapy comparator arm of PAPILLON. For the estimation of the PD utility a total of ██████████ missing observations were reported. The company argued that, given the similarity in baseline characteristics between patients with and without at least one post-PD EQ-5D assessment as shown in clarification response Table 28, the missing data within the PD health state were not expected to introduce bias. The company additionally stated that MMRM impute missing observations by assuming that patients with non-missing data are representative of patients with missing data across all MMRMs. It is, however, unclear to the EAG whether this assumption is valid, i.e., whether missing data for the estimation of PF and PD utilities were missing (completely) at random. Scenario analyses using data imputation methods were therefore requested. The company provided a scenario analysis using last observation carried forward (LOCF), which resulted in PF and PD utilities very similar to utilities

in the company's base-case. The EAG, however, considers LOCF an unsuitable imputation approach when data are potentially not missing (completely) at random. Multiple imputation is considered a better alternative, but the company stated that this approach failed to produce estimates in later cycles due to low number of patients. 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.

- b) The company used different approaches for the estimation of the PF and PD health state utilities. For PF, a separate MMRM was fit for each EQ-5D-5L collection time point using information only from patients who stayed progression free until that time point. The company stated that the area under the curve of the PF estimates per cycle was then used as the mean utility in PF state. It is, however, unclear to the EAG what the company's area under the curve approach exactly entails and how it was used to combine the different mean per-cycle PF utilities to the overall mean PF health state utility. Contrary to the PF utility, the PD utility was estimated based on patients who progressed in the PAPILLON trial, using a single MMRM. In response to the request for clarification, the company justified using different approaches by stating that for progression-free patients there is a defined start date (baseline), and generally more data are available across time compared to the PD state. The per cycle approach using data only from progression-free patients makes sure that patients who progress early do not impact mean utility estimates in later cycles. The company justifies the use of a single MMRM for the estimation of the PD utility by stating that contrary to the PF health state, patients enter the PD health state at different time points in the economic model and hence will include patients who have been in this health state for different durations. In Table 34 of the response to the request for clarification, additional MMRM results were provided, including 1) PF utility based on a per cycle approach (company's base-case), 2) PF and PD utility independently estimated based on a single MMRM (company's base-case for PD), and 3) PF and PD utilities estimated within the same MMRM including treatment, time, progression status, and treatment time as covariates. The independently estimated PF and PD utilities are similar to the PF and PD utilities estimated within the same MMRM, and the PF utility based on these approaches are slightly lower than the PF utility based on the per cycle approach. Of note, the treatment covariate in the multivariable MMRM indicated that treatment given in PAPILLON (i.e., amivantamab plus chemotherapy versus chemotherapy) did not significantly impact HRQoL. The EAG is unsure which approach is the most appropriate for the estimation of the PF and PD health state utilities in the economic model, but noticed that there were no large differences in estimated utility values between the different approaches. To explore the impact on the cost effectiveness results, the EAG performed a scenario analysis informing both the PF and PD health state utilities based on independently estimated single MMRMs.
- c) The EAG noticed that the modelled PF utility in the CS was relatively high (██████) and requested further clarification on this. The company responded that the estimated utility values were based on the best available EQ-5D data for the patient population relevant to the decision problem (i.e., untreated EGFR exon 20 insertion mutation-positive advanced NSCLC from PAPILLON trial). The company additionally stated that the estimated PF utility was lower than the sex- and age-matched general population utility value from Health Survey England (HSE) 2014 (0.8392).²⁴ Although the EAG agrees that HSE 2014 is the preferred source to inform general population utilities based on NICE TSD 23, it would like to note that the estimated PF utility by the company is higher than the sex- and age-matched general population utility value from HSE 2018 and a more recent paper (2023) from McNamara et al.²⁵ in which up-to-date estimates of the quality-adjusted life expectancy of the English population, based on the 2017 and 2018 waves of HSE, were reported. The EAG also requested a cross-validation of the company's PF and PD utilities to other

relevant technology assessments (TAs), which was provided in clarification response Table 35. The company justified the lower utilities in TA850 by its population having a more advanced disease stage and stated that utilities in TA653 were similar to those in the current appraisal. In TA683, which sourced HRQoL from KEYNOTE-189 (pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic NSCLC), a time-to-death approach was used with PF values ranging from 0.397 to 0.79 and PD values ranging from 0.300 to 0.693. Despite the different approach used for the modelling of HRQoL (time-to-death) and the fact that these patients had no EGFR mutation, 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.

4.2.9 Resources and costs

The cost categories included in the model were medical costs (treatment acquisition, treatment administration, and subsequent treatment), health state costs (disease monitoring and follow-up), costs of managing adverse events, and end-of-life costs.

Unit prices were based on the NHS reference prices, British National Formulary (BNF), Personal Social Services Research Unit (PSSRU) and Monthly Index of Medical Specialities (MIMS).

4.2.9.1 Resource use and costs data identified in the literature review

According to the CS Appendix I, the SLR identified four studies reporting on costs for patients with EGFR exon 20 insertion mutations. However, three of these studies investigated the costs in the second-line treatment setting and all of them were based in the US or Canada. Therefore, the company concluded that these had limited generalisability to UK clinical practice.

4.2.9.2 Treatment costs (with Patient Access Scheme)

Drug acquisition costs per administration were calculated based on dosage, unit drug costs, relative dose intensity (RDI), dose skipping, dosing schedules, and stopping rules (Table 4.7 and Table 4.8). Dosing schedules, dose skipping and RDI were based on the PAPILLON trial for amivantamab-chemotherapy and chemotherapy.^{13, 14}

Table 4.7: Dosing regimens

Component	Dose	Frequency	Stopping rule
Amivantamab (<80 kg patients)	1,400 mg	Weekly (From weeks 1 to 4)	Week 4
	1,750 mg	Every 3 weeks (From week 7 onward)	Disease progression or toxicity
Amivantamab (≥80 kg patients)	1,750 mg	Weekly (From weeks 1 to 4)	Week 4
	2,100 mg	Every 3 weeks (From week 7 onward)	Disease progression or toxicity
Pemetrexed	500 mg/m ²	Every 21 days	Disease progression or toxicity
Carboplatin	AUC 5 mg/mL per minute	Every 21 days	Up to 4 cycles of 21 days

Component	Dose	Frequency	Stopping rule
Pembrolizumab	200 mg	Every 3 weeks	Disease progression, toxicity or a maximum of 2 years
Reference: PAPILLON trial, NECTAR trial and the SmPC. ^{5, 13} AUC = area under the curve			

The RDI values were applied to the required number of vials for each study treatment (amivantamab, carboplatin, and pemetrexed), while the dose skipping percentages were applied to the dosing frequency per cycle. Dose skipping was applied to the treatment acquisition, administration, and monitoring costs. RDI was calculated by dividing the total prepared doses in milligrams by the total of the expected doses in milligrams in the PAPILLON trial. Dose skipping was calculated by dividing the number of doses that were observed to be given in the PAPILLON trial by the doses that were expected to be given, based on the label dosing, using the time to treatment discontinuation. For the modelled pembrolizumab-chemotherapy arm, pembrolizumab dose skipping was derived from TA683 and pembrolizumab RDI was assumed to be 100% (Table 4.7).

Drug acquisition costs per intervention are shown in CS Table 67. Amivantamab was offered with a Patient Access Scheme (PAS) at £[REDACTED] per pack (Patient Access Scheme (PAS) discount of [REDACTED]). The drug acquisition costs by treatment phase can be found in (Table 4.8) and the cost per cycle per arm can be found in (Table 4.9). According to the CS, the company's base-case assumed did not consider vial sharing (i.e., drug wastage was assumed).

Table 4.8: Drug acquisition costs by treatment phase

Arm	Component	Dose	RDI	Units per administration	Costs per average dose required (£)*	Dose skipping (%)
Amivantamab with chemotherapy	Amivantamab (<80 kg patients)	1,400 mg (after C2D1 1,750 mg)	██████	██████	██████	██████
	Amivantamab (≥80 kg patients)	1,750 mg (after C2D1 2,100 mg)	██████	██████	██████	██████
	Pemetrexed	500 mg/m ²	██████	██████	██████	██████
	Carboplatin	AUC 5 ^a	██████	██████	██████	██████
Chemotherapy	Pemetrexed	500 mg/m ²	██████	██	██████	██████
	Carboplatin	AUC 5 ^a	██████	██	██████	██████
Pembrolizumab with chemotherapy	Pembrolizumab	200 mg	100.00%	2.0	5,260.00	4.40
	Pemetrexed	500 mg/m ²	██████	██	██████	██████
	Carboplatin	AUC 5 ^a	██████	██	██████	██████
Subsequent treatment						
Platinum based chemotherapy	Pemetrexed	500 mg/m ²	██████	██	██████	██████
	Carboplatin	AUC 5 ^a	██████	██	██████	██████
Docetaxel	Docetaxel	75 mg/m ²	100.00%	2.0	18.14	0.00
Docetaxel + nintedanib	Docetaxel	75 mg/m ²	100.00%	2.0	18.14	0.00
	Nintedanib	200 mg	100.00%	2.0	35.85	0.00
IO monotherapy	Pembrolizumab	200 mg	100.00%	2.0	5,260.00	4.40**
Gemcitabine	Gemcitabine	1,000 mg/m ²	100.00%	9.0	36.93	0.00
Vinorelbine	Vinorelbine	25 mg/m ²	100.00%	1.0	17.26	0.00
Based on CS Table 68, 69, 70 and CEM 'Detailed Cost Inputs_SubTx'!E137:Q149						
^a An average dose per administration of 550 mg is assumed for carboplatin						
*Dose skipping not included **based on TA683						
AUC = area under the curve; C = cycle; CS = company submission; D = day; RDI = relative dose intensity						

Table 4.9: Acquisition cost per cycle per arm

Treatment arm	Component	Cost per week in cycle 1 (£)	Cost per week in cycle 2 (£)	Cost per week in cycle 3-4 (£)	Cost per week in subsequent cycles (£)
Amivantamab with chemotherapy	Amivantamab (<80 kg patients)	██████	██████	██████	██████
	Amivantamab (≥80 kg patients)	██████	██████	██████	██████
	Pemetrexed	██████	██████	██████	██████
	Carboplatin	██████	██████	██████	██████
Chemotherapy	Pemetrexed	██████	██████	██████	██████
	Carboplatin	██████	██████	██████	██████
Pembrolizumab with chemotherapy	Pembrolizumab	1,676.19	1,676.19	1,676.19	1,676.19
	Pemetrexed	██████	██████	██████	██████
	Carboplatin	██████	██████	██████	██████
Based on CEM ('Engine Ami+CP'!AI13:AS13, 'Engine CP'!AB13:AH13, 'Engine Other Comparators'!AB13:AH13)					

The unit administration costs were obtained from the National Cost Collection 2022/2023 based on route of administration for an outpatient procedure in the medical oncology service (Response to the request for clarification Table 38). The company assumed three possible administration paths: delivery of intravenous (IV) monotherapy (SB12Z, Simple Parenteral Chemotherapy at First Attendance, £191.96), delivery of IV combination therapy (SB14Z, Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance, £335.66), and oral administration one-off cost (SB11Z, Exclusively Oral Chemotherapy, £316.22). All treatments that required IV administration were assumed to happen in an outpatient setting. Table 4.10 summarises the administration costs per treatment arm.

Table 4.10: Administration cost per cycle per arm

Treatment arm	Component	Cost per week in cycle* 1 (£)	Cost per week in cycle* 2 (£)	Cost per week in cycle 3-4* (£)	Cost per week in subsequent cycles* (£)
Amivantamab with chemotherapy	Amivantamab (<80 kg patients)	██████	██████	██████	██████
	Amivantamab (≥80 kg patients)	██████	██████	██████	██████
	Pemetrexed	██████	██████	██████	██████
	Carboplatin	██████	██████	██████	██████
	Total	██████	██████	██████	██████
Chemotherapy	Pemetrexed	██████	██████	██████	██████
	Carboplatin	██████	██████	██████	██████

Treatment arm	Component	Cost per week in cycle* 1 (£)	Cost per week in cycle* 2 (£)	Cost per week in cycle 3-4* (£)	Cost per week in subsequent cycles* (£)
	Total				
Pembrolizumab chemotherapy	Pembrolizumab				
	Pemetrexed				
	Carboplatin				
	Total				
Based on post-clarification CEM ('Engine Ami+CP'!AI13:AS13, 'Engine CP'!AB13:AH13, 'Engine Other Comparators'!AB13:AH13)					
*Cycle length is 21 days					

Following disease progression, patients incurred a one-off cost to model the costs of subsequent treatments. The one-off cost was calculated based on the distribution and duration of each treatment (Table 4.11). The second- and third-line treatment distributions were obtained in the May 2024 advisory board conducted by Johnson & Johnson.⁶ The duration of the second- and third-line treatment were based on median PFS from Bazhenova et al. 2021, and Park et al. 2019 and Migliorino et al. 2017, respectively.²⁶⁻²⁸ Patients not receiving subsequent treatment following progression, received best supportive care (BSC), for which a £0 cost was assumed in the company's base-case (Table 4.11).

Table 4.11: Subsequent treatments distribution and duration

Setting	Component	Distribution			Duration (weeks)
First-line treatment		Amivantamab-chemotherapy	Chemotherapy	Pembrolizumab-chemotherapy	
Second-line setting	BSC	60%	60%	60%	-
	Active subsequent treatment	40%	40%	40%	-
	Platinum-based chemotherapy	10.0%	10.0%	25.0%	21.7
	Docetaxel	21.0%	21.0%	22.5%	18.7
	Docetaxel plus nintedanib	49.0%	49.0%	52.5%	18.7
	IO monotherapy	20.0%	20.0%	0.0%	10.0
Third-line setting	BSC	90%	90%	90%	-
	Active subsequent treatment	10%	10%	10%	-
	IO monotherapy	50.0%	50.0%	0.0%	18.3
	Gemcitabine	25.0%	25.0%	50.0%	10.9

Setting	Component	Distribution			Duration (weeks)
	Vinorelbine	25.0%	25.0%	50.0%	10.9
One-off costs for 2L treatment		██████	██████	██████	-
One-off costs for 3L treatment		██████	██████	██████	-
Total one-off cost		██████	██████	██████	-
Based on CS Table 75,76 and CEM ('Detailed Cost Inputs_SubTx'!F13:H15'; 'Detailed Cost Inputs_SubTx'!H89:H94;'Detailed Cost Inputs_SubTx'!H115:H120) BSC = best supportive care; CS = company submission; IO = immunotherapy					

Drug monitoring costs were applied for pemetrexed in each treatment arm (i.e., amivantamab-chemotherapy, chemotherapy, and pembrolizumab-chemotherapy). Monitoring unit costs and frequency per lab test can be found in the response to the request for clarification Table 39 and CS Table 78, respectively.

4.2.9.3 Health state costs

Health-state specific routine monitoring and follow-up care costs were included in the analysis (Table 4.12). Disease management costs were assumed to be the same for patients receiving amivantamab-chemotherapy, chemotherapy and pembrolizumab-chemotherapy. A summary of the total pre- and post-progression costs is presented in Table 4.12.

Table 4.12: Health state costs

Resource	Unit cost (£)	Source	Annual resource usage		Source
			PF	PD	
Oncology outpatient visit	190.53	National Schedule of NHS Costs 2022/23	9.6	7.9	NICE TA531
Clinical nurse specialist	88.00	PSSRU 2023	12.0 hours	12.0 hours	NICE TA584
GP surgery visit	49.00	PSSRU 2023	12.0	0.0	NICE TA584
Therapist visit	52.00	PSSRU 2023	0.0	26.1	NICE TA584
GP home visit	49.00	PSSRU 2023	0.0	26.1	NICE TA584
Community nurse home visit	76.00	PSSRU 2023	8.7 (visits of 20 minutes)	8.7 (visits of 20 minutes)	NICE TA584
Chest radiography	73.79	National Schedule of NHS Costs 2022/23	6.8	6.5	NICE TA531
CT scan (chest)	154.13	National Schedule of NHS Costs 2022/23	0.6	0.2	NICE TA531

Resource	Unit cost (£)	Source	Annual resource usage		Source
			PF	PD	
CT scan (other)	172.76	National Schedule of NHS Costs 2022/23	0.4	0.4	NICE TA531
Electrocardiogram	177.96	National Schedule of NHS Costs 2022/23	1.0	0.9	NICE TA531
Average annual cost by health state (£)			£4,980.06	£6,605.17	-
Average weekly cost by health state (£)			£95.44	£126.59	-
Based on CS Table 19, post-clarification CEM 'Detailed Cost Inputs_Others'!E12:K31, clarification response Table 40					
CT = computed tomography; GP = general practitioner; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PD = progressed disease; PF = progression free; PSSRU = Personal Social Services Research Unit					

4.2.9.4 Adverse events costs

Adverse event costs were applied as a lump sum upon treatment initiation for each treatment arm. The costs per AE (Table 4.13) were obtained by weighting the average non-elective short stay admission from NHS reference costs 2022-2023. In the CS, the reference costs of 2021/2022 were used, however, these were updated after the request for clarification. The unit costs per AE was assumed to be the same across treatment arms. Table 4.13 shows a summary of the AE incidence rates per arm. The lump sum cost per treatment arm can be found in Table 4.13.

Table 4.13: AEs incidence rates and individual costs

AE	Unit cost (£)	Amivantamab-chemotherapy	Chemotherapy	Pembrolizumab-chemotherapy
Anaemia	739.05	10.6%	12.3%	19.0%
Paronychia	483.99	6.6%	0.0%	0.0%
Hypokalaemia	540.34	8.6%	1.3%	0.0%
Asthenia	739.05	5.3%	2.6%	6.7%
Neutropenia	585.18	33.1%	22.6%	16.8%
Leukopenia	527.46	11.3%	3.2%	0.0%
Rash	483.99	11.3%	0.0%	2.0%
Thrombocytopenia	615.65	9.9%	10.3%	8.6%
Fatigue	739.05	0.7%	1.3%	7.7%
Diarrhoea	552.32	3.3%	1.3%	5.2%
Total lump sum (£)		588.02	346.45	436.50
Based on CS Table 64, CS Table 80, Clarification letter CEM ('Detailed Cost Inputs_Unit Cost'!F51:F54)				
AE = adverse event; CS = company submission				

4.2.9.5 End-of-life costs

A one-time terminal care cost of £4,680.87 before death was modelled to reflect the intensive palliative and hospice-related care that patients would require at the end of life. The breakdown of the end-of-life costs is presented in Table 41 of the response to the request for clarification.⁴

EAG comment: The main concerns of the EAG relate to: a) implementation of dose frequency and dose skipping; b) vial sharing for amivantamab; c) lower unit costs for AEs than similar TAs; d) administration unit costs; e) source of unit costs, and f) unit costs update in updated CEM.

- a) In the CS base-case, drug acquisition and administration were modelled using a suboptimal approach. Rather than simulating the standard treatment schedules, in which patients would receive the full dose at the start of each treatment cycle followed by a period in which the patients receive no more doses, the model assumed that patients would receive a fraction of the dose at regular intervals throughout each cycle. Specifically in this case, patients receiving a treatment once in every three weeks were not modelled to receive the full dose at day 0, and no dose for the 20 days thereafter. Instead, patients received one third of the dose every week (up to the recommended stopping treatment). This approach does not accurately represent real-world clinical practice and may lead to an underestimation of the per-cycle costs. As the number of patients on treatment decreases in every model cycle, spreading the acquisition and administration will result in less patients receiving the treatment, and therefore, less costs than in clinical practice. The EAG is concerned that this approach may misrepresent the actual acquisition and administration costs incurred. This could potentially benefit amivantamab, as patients stay longer in the PF health state. Therefore, the EAG considers this a key issue.
- b) According to the CS, the company's base case assumed no vial sharing (i.e., drug wastage was assumed). However, as seen in Table 4.8 of this report, the units (vials/caps) per admin were not round up for amivantamab (i.e., unlike the comparators, patients in amivantamab could receive [REDACTED] units). To estimate the number of vials needed for the comparators, the company divided the required dose (e.g., for pembrolizumab, 200mg) by the unit strength per pack (e.g., 100 mg of pembrolizumab per pack), multiplied the RDI (e.g., 100%), and rounded it up. However, for amivantamab the company applied the RDI after rounding up the division of the required dose by unit strength per pack. Therefore, implicitly allowing for vial sharing. The company justified this approach in clarification response B18 stating that *"We considered dose reductions for amivantamab to estimate the average number of vials received because dose reductions of amivantamab are based on the number of full vials (350mg) e.g. are not related to the assumptions on vial sharing. For example, a patient <80kg receives a dose of 1400 mg instead of 1750 mg would have incurred cost of 4 vials, instead of 5. In the economic model the dose reduction percentage is multiplied by the number of vials of amivantamab received per administration"*. However, this approach is flawed and downsizes the costs of amivantamab over its comparators. Therefore, the EAG adjusted this in its base-case analysis, not allowing vial sharing for amivantamab.
- c) The unit costs used in the company's base-case for AEs were significantly lower than those from other TAs reporting on patients with locally advanced or metastatic NSCLC. Most of the AE unit costs used in the CS base-case were obtained using a weighted average of the National Schedule of NHS Costs for 2022/2023. To calculate the weighted average, the company used all the codes of the relevant AE in non-elective short stay (including those with lower grade), multiplied by the number of events reported in the National Schedule of NHS Costs for 2022/2023 and divided by the total number of events of the AE (see Table 36 of the response to the request for clarification for an example for the AEs of anaemia). Given that only Grade 3 or 4 AEs were considered, including the unit costs of the AEs with lower grade decreases the actual impact of the AEs considered. Moreover, the average costs used by the company are significantly lower than those from other TAs. In the case of anaemia, for instance, other TAs reported significantly higher unit costs than the one selected by the company (i.e., £739.05) with TA484, TA520, and TA683 reporting £978.00, £1313.09, and £2,692.61, respectively. Moreover, it is unclear to the EAG why the company selected certain codes for the AE unit costs. For example, for anaemia the code for

acquired Pure Red Cell Aplasia or Other Aplastic Anaemia (SA01G-K) were selected over the code for iron Deficiency Anaemia (SA04G-L). The company did not provide sufficient evidence justifying why the non-elective inpatient short-stay code would be used over the other settings. Therefore, given the uncertainty surrounding the AE unit costs selected by the company the EAG will update their base-case with the severest AE unit costs for the non-elective inpatient short-stay code and will run a scenario analysis with the total value of the severest reported in the National Schedule of NHS Costs for 2022/2023.

- d) The administration unit costs were derived from the National Cost Collection 2022/2023 based on route of administration for an outpatient procedure in the medical oncology service. However, the selected unit costs for IV administration were lower than those from the previous National Cost Collection of 2021/2022 (Table 4.14). In addition, the company did not justify why the medical oncology service was selected over for instance the clinical oncology service (Table 4.14). Ideally the company would provide a rationale on the service selection as well as supporting evidence for this. Therefore, the EAG has provided a scenario analysis using the unit costs from the National Cost Collection 2022/2023 based on route of administration for an outpatient procedure in the clinical oncology service (instead of medical oncology service). In addition, for the amivantamab with chemotherapy and pembrolizumab with chemotherapy arms, the company applied the unit cost for monotherapy administration for the maintenance cycle, even though amivantamab and pemetrexed, and pembrolizumab and pemetrexed would be administered in combination, therefore incurring the unit costs per IV administration of combination therapy (SB14Z). The EAG is uncertain on why the company used this approach to model the subsequent administration of treatments. The EAG run a scenario using the unit cost of the combined administration which resulted in increased costs for amivantamab (£██████) and pembrolizumab (£██████). This increased the ICER of chemotherapy to £44,760/QALY (£1,776/QALY increase; 4.13% increase). Pembrolizumab continued to be dominated by amivantamab + chemotherapy.

Table 4.14: Drug administration unit cost comparison

Description	Company submission unit cost	Clarification letter unit cost	EAG scenario unit cost
Cost per IV administration, monotherapy (SB12Z)	£207.59	£191.96	£264.70
Cost per IV administration, combination therapy (SB14Z)	£440.71	£335.66	£455.54
Oral therapy one-off cost (SB11Z)	£216.9	£316.22	£290.14
EAG = Evidence Assessment Group; IV = intravenous			

- e) The EAG could not find the some of the parameters used by the company on its respective source.
- Monitoring costs were based on National Cost Collection 2022/2023 reference costs, and according to the company the codes used were DAPS05 – Haematology (£2.75) for full blood count, and DAPS04 – Clinical biochemistry for liver function and renal function tests (£1.61). However, the EAG could not find these unit costs. The closest unit costs for DAPS05 and DAPS04 were £2.74 and £1.57, respectively and were derived from “unknown” service. The EAG would like to ask the company to clarify from which service were the unit costs obtained. Moreover, the EAG would like to ask why the costs from the medical oncology service (DAPS05: £5.09 and DAPS04: £4.59) or clinical oncology service (DAPS05: £5.00 and DAPS04: £5.10) were not used, as they were deemed relevant for the administration costs. Likewise, these drug monitoring components and their

- frequency were derived from the pemetrexed SmPC. The company did not justify whether amivantamab, carboplatin, or pembrolizumab would require additional monitoring tests.
- b. Pembrolizumab was assumed to have an RDI of 100%, as there were no published data available to inform the RDI of pembrolizumab. However, TA683 reported a RDI of 95.6% based on KEYNOTE-189. The EAG would like to incorporate this into their base-case, although it will not have an impact due to the approach on vial sharing. However, the EAG was not able to find the dose skipping of 4.4% on the TA683, and would like to ask the company to provide more information on this.
- f) After the request for clarification, the company updated the unit costs of some cost categories using the National Cost Collection 2022/2023 reference costs. The updated costs included: administration costs, drug monitoring costs, AE unit costs, some resource use and costs for routine follow-up care, some of the cost components of the end-of-life costs.

4.2.10 Disease severity

The company's model was used for the QALY shortfall analysis. The expected general population quality-adjusted life expectancy (QALE) for the modelled population were calculated in the model using the Office for National Statistics (ONS) Life Tables²⁹ and QALYs for the SoC were derived from the cost effectiveness model (CEM), using the total discounted QALYs calculated for patients in the NCRAS dataset (n=24), as it represented the England-specific, real-world population dataset. The QALY shortfall calculator by Schneider et al. 2022³⁰ was utilised to validate the absolute and proportional shortfall estimates. The informing sex distribution, starting age and discount rate were consistent with the company's base-case (Table 4.15). A severity modifier of x1.2 was applied to the total QALYs.

Table 4.15: QALY shortfall analysis

QALY shortfall analysis: input factors	
Sex distribution	57.8
Starting age	59.6
Discount rate	3.5%
QALE after model starting age	12.58
QALY shortfall analysis: summary outputs	
Absolute QALY shortfall	████
Proportional QALY shortfall	████
QALY weight	x1.2
Source: CS Table 42, 82,83. Clarification letter Table 45	
CS = company submission; QALE = quality-adjusted life expectancy, QALY = quality-adjusted life year	

EAG comment: For the QALY shortfall analysis, the company implemented the total discounted QALYs for patients in the NCRAS dataset (n=24) (proportional shortfall: █████), as it was England-specific. In Table 45 of the response to the request for clarification, the company provided the QALY shortfall calculations for all the comparators including the weighted comparator (████) and the individual comparator arms (chemotherapy: █████ and pembrolizumab plus chemotherapy: █████), which also led to a severity modifier of 1.2. The EAG had no concerns regarding the QALY shortfall analysis. The EAG was unable to exactly reproduce the results reported by the company using the

QALY shortfall calculator (<https://shiny.york.ac.uk/shortfall/>) and got minor differences in their calculations. However, these did not change the severity modifier of x1.2.

4.2.11 Uncertainty

The company considered as the key areas of uncertainty:

- The comparative efficacy of OS for amivantamab-chemotherapy versus chemotherapy, given the presence of treatment switching from the chemotherapy treatment arm to amivantamab monotherapy.
- The comparison between data from the PAPILLON study (patients receiving amivantamab-chemotherapy) to pooled RWE from the NECTAR study (patients receiving pembrolizumab-chemotherapy regimens) due to the absence of studies evaluating pembrolizumab-chemotherapy in the population of interest to this submission.
- In the pembrolizumab-chemotherapy arm, the utilisation of HRs (TTNT versus PFS and TTNT versus TTDD) to generate PFS and TTDD data, respectively.
- Unavoidable uncertainties regarding the long-term extrapolation of survival data.

EAG comment: The EAG largely agrees with the company's assessment of the key areas of uncertainty.

5. Cost effectiveness results

5.1 Company's cost effectiveness results

The updated clarification letter base-case cost effectiveness results (probabilistic [95% CI]) for amivantamab with chemotherapy compared to the blended comparator (70% platinum chemotherapy, 30% pembrolizumab-chemotherapy) indicated that amivantamab with chemotherapy is more effective (incremental QALYs of [REDACTED]) and more costly (additional costs of [REDACTED] (with PAS) than the blended comparator, amounting to an ICER of £28,853 per QALY gained (Table 5.1). This result does not include the application of a 1.2x QALY weight. The probability of amivantamab with chemotherapy being cost-effective, at thresholds of £30,000 per QALY gained with and without the severity modifier, compared to the blended comparator are [REDACTED] and [REDACTED]%, respectively. The probabilistic results of the CS are shown in (Table 5.2)

Table 5.1: Summary of the company pairwise probabilistic results (Clarification letter)

Treatment	Total costs (£)	Total LYs	Total QALYs	Incr. cost (£)	Incr. LYs	Incr. QALYs	ICER (£/QALY)
Amivantamab - chemotherapy	[REDACTED]	3.92	[REDACTED]	[REDACTED]			
Platinum chemotherapy	[REDACTED]	1.98	[REDACTED]	[REDACTED]	1.93	[REDACTED]	41,241 (34,368*)
Pembrolizumab-chemotherapy	[REDACTED]	2.15	[REDACTED]	[REDACTED]	1.76	[REDACTED]	Dominant
Blended comparator	[REDACTED]	2.03	[REDACTED]	[REDACTED]	1.88	[REDACTED]	28,853 (24,044*)
*with severity modifier Based on the PSA sheet in the updated CEM. CEM = cost effectiveness model; ICER = incremental cost-effectiveness ratio; Incr. = incremental; LY = life year; NMB = net monetary benefit; QALY = quality-adjusted life year; PSA = probabilistic sensitivity analysis							

Table 5.2: Summary of the company pairwise probabilistic results (Original CS)

Treatment	Total costs (£)	Total LYs	Total QALYs	Incr. cost (£)	Incr. LYs	Incr. QALYs	ICER (£/QALY)
Amivantamab - chemotherapy	[REDACTED]	3.81	[REDACTED]	[REDACTED]	-	[REDACTED]	
Platinum chemotherapy	[REDACTED]	1.97	[REDACTED]	[REDACTED]	1.84	[REDACTED]	41,911 (34,926*)
Pembro-lizumab-chemotherapy	[REDACTED]	2.11	[REDACTED]	[REDACTED]	1.70	[REDACTED]	Dominant
Blended comparator	[REDACTED]	2.01	[REDACTED]	[REDACTED]	1.80	[REDACTED]	28,859 (24,049*)
*with severity modifier Based on CS Table 85 and CEM sheet PSA CEM = cost effectiveness model; CS = company submission; ICER = incremental cost-effectiveness ratio; Incr. = incremental; LY = life year; NMB = net monetary benefit; QALY = quality-adjusted life year; PSA = probabilistic sensitivity analysis							

The disaggregated results of the post-clarification letter CEM were not included in the clarification letter. Table 5.3 shows the updated disaggregated results.

Table 5.3: Disaggregated results (Original CS)

	Amivantamab - chemotherapy	Platinum chemotherapy		Pembrolizumab - chemotherapy	
	Absolute	Absolute	Increment	Absolute	Increment
Total life years	3.762	1.958	1.804	2.089	1.673
Progression free	1.215	0.633	0.582	0.685	0.530
Progressed disease	2.547	1.325	1.222	1.404	1.144
Total QALYs	■	■	■	■	■
Progression free	■	■	■	■	■
Progressed disease	■	■	■	■	■
Disutility	■	■	■	■	■
Total cost (£)	■	■	■	■	■
Total PF costs (£)	■	■	■	■	■
Treatment acquisition	■	■	■	■	■
Treatment administration	■	■	■	■	■
Monitoring	■	■	■	■	■
AEs	■	■	■	■	■
Resource use - PF	■	■	■	■	■
Total PD costs (£)	■	■	■	■	■
Subsequent treatment	■	■	■	■	■
Resource use - PD	■	■	■	■	■
End-of-life	■	■	■	■	■
Based on CEM sheet Deterministic Results CEM = cost effectiveness model; CS = company submission; PF = progression free, PD = progressed disease, QALY = quality-adjusted life year					

Overall, the technology is modelled to affect QALYs by:

- Increased health state occupancy duration in the progression free and progressed disease health states, with incremental QALYs of ■ (■% of the total incremental QALYs) and ■ (■% of the total incremental QALYs) for the progression free and progressed disease states, respectively for the weighted comparator. Similar percentages were seen in the chemotherapy (PF: ■% PD: ■%) and pembrolizumab-chemotherapy arms (PF: ■% PD: ■%).

Overall, the technology is modelled to affect costs by:

- Increased acquisition costs of amivantamab with chemotherapy (additional costs of ■, ■% of the total incremental costs for the weighted comparator). These were mainly due to the chemotherapy arm (additional costs of ■, ■% of the total incremental costs compared to the chemotherapy arm).

- Increased resource use of the progression free state for amivantamab with chemotherapy (■■■■■, ■% of the total incremental costs compared to the weighted comparator).
- Increased resource use of the progressed disease state for amivantamab with chemotherapy (■■■■■, ■% of the total incremental costs compared to the weighted comparator).
- Virtually no difference in the subsequent treatment costs (additional costs of ■■■, ■■■% of the total incremental costs compared to the weighted comparator). However, there was a significant difference between the chemotherapy arm (incremental costs: ■■■■, ■■■ of the total incremental costs compared to the chemotherapy arm) and the pembrolizumab with chemotherapy (■■■■■, ■■■ of the total incremental costs compared to the pembrolizumab with chemotherapy arm).

EAG comment: The main concerns of the EAG relate to: a) extrapolated health gains, and b) lack of fully incremental results.

- As shown in the results breakdown of the company's post-clarification economic model, the majority of life year (LY) gains and QALY gains for the intervention and competitors (i.e., weighted comparator, chemotherapy only, and pembrolizumab with chemotherapy) were modelled to occur in the progressed disease health state. The EAG, however, expected the majority of treatment benefits to occur in the progression-free health state, as patients on amivantamab were treated until disease progression (or unacceptable toxicity). Related to this, in Table 43 of the response to the request for clarification, the company provided the observed survival as well as TTNT using restricted mean survival time (RMST) with multiple truncation points. When considering the most mature truncation point of 28.58 months (selected by the company based on maximum follow-up period of chemotherapy only), the estimated incremental survival for amivantamab with chemotherapy versus chemotherapy only and pembrolizumab chemotherapy were ■■■■■■■■■■ respectively. Using the RMST results as well as the undiscounted (incremental) LYs from the updated CS base-case (incremental LYs: ■■■■■■■■■■ versus chemotherapy only and pembrolizumab chemotherapy), the EAG calculated the proportion of gains accumulated beyond the observed data period beyond (i.e., the truncation point). Based on these calculations it can be derived that the proportion of LY accumulated beyond the observed data is substantially larger for amivantamab with chemotherapy than for the comparators. Specifically, considering the increments versus amivantamab with chemotherapy, approximately ■■■■■■■■■■ (or more for earlier truncation points) of the LYs are gained beyond the observed data period when compared with chemotherapy only and pembrolizumab chemotherapy respectively. Therefore, additional explanation of the mechanism by which the model generated these differences as well as a justification for why they are plausible based upon available evidence is warranted (as requested but not provided in the company's response to the request for clarification question B23). This includes verifying the plausibility of the partitioned survival model extrapolations.
- The company did not provide fully incremental results, despite being asked in clarification question B2. The EAG prefers the full incremental cost-effectiveness results (without using a blended comparator are preferred), as also outlined in Section 4.2.4 of this report. Hence, to optimally inform the committee, it is recommended that the company uses this approach for presenting future results.

5.2 Company's sensitivity analyses

The company performed and presented the results of probabilistic sensitivity analyses (PSA), deterministic sensitivity analyses (DSA) as well as scenario analyses. The parameters that have the greatest effect on the ICER (based on the company's sensitivity analyses) is:

- The OS extrapolation of amivantamab-chemotherapy (values ranging from ■■■ decrease to ■■■% increase on the ICER).

Consistently, modelling assumptions that relate to these parameters likely have the greatest effect on the ICER. This is illustrated by the following CS scenarios that have a substantial impact on the ICER:

- The use of an alternative comparator distributions in the weighted comparison (90% IO+CP and 10% CP; reflecting insight from some experts in advisory board) (■■■% decrease on the ICER)
- Using NCRAS data to model comparator efficacy and treatment distribution, using the full dataset to model efficacy and the distribution of treatments (■■■% decrease on the original ICER)
- The use of gamma distribution to extrapolate the OS of amivantamab-chemotherapy (■■■% decrease on the ICER).

EAG comment: The main concerns of the EAG relate to: a) the INHB convergence plot change in post-clarification CEM, b) missing scenario.

- In the CS, the INHB convergence plot stabilised around the 400 simulation (CS, Figure 49). However, in the post-clarification CEM, the probabilistic cost effectiveness did not stabilise until approximately the 750 simulations. Therefore, the EAG would run their PSA with 1,000 simulations.
- The scenario of using NCRAS data to model comparator efficacy and treatment distribution, using the full dataset to model efficacy and the distribution of treatments (■■■% decrease on the original ICER) could not be replicated by the EAG.

5.3 Model validation and face validity check

5.3.1 Face validity assessment

The company held three advisory boards with UK oncologists to ensure that the inputs, assumptions, and outcomes were relevant and plausible to the UK clinical practice.⁶⁻⁸ The model inputs which were validated by the clinical experts can be found in CS section B.3.14.1.

5.3.2 Technical verification

The CEM was developed in accordance with the 'Modelling Good Research Practices' from the International Society of Pharmacoeconomics and Outcomes Research and the Society for Medical Decision Making. In addition, the company held an advisory board with four health economic experts to discuss the most appropriate assumptions and inputs to include in the CEM.

As per clarification response B25, the model underwent an in-depth technical validation, quality check, and input review with an external vendor.⁴ A 'black-box' evaluation was performed in the form of a 'stress-test' in which involved setting model input values to their extremes, and confirming the model returned the appropriate values on the results page. When the appropriate results values were not returned, the error in the model programming were identified.

5.3.3 *Comparisons with other technology appraisals*

Cross validation with other technology appraisals was performed for different input parameters, the model structure and other model features (see for example Table 40 of the CS).

5.3.4 *Comparison with external data used to develop the economic model*

Validation of extrapolation data was performed against observed survival rates from PAPILLON and NECTAR and reported in CS Section 3.3.2.

5.3.5 *Comparison with external data not used to develop the economic model*

The CS base-case OS long-term extrapolation of amivantamab-chemotherapy was compared to the long-term data available from the CHRYSALIS trial for amivantamab monotherapy following progression on chemotherapy as second line treatment.³¹ Other external data validation was not explicitly mentioned in the CS or its appendices.

EAG comment: The main concerns of the EAG relate to: a) insufficient technical verification, and b) missing cross comparison with other TAs.

- a) The EAG is concerned with the information on the model's technical verification offered by the company. In clarification response B25, the company confirmed that a 'black-box' test was performed, however, the results of this test were not provided. Likewise, the EAG would like to receive more information on how the model implementations and formulas were verified and debugged. Despite being asked in request for clarification B25, the company did not complete the TECH-VER checklist,³² as the company considered the model had gone through appropriate and extensive validation given that "*the model structure [aligned] with prior models within advanced NSCLC, [had] been validated at an advisory board with health economists and clinical experts, and [had] undergone in-depth technical validation plus [quality control]*" and the limited timeframe. However, the fact that similar model structures were used in before, does not ensure that this particular model is correctly implemented. The TECH-VER checklist aids the technical verification, helps the identification of errors and their causes, and allows for its documentation. Therefore, the EAG would like to ask the company to fill out the checklist and provide further information on the technical validation of the CEM.
- b) In clarification response B26 and CS Table 40, the company provided some cross-validation with other TAs regarding model structure (including time horizon, cycle length, and discount rate), clinical effectiveness outcomes, utility values, and resource use and costs sources. However, only TA850 and TA855 was used for comparison, due to the limited number of TAs on patients with EGFR exon 20 insertion mutated advanced NSCLC. The EAG understands that ideally the same exact population should be used for cross-validation, however, other TAs focused on first-line treatment of adult patients with advanced NSCLC (e.g., TA683, TA761) could have been insightful. Moreover, as discussed in Section 4.2.9, the EAG has some concerns regarding some of the unit costs used and would like to ask the company a cross-validation, not only on the sources or cost categories, but on the unit costs (e.g., administration, AEs, resource use, end-of-life), and the actual costs incurred per category.

6. Evidence Assessment Group's Additional Analyses

6.1 Exploratory and sensitivity analyses undertaken by the EAG

Table 6.1 summarises the key issues related to the cost effectiveness categorised according to the sources of uncertainty as defined by Grimm et al. 2020³³:

- Transparency (e.g., lack of clarity in presentation, description, or justification)
- Methods (e.g., violation of best research practices, existing guidelines, or the reference case)
- Imprecision (e.g., particularly wide confidence intervals, small sample sizes, or immaturity of data)
- Bias and indirectness (e.g., there is a mismatch between the decision problem and evidence used to inform it in terms of population, intervention/comparator and/or outcomes considered)
- Unavailability (e.g., lack of data or insight).

Identifying the source of uncertainty can help determine what course of action can be taken (i.e., whether additional clarifications, evidence and/or analyses might help to resolve the key issue). Moreover, Table 6.1 lists suggested alternative approaches, expected effects on the cost effectiveness, whether it is reflected in the EAG base-case as well as additional evidence or analyses that might help to resolve the key issues.

Based on all considerations in the preceding Sections of this EAG report, the EAG defined a new base-case. This base-case included multiple adjustments to the original base-case presented in the previous sections. These adjustments made by the EAG form the EAG base-case and were subdivided into three categories (derived from Kaltenthaler 2016):

- Fixing errors (FE) (correcting the model where the company's submitted model was unequivocally wrong)
- Fixing violations (FV) (correcting the model where the EAG considered that the NICE reference case, scope or best practice had not been adhered to)
- Matters of judgement (MJ) (amending the model where the EAG considers that reasonable alternative assumptions are preferred)

6.1.1 EAG base-case

Adjustments made by the EAG, to derive the EAG base-case (using the CS base-case as starting point) are listed below. Table 6.2 shows how individual adjustments impact the results plus the combined effect of all abovementioned adjustments simultaneously, resulting in the EAG base-case. The 'fixing error' adjustments were combined and the other EAG analyses were performed also incorporating these 'fixing error' adjustments given the EAG considered that the 'fixing error' adjustments corrected unequivocally wrong issues.

6.1.1.1 Fixing errors

No fixing errors.

6.1.1.2 Fixing violations

No fixing violations.

6.1.1.3 Matters of judgement

1. Estimation of OS for chemotherapy only (Section 4.2.6)
Log-logistic distribution for chemotherapy only
2. Estimation of TTDD for amivantamab with chemotherapy (Section 4.2.6)
Log-logistic distribution for amivantamab and Exponential distribution for chemotherapy (administered with amivantamab)
3. Estimation of treatment costs (Section 4.2.9)
Round up units per administration for amivantamab in line with comparators and RDI for pembrolizumab based on TA683 (instead of assuming 100%)
4. Adverse event costs (Section 4.2.9)
Adverse event costs based on “severest” cost rather than weighted.

6.1.2 EAG exploratory scenario analyses

The EAG performed the following exploratory scenario analyses to explore the impact of alternative assumptions conditional on the EAG base-case.

6.1.2.1 Exploratory scenario analyses

5. Estimation of OS for amivantamab with chemotherapy (Section 4.2.6)
Gompertz for estimating OS for amivantamab with chemotherapy
6. Estimation of TTNT for pembrolizumab with chemotherapy (used to approximate both PFS and TTDD for pembrolizumab with chemotherapy; Section 4.2.6)
Gompertz for pembrolizumab with chemotherapy
7. Health state utility values based on alternative regression model (Section 4.2.8)
Use PF and PD utility based on independently estimated single MMRMs
8. Health state utility values based on alternative evidence (Section 4.2.8)
Use PF and PD utility from TA683
9. Adverse event costs (Section 4.2.9)
Adverse event costs based on “severest” cost rather than weighted, not including only short-stay.

6.1.3 EAG subgroup analyses

No subgroup analyses were performed by the EAG.

Table 6.1: Overview of key issues related to the cost effectiveness

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER ^a	Resolved in EAG base-case ^b	Required additional evidence or analyses
Blended comparator approach	4.2.4	Methods	Provide results for the treatment options within the blended comparator separately.	+	Yes	Future analyses should be presented separately for all treatment options
Survival extrapolation for amivantamab with chemotherapy and chemotherapy only	4.2.6	Unavailability / methods	Alternative parametric models to estimate OS for amivantamab with chemotherapy	+	Explored	See alternative approach
Assuming no waning of the relative treatment effect	4.2.6	Unavailability / methods	Assuming waning or relative treatment effect over time	+	No	Scenario analyses while assuming treatment waning (at different time points), as requested in clarification question B11.
Missingness in HRQoL data	4.2.8	Unavailability / methods	Alternative handling of missing HRQoL data	+/-	No	Further evidence to support the company's assumption that data was missing (completely) at random to address this issue.
Implementation of dose frequency for the estimation of treatment costs	4.2.9	Methods	Accurately reflect treatment administration over time	+/-	No	See alternative approach
Assumption of no-vial sharing	4.2.9	Methods	No implicit vial sharing for amivantamab with chemotherapy.	+	Yes	See alternative approach
Extrapolated benefit	5.1	Unavailability	Explanation of the mechanism by which the economic model generated the extrapolated benefits.	+/-	No	Further evidence to support the company's extrapolated benefits. And related assumptions

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER ^a	Resolved in EAG base-case ^b	Required additional evidence or analyses
Technical verification of economic model	5.3	Methods / Transparency	Complete the TECH-VER and provide further information on the technical verification on the economic model	+/-	No	See alternative approach
^a Likely conservative assumptions (of the intervention versus all comparators) are indicated by '-'; while '+/-' indicates that the bias introduced by the issue is unclear to the EAG and '+' indicates that the EAG believes this issue likely induces bias in favour of the intervention versus at least one comparator; ^b Explored EAG = Evidence Assessment Group; HRQoL = health-related quality of life; ICER = incremental cost effectiveness ratio						

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

In Section 6.1 the EAG base-case was presented, which was based on various changes compared to the company base-case. Table 6.2 shows how individual changes impact the results plus the combined effect of all changes simultaneously. The exploratory scenario analyses are presented in Table 6.3. These are all conditional on the EAG base-case. Similarly, Tables 6.4 and 6.5 present the same analyses whilst also including the severity modifier. The analyses numbers in Tables 6.2-6.5 correspond to the numbers reported in Section 6.1. All analyses are deterministic unless otherwise specified (by adding probabilistic). The submitted model file contains technical details on the analyses performed by the EAG (e.g., the “EAG” sheet provides an overview of the cells that were altered for each adjustment).

Table 6.2: EAG base-case without severity modifier

Technologies	Total costs	Total LY	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)
CS base-case (updated in clarification response)							
Amivantamab - chemotherapy	████	3.762	████				
Platinum chemotherapy	████	1.958	████	████	1.804	████	42,984
Pembrolizumab-chemotherapy	████	2.089	████	████	1.673	████	Dominant
Blended comparator	████	1.997	████	████	1.765	████	29,806
Matter of judgement (1- Log-logistic distribution for estimating OS for chemotherapy only)							
Amivantamab - chemotherapy	████	3.762	████				
Platinum chemotherapy	████	2.204	████	████	1.558	████	48,089
Pembrolizumab-chemotherapy	████	2.089	████	████	1.673	████	Dominant
Matter of judgment (2- Log-logistic distribution for estimating TTDD for amivantamab AND Exponential distribution for estimating TTDD for chemotherapy (administered with amivantamab)							
Amivantamab - chemotherapy	████	3.762	████				
Platinum chemotherapy	████	1.958	████	████	1.804	████	54,995
Pembrolizumab-chemotherapy	████	2.089	████	████	1.673	████	9,502
Matter of judgment (3 – No vial sharing for amivantamab and RDI based on TA683 for pembrolizumab)							
Amivantamab - chemotherapy	████	3.762	████				
Platinum chemotherapy	████	1.958	████	████	1.804	████	45,262
Pembrolizumab-chemotherapy	████	2.089	████	████	1.673	████	Dominant

Technologies	Total costs	Total LY	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Matter of judgement (4 -Use of severest AE unit costs for non-elective short stay)							
Amivantamab - chemotherapy	██████	3.762	██████				
Platinum chemotherapy	██████	1.958	██████	██████	1.804	██████	43,048
Pembrolizumab-chemotherapy	██████	2.089	██████	██████	1.673	██████	Dominant
EAG base-case							
Amivantamab - chemotherapy	██████	3.762	██████				
Platinum chemotherapy	██████	2.204	██████	██████	1.558	██████	65,493
Pembrolizumab-chemotherapy	██████	2.089	██████	██████	1.673	██████	12,863
EAG base-case probabilistic							
Amivantamab - chemotherapy	██████	3.881	██████				
Platinum chemotherapy	██████	2.234	██████	██████	1.647	██████	62,978
Pembrolizumab-chemotherapy	██████	2.144	██████	██████	1.737	██████	11,711
AE = adverse event; CS = company submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; LY = life year; OS = overall survival; QALY = quality-adjusted life year; RDI = relative dose intensity; TTDD = time to treatment discontinuation or death							

Table 6.3: Scenario analyses (conditional on EAG base-case) without severity modifier

Technologies	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)
EAG base-case							
Amivantamab - chemotherapy	██████	3.762	██████				
Platinum chemotherapy	██████	2.204	██████	██████	1.558	██████	65,493
Pembrolizumab-chemotherapy	██████	2.089	██████	██████	1.673	██████	12,863
Scenario 1 (Gompertz for estimating OS for amivantamab with chemotherapy)							
Amivantamab - chemotherapy	██████	2.724	██████				
Platinum chemotherapy	██████	2.204	██████	██████	0.519	██████	142,941
Pembrolizumab-chemotherapy	██████	2.089	██████	██████	0.635	██████	547
Scenario 2 (Gompertz for estimating TTNT for pembrolizumab with chemotherapy)							
Amivantamab - chemotherapy	██████	3.762	██████				
Platinum chemotherapy	██████	2.204	██████	██████	1.558	██████	65,493

Technologies	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Pembrolizumab-chemotherapy	██████	2.089	██████	██████	1.673	██████	18,409
Scenario 3 (Utility values based on single MMRM)							
Amivantamab - chemotherapy	██████	3.762	██████				
Platinum chemotherapy	██████	2.204	██████	██████	1.558	██████	66,467
Pembrolizumab-chemotherapy	██████	2.089	██████	██████	1.673	██████	13,025
Scenario 4 (Utility values based on TA683)							
Amivantamab - chemotherapy	██████	3.762	██████				
Platinum chemotherapy	██████	2.204	██████	██████	1.558	██████	69,230
Pembrolizumab-chemotherapy	██████	2.089	██████	██████	1.673	██████	13,625
Scenario 5 – Assuming severest AE unit cost							
Amivantamab - chemotherapy	██████	3.762	██████				
Platinum chemotherapy	██████	2.204	██████	██████	1.558	██████	66,790
Pembrolizumab-chemotherapy	██████	2.089	██████	██████	1.673	██████	13,866
AE = adverse event; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; LY = life year; MMRM = mixed-model repeated measures; OS = overall survival; QALY = quality-adjusted life year; TTNT = time to next treatment							

Table 6.4: EAG base-case with severity modifier

Technologies	Total costs	Total LY	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)
CS base-case (updated in clarification response)							
Amivantamab - chemotherapy	██████	3.762	██████				
Platinum chemotherapy	██████	1.958	██████	██████	1.804	██████	35,820
Pembrolizumab-chemotherapy	██████	2.089	██████	██████	1.673	██████	Dominant
Blended comparator	██████	1.997	██████	██████	1.765	██████	24,839
Matter of judgement (1- Log-logistic distribution for estimating OS for chemotherapy only)							
Amivantamab - chemotherapy	██████	3.762	██████				
Platinum chemotherapy	██████	2.204	██████	██████	1.558	██████	40,074
Pembrolizumab-chemotherapy	██████	2.089	██████	██████	1.673	██████	Dominant

Technologies	Total costs	Total LY	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Matter of judgment (2- Log-logistic distribution for estimating TTDD for amivantamab AND Exponential distribution for estimating TTDD for chemotherapy (administered with amivantamab))							
Amivantamab - chemotherapy	██████	3.762	██████				
Platinum chemotherapy	██████	1.958	██████	██████	1.804	██████	45,829
Pembrolizumab-chemotherapy	██████	2.089	██████	██████	1.673	██████	7,919
Matter of judgment (3 – No vial sharing for amivantamab and RDI based on TA683 for pembrolizumab)							
Amivantamab - chemotherapy	██████	3.762	██████				
Platinum chemotherapy	██████	1.958	██████	██████	1.804	██████	37,719
Pembrolizumab-chemotherapy	██████	2.089	██████	██████	1.673	██████	Dominant
Matter of judgement (4 -Use of severest AE unit costs for non-elective short stay)							
Amivantamab - chemotherapy	██████	3.762	██████				
Platinum chemotherapy	██████	1.958	██████	██████	1.804	██████	35,873
Pembrolizumab-chemotherapy	██████	2.089	██████	██████	1.673	██████	Dominant
EAG base-case							
Amivantamab - chemotherapy	██████	3.762	██████				
Platinum chemotherapy	██████	2.204	██████	██████	1.558	██████	54,577
Pembrolizumab-chemotherapy	██████	2.089	██████	██████	1.673	██████	10,719
EAG base-case probabilistic							
Amivantamab - chemotherapy	██████	3.881	██████				
Platinum chemotherapy	██████	2.234	██████	██████	1.647	██████	52,482
Pembrolizumab-chemotherapy	██████	2.144	██████	██████	1.737	██████	9,759
AE = adverse event; CS = company submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; LY = life year; OS = overall survival; QALY = quality-adjusted life year; RDI = relative dose intensity; TTDD = time to treatment discontinuation or death							

Table 6.5: Scenario analyses (conditional on EAG base-case) with severity modifier

Technologies	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)
EAG base-case							
Amivantamab - chemotherapy	██████	3.762	██████				

Technologies	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Platinum chemotherapy	██████	2.204	██████	██████	1.558	██████	54,577
Pembrolizumab-chemotherapy	██████	2.089	██████	██████	1.673	██████	10,719
Scenario 1 (Gompertz for estimating OS for amivantamab with chemotherapy)							
Amivantamab - chemotherapy	██████	2.724	██████				
Platinum chemotherapy	██████	2.204	██████	██████	0.519	██████	119,117
Pembrolizumab-chemotherapy	██████	2.089	██████	██████	0.635	██████	456
Scenario 2 (Gompertz for estimating TTNT for pembrolizumab with chemotherapy)							
Amivantamab - chemotherapy	██████	3.762	██████				
Platinum chemotherapy	██████	2.204	██████	██████	1.558	██████	54,577
Pembrolizumab-chemotherapy	██████	2.089	██████	██████	1.673	██████	15,341
Scenario 3 (Utility values based on single MMRM)							
Amivantamab - chemotherapy	██████	3.762	██████				
Platinum chemotherapy	██████	2.204	██████	██████	1.558	██████	55,389
Pembrolizumab-chemotherapy	██████	2.089	██████	██████	1.673	██████	10,854
Scenario 4 (Utility values based on TA683)							
Amivantamab - chemotherapy	██████	3.762	██████				
Platinum chemotherapy	██████	2.204	██████	██████	1.558	██████	57,691
Pembrolizumab-chemotherapy	██████	2.089	██████	██████	1.673	██████	11,354
Scenario 5 – Assuming severest AE unit cost							
Amivantamab - chemotherapy	██████	3.762	██████				
Platinum chemotherapy	██████	2.204	██████	██████	1.558	██████	55,659
Pembrolizumab-chemotherapy	██████	2.089	██████	██████	1.673	██████	11,555
AE = adverse event; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; LY = life year; MMRM = mixed-model repeated measures; OS = overall survival; QALY = quality-adjusted life year; TTNT = time to next treatment							

6.3 Conclusions of the cost effectiveness section

The CS, appendices and response to the request for clarification^{1, 4, 11} provided sufficient details for the EAG to appraise the literature searches conducted to identify relevant studies on cost effectiveness, HRQoL and cost/health care resource use on the treatment of patients with advanced NSCLC. Searches

were conducted in May 2020 and updated in August 2022, October 2023, March 2024 and July 2024. Searches were transparent and reproducible, and comprehensive strategies were used. Databases, conference proceedings and HTA resources were searched. Overall, the EAG has no major concerns about the literature searches conducted.

The company's cost effectiveness model partly complied with the NICE reference case. Deviations from the NICE reference case related to the use of a 'blended' comparator, and it was unclear whether the UK tariff was used for the health state utility values. The most prominent issues highlighted by the EAG related to 1) the estimation of OS and TTDD, 2) the estimation of HRQoL, 3) the estimation of treatment costs, and 4) the technical verification of the economic model.

Firstly, a key challenge was the immaturity of the OS data from the PAPILLON trial, which introduced significant uncertainty related to the extrapolated OS. This issue was particularly influential due to a large proportion of life-year being gained beyond the available trial data. To support the company's partitioned survival modelling approach, further explanation of the mechanisms by which the economic model generated these results would be informative. The uncertainty surrounding the modelled comparative effectiveness was further complicated by treatment switching from the chemotherapy arm to amivantamab monotherapy in the PAPILLON trial and the assumptions required for the comparison with pembrolizumab-chemotherapy, which involved an unanchored comparison. Therefore, the implicit assumption in the CS base-case of no waning of relative treatment effectiveness is questionable and should be explored as suggested by the EAG. Additionally, the estimation of TTDD was uncertain due to the lack of data on this outcome for pembrolizumab-chemotherapy, relying instead on substantial assumptions informed by data from amivantamab with chemotherapy. Both the long-term OS and TTDD estimates in the CS base-case were suboptimal when compared with clinical expert input.

Secondly, the estimation of health state utility values based on the PAPILLON trial was impeded by substantial missing data across treatment cycles. The EAG noted that it was unclear whether the missing data were completely at random and to what extent this impacted the PF and PD health state utility estimates.

Thirdly, the company's approach to estimating treatment costs was suboptimal. It did not accurately reflect treatment administration over time, such as patients receiving a full dose at the required time point followed by stipulated periods of no administration. Additionally, the assumption of no vial sharing was inconsistently applied in the economic model, which was adjusted in the EAG base-case analysis.

Finally, the EAG expressed concerns regarding the technical verification of the model. The company did not provide the TECH-VER checklist despite requests in the request for clarification, nor did it offer a detailed overview of the validation efforts to verify the model's implementation.

The CS base-case probabilistic ICERs (with severity modifier) for amivantamab with chemotherapy versus chemotherapy only and versus pembrolizumab with chemotherapy were £34,368 per QALY gained and dominant respectively. The estimated EAG base-case probabilistic ICERs (with severity modifier), based on the EAG preferred assumptions highlighted in Section 5.1, for amivantamab with chemotherapy versus chemotherapy only and versus pembrolizumab with chemotherapy were £52,482 and £9,759 per QALY gained. The probabilistic EAG base-case analyses indicated cost effectiveness probabilities of [REDACTED] at willingness to pay thresholds of £20,000 and £30,000 per QALY gained for amivantamab with chemotherapy. The most influential adjustments were alternative TTDD approach for amivantamab with chemotherapy, alternative approach for the estimation of treatment costs and alternative approach to estimate OS for chemotherapy only. The ICER increased most in the

scenario analysis with alternative assumptions regarding the estimation of OS for amivantamab with chemotherapy, alternative TTDD approach for pembrolizumab with chemotherapy and using utility values from TA683. Notably, in the EAG base-case pembrolizumab with chemotherapy is less effective than chemotherapy only, this illustrates the uncertainty related to the unanchored comparison with pembrolizumab with chemotherapy. The EAG has identified a number of key issues with ATT weighting for the ITC: a) there was a lack of adjustment for some important prognostic variables in the base-case ATT analyses; b) sensitivity analyses by using alternative adjustment methods were not conducted for the data of base-case ATT analyses; and c) the additional ITC analysis for the comparison of amivantamab plus chemotherapy versus immunotherapy alone was not conducted by using ATT adjustment and/or alternative adjustment methods. Due to these issues, there were uncertainties in the results of ITC.

There is large remaining uncertainty about the effectiveness and relative effectiveness of amivantamab chemotherapy, which can be at least partly resolved by the company by conducting further analyses.

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OS

Could you please fill in (see Table 6 below), based on your expertise, the expected overall survival (OS) for carboplatin and pemetrexed, amivantamab with carboplatin and pemetrexed, pembrolizumab with carboplatin and pemetrexed and pembrolizumab monotherapy received as first-line treatment of adult patients with advanced NSCLC with activating EGFR Exon 20 insertion mutations in UK clinical practice.

Table 6: Estimated overall survival in UK clinical practice

Treatment	Patients remaining alive at		
	3 years (%)	5 years (%)	10 years (%)
Carboplatin and pemetrexed	20%	5%	<1%
Amivantamab with carboplatin and pemetrexed	25-30%	10-15%	Unknown
Pembrolizumab with carboplatin and pemetrexed	15-20%	5-10%	<1%
Pembrolizumab monotherapy	<10%	<5%	<1%

PFS

Could you please fill in (see Table 7 below), based on your expertise, the expected progression-free survival (PFS) for carboplatin and pemetrexed, amivantamab with carboplatin and pemetrexed, pembrolizumab with carboplatin and pemetrexed and pembrolizumab monotherapy received as first-line treatment of adult patients with advanced NSCLC with activating EGFR Exon 20 insertion mutations in UK clinical practice.

Table 7: Estimated progression-free survival in UK clinical practice

Treatment	Patients remaining progression free and alive at		
	3 years (%)	5 years (%)	10 years (%)
Carboplatin and pemetrexed	<5%	<1%	<1%
Amivantamab with carboplatin and pemetrexed	10%-15%	5-10%	0-5%
Pembrolizumab with carboplatin and pemetrexed	5-10%	5-10%	<1%
Pembrolizumab monotherapy	5%	<1%	<1%

TTDD

Could you please fill in (see Table 8 below), based on your expertise, the expected time to treatment discontinuation or death (TTDD) for carboplatin and pemetrexed, amivantamab with carboplatin and pemetrexed, pembrolizumab with carboplatin and pemetrexed and pembrolizumab monotherapy received as first-line treatment of adult patients with advanced NSCLC with activating EGFR Exon 20 insertion mutations in UK clinical practice.

Table 8: Estimated time to treatment discontinuation or death in UK clinical practice

Treatment	Component	Patients remaining on treatment at		
		3 years (%)	4 years (%)	5 years (%)
Carboplatin and pemetrexed	Carboplatin and pemetrexed	<5%	<2%	<1%
Amivantamab with carboplatin and pemetrexed	Amivantamab	15-20%	10-15%	5-10%
	Carboplatin and pemetrexed	10-15%	5-10%	<5%
Pembrolizumab with carboplatin and pemetrexed	Pembrolizumab	5-10%	<5%	<5%
	Carboplatin and pemetrexed	5-10%	<5%	<5%
Pembrolizumab monotherapy	Pembrolizumab	<5%	<2%	<1%

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Single Technology Appraisal

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

EAG report – factual accuracy check and confidential information check

“Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release.” (Section 5.4.9, [NICE health technology evaluations: the manual](#)).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Tuesday 26 November 2024** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as [REDACTED] should be highlighted in turquoise and all information submitted as '[REDACTED]' in pink.

Issue 1 Identified Factual Issues

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 15, Section 1.2 states: • <i>'Increased resource use of the progression free state for amivantamab with chemotherapy (■■■■■, ■■■% of the total incremental costs)</i> • <i>Increased resource use of the progressed disease state for amivantamab with chemotherapy (■■■■■, ■■■% of the total incremental costs)</i> • <i>Virtually no difference in the subsequent treatment costs (additional costs of ■■■, ■■■% of the total incremental costs). However, there was a significant difference between the chemotherapy</i>	Each time the EAG state the % of the total incremental results, please can the EAG note which comparator this refers to (e.g., X% of the total incremental costs compared to the weighted comparator).	Given the ongoing discussions and different perspectives around the comparators, it would be useful if the comparison the EAG are referring to is clear.	Thank you for highlighting this issue. We have now included which comparator we are referring to in each statement. The text has also been updated in section 5.1. In addition the increased resource use of the progression free state has been corrected as it included the value of a different category.

arm (incremental costs: [REDACTED], [REDACTED] of the total incremental costs) and the pembrolizumab with chemotherapy ([REDACTED], [REDACTED] of the total incremental costs).’			
Page 16, Section 1.3, Table 1.3 states: <i>‘...in response to the request for clarification that the NECTAR study data are too few and too old...’</i> This statement is repeated on Page 34, Section 2.3.	The statement should be updated as follows: <i>‘...in response to the request for clarification that the NCRAS data within the NECTAR study data are too few and only cover patients diagnosed up to 2021...’</i>	The original statement from the EAG oversimplifies the arguments made by Johnson & Johnson in response to the clarification questions. Instead of the data being too old, the limitation is that there have been changes to the testing landscape since the conclusion of the study that have resulted in clinicians being better able to identify EGFR Exon20 insertion mutations. Additionally, this statement should only reference the NCRAS (English) data within the NECTAR study.	Amended for increasing accuracy. Please note that there was no typographical error with ‘the’ in the EAG report as suggested.

Page 16, Section 1.3, Table 1.3 states: <i>'and t he company did include an unadjusted overall survival and time to next treatment results for immuno-therapy (assumed to be pembrolizumab monotherapy) in response to the request for clarification.'</i>	The statement should be updated as follows: <i>'and the company did include results of an unadjusted overall survival and time to next treatment indirect treatment comparison for immuno-therapy (assumed to be pembrolizumab monotherapy) in response to the request for clarification.'</i>	To avoid confusion, the type of results presented here should be clarified.	
Page 19, Section 1.5, Table 1.7 states: <i>'The pairwise comparison versus carboplatin and paclitaxel increases the ICER substantially, whereas the pairwise comparison versus pembrolizumab plus carboplatin and paclitaxel results in amivantamab being dominant'</i>	The statement should be updated as follows: <i>'The pairwise comparison versus carboplatin and pemetrexed increases the ICER substantially, whereas the pairwise comparison versus pembrolizumab plus carboplatin and pemetrexed results in amivantamab being dominant.'</i>	The chemotherapy comparator regimen should be carboplatin with pemetrexed and not carboplatin with paclitaxel.	Amended.
Page 21, Section 1.5, Table 1.12 states: <i>'The company implicitly allowed vial sharing for</i>	The statement should be removed. The model does not permit vial sharing for amivantamab	No vial sharing was allowed for amivantamab within the model.	Not a factual inaccuracy

<i>amivantamab with chemotherapy, but not for the comparators, without providing sufficient justification'</i> This is also related and applicable to matter of judgement 3 (referenced throughout the EAG report).	and assumes that the entire 350 mg vial is always used. However, the number of vials required is determined based on the patient's weight.	The model assumed the full cost of each 350mg vial of amivantamab that patients were using. The expected number of vials used per administration was calculated at the cohort level by comparing the total dose prepared in the trial with the total expected dose given baseline weight distribution and original dosing schedule. Therefore, the fractional values in the number of vials refer to an average number of vials at the cohort level. In line with the SmPC, dose reductions of amivantamab were based on the number of full vials (350mg) and are not related to any assumptions on vial sharing. For example, a patient <80kg who received a dose of 1400 mg instead of 1750 mg would have incurred the cost of 4 full vials, instead of 5.	

		Within the model, this is labelled as “Proportion of full dose administered (amivantamab)” (Detailed Cost Inputs_1L Tx column K) and relates to the average number of full vials used at the cohort level. Therefore, no vial sharing is assumed, instead the total number of vials for amivantamab is reduced based on the actual vs expected dose, which is permitted as per the amivantamab SmPC.	
Page 34, Section 2.3 states: <i>‘It does appear to the EAG that ABCP cannot be ruled out as a comparator on the basis of clinical expert opinion. Neither can it be excluded according to the NECTAR study, given that Table 3 of the report shows that 17.4% of patients in England received “Platinum+IO”.’</i>	The statement should be updated as follows: <i>‘There was no use of ABCP in the English data within the NECTAR study, as 0% of patients in England received Platinum+VEGF.’</i>	ABCP is not included as a component regimen within the ‘platinum+IO’ treatment class. ABCP belongs to the ‘platinum+VEGF’ treatment class instead. Therefore, it is inaccurate to state the proportional use of ‘platinum+IO’ (17.4%) supports ABCP use.	Amended in light of this information.

		0% usage of ABCP was captured in the English data within the NECTAR study (NCRAS dataset). Given 0% use, the English data within the NECTAR study, in-fact, support Johnson & Johnson's position that ABCP is not used in practice and is not a relevant comparator. The 17.4% cited by the EAG refers to the use of the 'platinum+IO' treatment class in the NCARS dataset within the NECTAR study. This solely comprised patients receiving pembrolizumab with carboplatin and pemetrexed, and therefore formed part of the argumentation used in the CS that pembrolizumab with chemotherapy is used in UK practice and is therefore a relevant comparator along with chemotherapy.	
Page 35, Section 2.5 states: <i>'According to the company, no equality issues were related to</i>	The statement should be corrected as follows:	Important equality issues have been raised within the CS	Amended.

<i>the use of amivantamab in combination with carboplatin and pemetrexed for the first-line treatment of adult patients with advanced NSCLC with activating EGFR exon 20 insertion mutations'</i>	<i>'The company submission included equality issues pertaining to stigma, ethnicity, along with the gap in treatment options and outcomes between patients with EGFR Exon20 mutations versus patients with common EGFR mutations. These are detailed within Sections A3, A.1.6, B.1.3.2.2, and B.1.4 of the CS.'</i>	which should be acknowledged.	
Page 36, Section 3.1.1, Table 3.1, row for 'CENTRAL' states: 'to Issue 5/12 2024.'	The statement should be corrected as follows: 'to Issue 2 of 12, June 2024'	The statement should be corrected to reflect the date range included in Section D.1.1.1 in the Appendices.	Not a factual inaccuracy. According to the Company's response to clarification (Q A1), the issue given in the CS Appendix was incorrect and was a copying error. The correct issue was Issue 5 of 12 2024, as stated in the EAG report
Page 36, Section 3.1.1, Table 3.1, row for 'CDSR' states: 'to Issue 6/12 2024.'	The statement should be corrected as follows: 'to Issue 2 of 12, June 2024'	The statement should be corrected to reflect the date range included in Section D.1.1.1 in the Appendices.	Not a factual inaccuracy. According to the Company's response to clarification (Q A1), the issue given in the CS Appendix was incorrect and was a copying error. The correct issue was Issue 6 of

			12 2024, as stated in the EAG report.
Page 47, Section 3.2.6 states: <i>'The majority of patients were diagnosed with adenocarcinoma (98.7%) and Stage IV disease (approximately 86%–87% at initial diagnosis).'</i>	The statement should be corrected as follows: <i>'The majority of patients were diagnosed with adenocarcinoma (98.7%) and Stage IV disease (approximately 81.2%–86.9% at initial diagnosis).'</i>	The statement should be corrected as per Section B.2.3.3 of the CS.	This has been corrected.
Page 51, Section 3.2.6 states: <i>'In clinical practice, patients often receive multiple lines of therapy before being treated with new agents like amivantamab, so the trial's exclusion of pre-treated patients may not accurately reflect real-world treatment pathways.'</i>	The statement should be updated as follows: <i>'In clinical practice, patients often receive multiple lines of therapy prior to the advanced setting before being treated with new agents like amivantamab, so the trial's exclusion of pre-treated patients may not accurately reflect real-world treatment pathways.'</i>	This statement should be clarified to reflect that the EAG are referring to treatments received prior to the advanced setting. Within the advanced setting, amivantamab-chemotherapy is positioned at first-line.	Amended.
Page 56, Section 3.2.11 states: <i>'In the absence of adequate concealment, there is a risk</i>	This statement should be removed.	As the PAPILLON trial was randomised, researchers were not able to influence what treatment groups were	This is not a factual inaccuracy, as there was a crossover design which dilutes

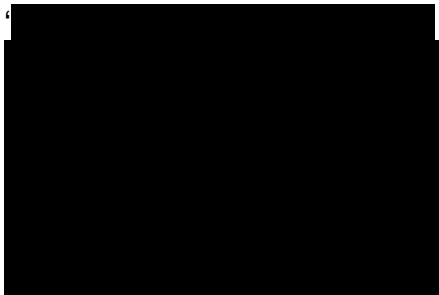
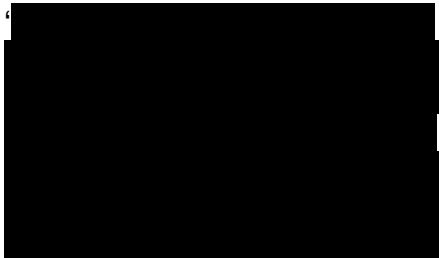
<i>that patients more likely to benefit from one treatment could have been systematically assigned to that group, potentially distorting the baseline characteristics of the treatment arms.'</i>		assigned to, this statement is therefore not accurate and should be removed. Additionally, Johnson & Johnson note that most oncology trials, including trials within EGFR mutated advanced NSCLC, are open-label, where concealment is an area of potential bias.	the initial randomisation of the PAPILLON trial.
Page 73, Section 3.2.12.2 states : <i>'Looking at TEAEs individually, the larger proportion of skin, subcutaneous and tissue disorders correspond to a higher incidence of rash and dermatitis acneiform (as stated in the CS), as well as dry skin and ulcer in the amivantamab-chemotherapy arm (■■■■ and ■■■■ respectively)'</i>	The statement should be corrected as follows: <i>'as well as dry skin and ulcer in the amivantamab-chemotherapy arm (■■■■ and 6.6%, respectively).'</i>	The statement should be corrected to reflect the correct value reported in Table 35 in Section B.2.10.2.2 in the CS.	This has been corrected by the EAG to reflect the number reported Table 35 in Section B.2.10.2.2 in the CS.

Page 76, Section 3.2.13.3 states: <i>‘and 41 participants (31.0%) in the chemotherapy arm.’</i>	The statement should be corrected as follows: <i>‘and 48 participants (31.0%) in the chemotherapy arm.’</i>	The statement should be corrected to accurately reflect the correct number of participants reported in Section B.2.10.2.4 in the CS.	This correction has been updated to reflect the number reported in Section B.2.10.2.4 in the CS.
Page 76, Section 3.2.13.3 states: <i>‘The most common SAEs for the amivantamab-chemotherapy arm are pneumonia (6%; 2.6% in chemotherapy arm)’</i>	The statement should be corrected as follows: <i>‘The most common SAEs for the amivantamab-chemotherapy arm are pneumonia (4%; 2.6% in chemotherapy arm)’</i>	The statement should be corrected to accurately reflect the correct value reported in Table 37 in Section B.2.10.2.4 in the CS.	This correction has been updated to reflect the number reported in Table 37 in Section B.2.10.2.4 in the CS.
Page 80, Section 3.2.13.3 states: <i>‘A further 3 deaths (4.6%) occurred in the amivantamab-chemotherapy safety population due to AE’</i>	The statement should be corrected as follows: <i>‘A further 3 deaths (2%) occurred in the amivantamab-chemotherapy safety population due to AE’</i>	The statement should be corrected to accurately reflect the correct value reported in Table 38 in Section B.2.10.2.5 in the CS.	This correction has been updated to reflect the number reported in Table 38 in Section B.2.10.2.5 in the CS.
Page 97, Section 3.4.8.2 states: <i>‘The EAG considers that, while SMDs together with the distribution of PS scores showed that the ATT weighted</i>	The statement should be corrected as follows: <i>‘The EAG considers that, while SMDs together with the distribution of PS scores showed that the ATT weighted</i>	SMD plots and distribution of PS scores are available for five baseline characteristics not four (ECOG, metastatic brain site, metastatic liver site, age group, and sex). These	Amended for increasing accuracy.

<i>real-world cohort was well balanced across all baseline characteristics versus the observed amivantamab plus chemotherapy cohort for four adjusted baseline characteristics, it was unclear whether some important prognostic variables at baseline (e.g. any other metastatic locations, smoking history and Asian ethnicity) were balanced between the two treatment cohorts due to the lack of adjustment on these important prognostic variables at baseline.'</i>	<i>real-world cohort was well balanced across all baseline characteristics versus the observed amivantamab plus chemotherapy cohort for five adjusted baseline characteristics, it was unclear whether some important prognostic variables at baseline (e.g. any other metastatic locations, smoking history and Asian ethnicity) were balanced between the two treatment cohorts due to the lack of adjustment on these important prognostic variables at baseline.'</i>	are presented in Section A.1.3 of the NECTAR study report.	
Page 104, Section 4.2.2 states: <i>'Notably, the company argued that "neither use of a PSM nor an STM is able to resolve uncertainty associated with immature trial data. Indeed, the immaturity of the PAPILLON trial does not provide sufficiently mature data to populate model</i>	The statement should be updated as follows: <i>'Notably, the company argued that "neither use of a PSM nor an STM is able to resolve uncertainty associated with immature trial data. Indeed, the immaturity of the PAPILLON trial does not provide sufficiently mature data to populate model</i>	The full quote from the CS to be included so as not to present a biased view of the justification provided by Johnson & Johnson.	Not a factual inaccuracy.

transitions beyond progression”, underscoring the uncertainty related to long-term effectiveness.’	<i>transitions beyond progression. As such, the survival inputs included in the PSM adopted by Johnson & Johnson were reviewed for their long-term clinical validity by UK clinical experts, as described in Section B.3.3.2 of the CS, with scenario analyses performed exploring alternative survival extrapolations to ensure the robustness of the model to uncertainty in long-term survival estimations.”</i>		
Page 106, Section 4.2.4, Subpoint a) states: <i>‘the probabilistic results of the updated economic model post clarification show that the incremental cost-effectiveness ratio (ICER) versus the blended comparator is £28,853 per QALY gained, while pairwise comparisons versus carboplatin plus</i>	The statement should be corrected as follows: <i>‘the probabilistic results of the updated economic model post clarification show that the incremental cost-effectiveness ratio (ICER) versus the blended comparator is £24,044 per QALY gained (with severity modifier), while pairwise comparisons</i>	The statement should be updated to reflect the correct ICERs presented by Johnson & Johnson within the clarification question response, with the 1.2x severity modifier applied.	Not a factual inaccuracy.

<i>pemetrexed and carboplatin plus pemetrexed plus pembrolizumab result in an ICER of £41,241 per QALY gained and amivantamab being dominant respectively.'</i>	<i>versus carboplatin plus pemetrexed and carboplatin plus pemetrexed plus pembrolizumab result in an ICER of £34,368 per QALY gained and amivantamab being dominant respectively (with severity modifier).'</i>		
Page 105, Section 4.2.4, Subpoint a) states: <i>'In response to the request for clarification, the company's main arguments for modelling a blended comparator were the lack of a NICE treatment pathway for patients with EGFR exon 20 insertion mutation-positive advanced NSCLC and the lack of a single dominant comparator within this population'</i>	This statement should be corrected as follows: <i>'In response to the request for clarification, the company's main arguments for modelling a weighted comparator were the lack of NICE-recommended treatment options for patients following the withdrawal of mobocertinib, the lack of a NICE treatment pathway for patients with EGFR exon 20 insertion mutation-positive advanced NSCLC, the varying treatment splits between chemotherapy and pembrolizumab with chemotherapy across different centers, which was evidenced</i>	This statement should be clarified to make clear Johnson & Johnson's main arguments for modelling a blended comparator were much broader and detailed than the two reasons the EAG list, as per the company response at clarification questions.	Not a factual inaccuracy.

	<i>by expert clinical opinion obtained in three advisory boards and the UK based RWE, and the fact that there is no particular group of patients where chemotherapy or pembrolizumab with chemotherapy are preferentially used over one another. All of these arguments contribute to there not being one single dominant standard of care within this population and show that amivantamab will displace two therapies collectively (chemotherapy and pembrolizumab with chemotherapy) if reimbursed'</i>		
Page 110, Table 4.4 states: 	The statement should be corrected as follows: 	This should be corrected as per Section B.3.3.2.1 of Document B.	Thank you for highlighting this error in the Table footnote, this is now corrected.

Page 111, Section 4.2.6.2, Table 4.5 states: <i>‘Amivantamab: EO: 3-, 4- and 5-year TTD were 32.5% (10.0%-55.0%), 13.5% (2.0%-25.0%) and 5.0% (0.0%-10.0%) respectively.’</i> <i>‘CP: EO: 3-, 4- and 5-year TTD were 10.5% (1.0%-20.0%), 5.0% (0.0%-10.0%) and 2.5% (0.0-5.0%) respectively.’</i> In the ‘Clinical plausibility of the extrapolation based on clinical expert opinion’ row.	The statement should be corrected as follows: <i>‘Amivantamab: EO from the pre meeting survey (not the consensus reached): 3-, 4- and 5-year TTDD were 35% (15.0%-55.0%), 13.5% (2.0%-25.0%) and 5.0% (0.0%-10.0%) respectively.’</i> <i>‘CP: EO from the pre meeting survey (not the consensus reached): 3-, 4- and 5-year TTDD were 10.5% (1.0%-20.0%), 5.0% (0.0%-10.0%) and 2.5% (0.0-5.0%) respectively.’</i>	It is inaccurate to cite the elicitations from the pre-meeting survey without specifying these differ from the advisory board consensus. The statement should be updated to reflect that these data reflect the aggregated responses from the pre meeting survey (and not the advisory board consensus). Further, the amivantamab statement should also be updated to correctly reflect the numbers presented in Table 4 of the August advisory board report.	The numbers have been corrected, thank you for highlighting this. No ‘consensus’ numbers were provided and hence these could not be included.
Page 111, Section 4.2.6.2, Table 4.5 states: <i>‘CP. EO: 5- and 10-year OS was stated to be around</i>	The statement should be amended as follows: <i>‘CP. EO: 5- and 10-year OS was stated to be around</i>	This statement should be updated to reflect the conclusions made in the CS.	Not a factual inaccuracy. This was based on the CS statement:

10.0% (5.0%-15.0%) and 1.0% (0.0%-2.0%). According to the CS, this was most aligned with the gamma distribution (2.9% and 0.0% at 5- and 10-year respectively).’ In the ‘Clinical plausibility of the extrapolation based on clinical expert opinion’ row.	10.0% (5.0%-15.0%) and 1.0% (0.0%-2.0%). According to the CS, the consensus that the Weibull extrapolation was most clinically plausible was based on CP OS data that had been adjusted via the TSE approach. <i>The Weibull extrapolation for two-stage-adjusted CP OS data predicted survival rates of 22%, 2%, and 0% at 3-, 5-, and 10-years respectively, which were most aligned to the survival estimates for the gamma extrapolation of IPCW-adjusted CP OS data.’</i>		“The consensus that the Weibull extrapolation was most clinically plausible was based on CP OS data that had been adjusted via the TSE approach, given this was the defensible adjustment methodology at the time of the advisory board. <i>The Weibull extrapolation for two-stage-adjusted CP OS data predicted survival rates of 22%, 2%, and 0% at 3-, 5-, and 10-years respectively, which were most aligned to the survival estimates for the gamma extrapolation of IPCW-adjusted CP OS data.”</i>
Page 112, Section 4.2.6.3 states: ‘Therefore, TTNT was used for pembrolizumab-chemotherapy.’	The statement should be amended as follows: ‘<i>Therefore, TTNT was explored as a proxy for PFS for pembrolizumab-chemotherapy</i>’	The statement should be updated to reflect the conclusions made in the CS, where it was concluded that TTNT was not a valid proxy for PFS.	Not a factual inaccuracy.
Page 112, Section 4.2.6.4, Subpoint a) states that:	This statement should be amended as follows:	It is inaccurate to state the Weibull distribution overestimates OS compared	Not a factual inaccuracy.

<i>'The OS estimated using the Weibull distribution for amivantamab with chemotherapy was overestimated based on the company's advisory board report'</i>	<i>'The Weibull distribution used to estimate the OS of amivantamab with chemotherapy is aligned with the consensus reached at the company's advisory board.'</i>	with the company's advisory board given it aligns with the consensus reached. Furthermore, the Gamma distribution presents an even more optimistic view, which has also been validated as a realistic OS during the advisory board. As per the meeting report, advisors agreed that: <i>"the Weibull and gamma curves were the most plausible extrapolations for ACP OS."</i> Johnson & Johnson understand that the EAG have made the statement that the Weibull distribution is a minor overestimation of OS compared with the company's advisory board because it predicts a slightly higher 5-year survival rate compared with the aggregated responses for survival after 5-years that were elicited from the pre-meeting survey (32.1% vs 27.5%).	No 'consensus' numbers were provided and thus these could not be considered. Hence, the pre-meeting survey results (presented in the advisory board report) were considered.

		It should be noted that the Weibull distribution predicts a similar 10-year survival rate versus the aggregated elicitations from the pre-meeting survey (7.04% vs 7.5%). However, Johnson & Johnson firmly stress that the group consensus reached during the advisory board meeting should be the focus of any justification for curve selection, rather than results from the pre-meeting survey. Johnson & Johnson structured the advisory board such that each advisor provided estimates of survival at 3, 5, and 10 years in a pre-meeting survey, the aggregated estimates were then discussed during the meeting, and a group consensus was reached over the most plausible survival curve (this followed SHELF methodology). When making statements regarding how well	

		the selected curve fitted the company's advisory board, it is therefore imperative to consider the consensus rather than aggregated elicitations from the pre-meeting survey. Suggesting the Weibull is an overestimation compared with the company's advisory board is inaccurate given the Weibull distribution aligns with the consensus and predicts lower OS rates compared with the gamma curve, which was also validated to be plausible by the clinical experts (as per the consensus reached).	
Page 112, Section 4.2.6.4, Subpoint a) states that: <i>'the EAG adopted a more conservative distribution (i.e., the Gompertz distribution) in a scenario analysis'</i>	The Gompertz distribution is not a plausible extrapolation for amivantamab with chemotherapy OS based on expert opinion from the company's advisory board and an assessment of hazard plots. Therefore, it is inaccurate to include this as a plausible scenario.	Scenarios provided must be plausible and no evidence justifying the Gompertz distribution for amivantamab with chemotherapy OS has been provided by the EAG, other than it being 'more conservative' than the CS base-case. Further, there is ample evidence showing that the	Not a factual inaccuracy.

		Gompertz is not an appropriate distribution to select: 1. Clinical expert opinion: At the company advisory board, clinical experts agreed that <i>'the Gompertz and generalised gamma extrapolations were overly pessimistic and could be discounted'</i>. 2. Assessment of hazard plots: The Gompertz distribution predicts a rapidly increasing hazard, which does not align with the hazard function of the observed OS data from the PAPILLON trial. Further, a rapidly increasing hazard is much more severe compared with the hazard function associated with the gamma distribution of chemotherapy OS (CS base-case), which wanes over time. Therefore, selecting the Gompertz distribution for amivantamab with	

		chemotherapy OS and the gamma distribution for chemotherapy OS would mean that patients receiving amivantamab with chemotherapy would be dying faster than patients receiving chemotherapy, which is implausible given the OS benefit associated with amivantamab with chemotherapy observed in the PAPILLON trial, and the fact that chemotherapy is a component of the regimen.	
Page 112, Section 4.2.6.4, Subpoint a) states: <i>'The OS estimated for chemotherapy only using the gamma distribution underestimated OS'</i> This is also related and applicable to matter of judgement 1 (referenced throughout the EAG report).	This statement should be amended as follows: <i>'The gamma distribution used to estimate the OS of chemotherapy, after adjustment for treatment switching via the IPCW methodology, is in-line with the consensus reached at the company's advisory board.'</i>	The gamma distribution for the OS of chemotherapy is in-line with the consensus reached at the company's advisory board and is not therefore an underestimation. Johnson & Johnson acknowledge that the gamma distribution predicts lower 3-, 5-, and 10-year survival rates (19.3%, 2.9%, and 0.0%) compared with the aggregated results from the pre-meeting	Not a factual inaccuracy. No 'consensus' numbers were provided and thus these could not be considered. Hence, the pre-meeting survey results (presented in the advisory board report) were considered.

		survey (35%, 10%, and 1%). However, during the advisory board discussion, it was noted that <i>“patients receiving chemotherapy have a particularly poor survival”</i> and, as such, the advisors agreed that the survival rates for chemotherapy would be lower than the aggregated results from the pre-meeting survey. Johnson & Johnson firmly stress that the group consensus reached during the advisory board, after discussing the elicitations from the pre-meeting survey, should be the basis of curve selection. During the meeting, as per the meeting report, advisors reached a consensus that: <i>“the Weibull curve presented the most realistic survival extrapolation after the chemotherapy OS data had been adjusted for via the two-stage estimation”</i>. The consensus was based on	

		chemotherapy OS data that had been adjusted via the two-stage estimation approach given this was the defensible adjustment methodology at the time of the advisory board. Following insight from health economic experts during the advisory board, Johnson & Johnson amended the switching methodology used in the base-case to the IPCW approach. The Weibull distribution for two-stage-adjusted CP OS data (advisory board consensus) predicted survival rates of 22%, 2%, and 0% at 3-, 5-, and 10-years respectively, which are aligned to the survival estimates predicted by the gamma distribution of IPCW-adjusted CP OS data (19.3%, 2.9%, and 0.0%, respectively). Therefore, it is inaccurate to suggest that the gamma distribution for chemotherapy	

		underestimated OS compared with the company's advisory board.	
Page 113, Section 4.2.6.4, Subpoint a) states: <i>'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'</i> This is also related and applicable to matter of judgement 1 (referenced throughout the EAG report).	This statement should be updated given that, compared to the gamma curve selected in the CS base-case, the Log-Logistic curve does not better align with the consensus reached from the company's advisory board.	It is inaccurate to state that the Log-Logistic distribution for chemotherapy OS is more aligned to the company advisory board compared to the gamma distribution (CS base-case). After discussing the aggregated elicitations from the pre-meeting survey, the clinical experts reached a consensus that: <i>"the Weibull curve presented the most realistic survival extrapolation after the CP OS data had been adjusted for via the two-stage estimation (company base-case at the time)"</i>. The Weibull distribution for two-stage adjusted CP OS data predicts 3-, 5-, and 10-years survival rates of 22%, 2%, and 0%, respectively.	Not a factual inaccuracy. No 'consensus' numbers were provided and thus these could not be considered. Hence, the pre-meeting survey results (presented in the advisory board report) were considered.

		After the advisory board, the company switched the treatment adjustment approach to the IPCW methodology. The Log-Logistic distribution for IPCW-adjusted chemotherapy OS (EAG base-case) predicts 3-, 5-, and 10-year survival rates of 21.9%, 7.7%, and 1.6%, respectively. These are higher than the rates predicted by the advisory board consensus. The gamma distribution for IPCW-adjusted chemotherapy OS (CS base-case) predicts 3-, 5-, and 10-year survival rates of 19.3%, 2.9%, and 0.0%, respectively. These closely align with the rates predicted by the advisory board consensus. Therefore, it is inaccurate to state that the Log-Logistic distribution is better aligned to the company advisory board compared with the gamma	

		distribution, because this does not align with the consensus that was reached.	
Page 113, Section 4.2.6.4, Subpoint b) states: <i>'Based on the company's advisory board report, as well as clinical opinion obtained by the EAG, the estimated TTDD in the CS base-case for both amivantamab and chemotherapy is substantially underestimated'</i> This is also related and applicable to matter of judgement 2 (referenced throughout the EAG report).	This statement should be amended as follows: <i>'The TTDD distributions used in the CS base-case for both amivantamab and chemotherapy are aligned to the consensus reached during the company's advisory board.'</i>	It is inaccurate to state that the Weibull curves for both the amivantamab and chemotherapy components of amivantamab with chemotherapy underestimate TTDD given they are aligned to the consensus reached during the August 2024 advisory board. Therefore, the CS base-case did not underestimate TTDD compared with the company's advisory board. Johnson & Johnson firmly stress that the consensus reached during the advisory board should be considered, rather than elicitations from the pre-meeting survey, when making statements related to the alignment between curve selection in the CS base-case and the company's advisory board.	Not a factual inaccuracy. No 'consensus' numbers were provided and thus these could not be considered. Hence, the pre-meeting survey results (presented in the advisory board report) were considered.

		Amivantamab (part of ACP) TTD: Johnson & Johnson acknowledge that the aggregated elicitations from the pre-meeting survey showed TTDD estimates at 3, 4, and 5 years of 35% (15–55%), 13.5% (2–25%), and 5% (0–10%) for amivantamab, respectively, which are indeed higher than the proportions associated with the Weibull extrapolation that was selected in the CS base-case. However, during the advisory board meeting, the elicitations from the pre-meeting survey were discussed and advisors agreed (as cited within the meeting report) that the actual values would be: “<i>towards the lower ends of the estimates (i.e., 15%, 2%, and 0%)</i>”. This was decided given the upper estimates from the pre-meeting survey (e.g., 55% after 3-years) were higher than the observed TTDD rate	

		after 1.5 years (38%), which is unequivocally implausible. Whilst the Weibull extrapolation has a lower 3-year TTDD compared to this consensus (7.7% vs 15%), the 4- and 5-year estimates align well with the advisory board consensus (2.4% vs 2%, and 0.7% vs 0%, respectively). Further, Johnson & Johnson would like to stress that the agreed consensus from the advisory board was that the gamma or Weibull distributions were accepted as the most suitable curves for TTDD and the suggested TTDD curve has not been validated and is factually inaccurate. Chemotherapy (part of ACP) TTDD: Johnson & Johnson acknowledge that the aggregated elicitations from	

		the pre-meeting survey showed TTDD estimates at 3, 4, and 5 years of 10.5%, 5%, and 2.5% for chemotherapy, which are indeed higher than the proportions associated with the Weibull extrapolation selected in the CS base-case. However, during the advisory board meeting, the elicitations from the pre-meeting survey were discussed and advisors agreed (as cited within the report) that <i>“the gamma and Weibull extrapolations would be appropriate”</i>. Given it aligns with the consensus reached during the advisory board, it is inaccurate to suggest that the Weibull distribution for the TTDD of chemotherapy (CS base-case) is a substantial underestimation compared with the company’s advisory board.	

Page 113, Section 4.2.6.4, Subpoint b) states: <i>‘the EAG selected the log-logistic distribution for amivantamab and the exponential distribution for chemotherapy as these were more in line with the company’s advisory board report’</i> This is also related and applicable to matter of judgement 2 (referenced throughout the EAG report).	This statement should be updated given that, compared to the Weibull distributions for amivantamab and chemotherapy (CS base-case), the Log-Logistic and exponential distributions are not more in line with the consensus reached during the company’s advisory board.	The distributions selected by the EAG do not align with the consensus reached at the company’s advisory board and is therefore factually inaccurate. Further, both the distributions selected by the EAG do not align with the observed KM data based on visual inspection. Beyond the one-year timepoint, the Log-Logistic curve chosen by the EAG for amivantamab is much higher than the observed KM data and has a worse alignment with the KM data compared with the Weibull distribution (CS base-case) which more closely fits the KM data. Additionally, the distributions selected by the EAG have a poor statistical fit (AIC/BIC) for both. Amivantamab component: The log-logistic distribution for the TTDD of amivantamab does not align with the	Not a factual inaccuracy. No ‘consensus’ numbers were provided and thus these could not be considered. Hence, the pre-meeting survey results (presented in the advisory board report) were considered.

		consensus reached during the company's advisory board, where either the gamma or Weibull were accepted as the most suitable curves. After discussing the pre-meeting survey results, the advisors agreed that the most likely estimates for the TTDD of amivantamab at 3, 4, and 5 years would be: 15%, 2%, and 0% (as described above). This is not aligned to the rates at those respective landmarks predicted by the log-logistic extrapolation selected by the EAG (17.4%, 11.8%, and 8.6%, respectively). Chemotherapy component: The exponential distribution for the TTDD of chemotherapy does not align with the consensus reached during the company's advisory board, where advisors agreed that the <i>“gamma and Weibull curves would be appropriate.”</i>	

		The gamma and Weibull distributions for the TTDD of chemotherapy predict substantially lower 3-year (7.5% and 5.7%), 4-year (2.7% and 1.5%), and 5-year (1.0% and 0.4%) TTDD rates compared with the exponential distribution selected by the EAG (12.5%, 6.3%, and 3.2%).	
Page 113, Section 4.2.6.4, Subpoint c) states: <i>'However, it should be noted that this statement is applicable to amivantamab with chemotherapy and chemotherapy only and is not necessarily also applicable to pembrolizumab with chemotherapy given that PFS for the latter is used to approximate TTDD'</i>	This statement should be amended as follows: <i>'However, it should be noted that this statement is applicable to amivantamab with chemotherapy and chemotherapy only and is not necessarily also applicable to pembrolizumab with chemotherapy given that TTNT for the latter is used to approximate TTDD'</i>	Pembrolizumab-chemotherapy PFS is not used directly to approximate TTDD. It is approximated by applying the per cycle HR of TTNT vs PFS based on amivantamab-chemotherapy in the PAPILLON trial, to provide an approximation of PFS for pembrolizumab-chemotherapy.	Not a factual inaccuracy. As detailed in section "4.2.6.3 Assumptions for pembrolizumab-chemotherapy" of the EAG report PFS is used to approximate TTDD
Page 113, Section 4.2.6.4, Subpoint c) states: <i>'In addition, the company provided the requested</i>	This statement should be removed.	The statement is incorrect as a scenario analysis exploring an alternative extrapolation for pembrolizumab-chemotherapy	Not a factual inaccuracy.

scenarios using alternative parametric survival distributions for amivantamab with chemotherapy and chemotherapy only.’		(log normal) was provided in the response to clarification question B12d.	The statement indeed highlights that a scenario is provided.
Page 116, Subpoint a) states: <i>“The company additionally stated that MMRM impute missing observations by assuming that patients with non-missing data are representative of patients with missing data across all MMRMs. It is, however, unclear to the EAG whether this assumption is valid, i.e., whether missing data for the estimation of PF and PD utilities were missing (completely) at random. Scenario analyses using data imputation methods were therefore requested. The company provided a scenario analysis using last observation carried forward (LOCF), which resulted in PF and PD utilities very similar to utilities in the</i>	The ERG should acknowledge that MMRM is an appropriate approach and can serve as a valid alternative to MI given both rely on a similar assumption of ‘missing at random’, borrowing information from patients with similar characteristics. Therefore, MMRM is a valid choice, particularly in this case where the MI approach failed to produce estimates in later cycles due to low number of patients.	As MMRM leverages the information on observed values from other patients with similar values at other timepoints to inform the missing values for patients at a particular timepoint through the specified correlation structure across timepoints, this approach only relies on missingness at random and does not require the stronger assumption of missing completely at random (which would simply inform the missing data using the observed values from patients at the same timepoint). The alternative approach of multiple imputation relies on a similar assumption of missing at random, borrowing information from patients with similar characteristics, and	Not a factual inaccuracy.

<i>company's base-case. The EAG, however, considers LOCF an unsuitable imputation approach when data are potentially not missing (completely) at random. Multiple imputation is considered a better alternative, but the company stated that this approach failed to produce estimates in later cycles due to low number of patients. 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"</i>		both EMA as FDA consider both approaches to be valid. However, publications in the literature rather support MMRM as the better choice in maintaining statistical properties of a test as compared to the MI Reference: Siddiqui, O. (2011). MMRM versus MI in Dealing with Missing Data. A Comparison Based on 25 NDA Data Sets. <i>Journal of Biopharmaceutical Statistics</i>, 21(3), 423–436. https://doi.org/10.1080/10543401003777995	
Page 117, subpoint b) states: <i>'It is, however, unclear to the EAG what the company's area under the curve approach exactly entails and how it was</i>	This statement should either be removed or be updated to the following: <i>'Following questions raised by the EAG at clarification (Q16</i>	The area under the curve approach was described in detail within the responses to clarification questions 16 and 17. Therefore, it is inaccurate to state there was a lack of	Not a factual inaccuracy.

<i>used to combine the different mean per-cycle PF utilities to the overall mean PF health state utility.'</i>	<i>and Q17), the company provided details of the AUC approach to calculating the progression-free utilities.</i> <i>The CQ response detailed how time-specific utility estimates were calculated and then how the mean utility estimates were plotted across each cycle. The mean utility estimates were linearly interpolated and the area under this curve was used as the PF state utility.'</i>	clarity provided by the Johnson & Johnson over how PF utilities were calculated. As per the CQ response: First, for each EQ-5D-5L collection time point, a separate MMRM was fit using information only from patients who stayed progression free until that time point, including all their available EQ-5D-5L results up to and including that time point, and using visit as a categorical predictor, to get time specific utility estimates. Second, from each of these MMRMs, the least squares (LS) mean estimate of the last time point was used as the utility estimate for that time point. The time specific LS estimates (each of which were obtained from a different MMRM) were plotted across each cycle (Figure 66 of CQ response).	

		For the AUC approach, the mean utility values obtained from the per-cycle MMRMs were first interpolated to each cycle. This provided 28 mean estimates (27 cycles plus baseline). The standard error reported is the standard error of these 28 mean estimates (Table 32 of the CQ responses). The area under the curve of the progression-free estimates were used as the mean state utility in progression-free state.	
Page 124, Section 4.2.9.2, Table 4.11: Row 'One-off costs for 2L treatment' notes '4,215.66' and Row 'Total one-off cost' notes '5,904.98' as the relevant costs for chemotherapy.	The values should be updated to: '4,216.06' in Row 'One-off costs for 2L treatment' notes and '5,905.38' in Row 'Total one-off cost'.	The values should be corrected as per the CEM ('Detailed Cost Inputs_SubTx'!F13:H15').	Thanks for highlighting these typos. The values have been corrected.
Page 125, Section 4.2.9.5, Subpoint a) states:	This statement should be updated to:	Assuming patients receive a fraction of the dose at regular intervals throughout each cycle would not 'misrepresent'	Not a factual inaccuracy.

<i>'The EAG is concerned that this approach may misrepresent the actual acquisition and administration costs incurred. This could potentially benefit amivantamab, as patients stay longer in the PF health state. Therefore, the EAG considers this a key issue.'</i>	<i>'The EAG is concerned that this approach may misrepresent the actual acquisition and administration costs incurred in both the intervention and comparator. This could potentially benefit amivantamab as patients stay longer in the PF health state. However, the impact is very marginal.</i>	the acquisition and administration costs; particularly considering that, in reality, not every patient would enter the model and accrue costs at the same time. Further, this assumption is expected to have a very minor impact on the costs in both the intervention and comparator arms, leading to a very minor impact on the ICER (~1%). Therefore, it is inaccurate to state this is a key issue, as the impact of applying the full treatment dose at day 0 instead of spreading across the three weeks has a minor impact on the ICER.	
Page 125, Section 4.2.9.5, all of Subpoint b) discusses vial sharing within the model.	All text within this Subpoint b) should be removed.	As noted in the response in row 5 of this table, no vial sharing was allowed for amivantamab within the model.	Not a factual inaccuracy.
Page 125, Section 4.2.9.5 Subpoint c) states:	This statement should be updated to:	The 'other TAs' that the EAG have cited are not specific to patients with advanced	The text has been updated.

<i>'The unit costs used in the company's base-case for AEs were significantly lower than those from other TAs reporting on patients with advanced NSCLC with activating EGFR exon 20 insertion mutations in the first-line setting</i> This is also related and applicable to matter of judgement 4 (referenced throughout the EAG report).	<i>'The unit costs used in the company's base-case for AEs were lower than those from other TAs reporting on patients with locally advanced or metastatic NSCLC</i>	NSCLC with activating EGFR exon 20 insertion mutations in the first-line setting. The other TAs cited by the EAG in this paragraph are TA484 (nivolumab in previously treated non-squamous NSCLC), TA520 (atezolizumab in locally advanced or metastatic NSCLC after chemotherapy), and TA683 (pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, NSCLC). None of these TAs are specific to patients with advanced NSCLC with activating EGFR exon 20 insertion mutations in the first-line setting. Therefore, the wording should be updated to specify what population the 'other TAs' relate to. Further, Johnson & Johnson notes that the unit costs for AEs included in the model were based on AE codes that were used in the most recent	

		TA in patients with EGFR Exon20 insertion mutation-positive advanced NSCLC (TA850), except where that AE was not present in the submission.	
Page 126, Section 4.2.9.5, Subpoint c) states: <i>'The company did not provide sufficient evidence justifying why the non-elective inpatient short-stay code would be used over the other settings'</i> This is also related and applicable to matter of judgement 4 (referenced throughout the EAG report).	This statement should be amended to the following: <i>'In response to clarification question B20b (justifying the selected codes per individual AE), the company stated that all AE codes were based on the most recent TA in patients with EGFR Exon20 insertion mutation-positive NSCLC (TA850) except where that AE was not present in the submission; in this case other similar TAs in NSCLC where the AE and a suitable code were available were used. When not able to be sourced from other TAs, the codes were validated with medical opinion, to ensure they were appropriate to the specified adverse event.'</i>	Johnson & Johnson has provided a justification for why non-elective inpatient short stay codes were used at clarification, highlighting that this followed precedent set in recent TAs. The codes used for each adverse event have been based primarily on TA850, and the costs reflect the most recent 2022/2023 schedule of NHS costs. For example, for anaemia (given at clarification), the SA01G-SA01K codes reflect TA850 (noting that, in the committee papers, SA04 codes were erroneously included), as well as other TAs	Not a factual inaccuracy.

		in NSCLC such as TA653 and TA898. Further, Johnson & Johnson note that only incorporating the severest AE unit costs for the non-elective inpatient short-stay code is inappropriate and overestimates the AE costs.	
Page 126, Section 4.2.9.5, Subpoint d) states: <i>'In addition, the company did not justify why the medical oncology service was selected over for instance the clinical oncology service (Table 4.14).'</i>	This statement and the Table 4.14 with the alternative clinical oncologist unit costs should be deleted:	Johnson & Johnson have used the medical oncology codes as these are most appropriate given nearly all patients would be treated by a Medical Oncologist rather than a Clinical Oncologist. Therefore, it is not correct in the EAG scenario unit costs in Table 4.14 to use Clinical Oncologist codes as these do not represent the suitable codes for patients receiving treatment for this population.	Not a factual inaccuracy.
Page 127, subpoint e) b. states:	It is inaccurate to highlight the lack of justification given no additional monitoring tests are	Within the PAPILLON trial, as well as the KEYNOTE-189 trial for pembrolizumab with chemotherapy, patients were	Not a factual inaccuracy

<i>'The company did not justify whether amivantamab, carboplatin, or pembrolizumab would require additional monitoring tests (Page 127)'</i>	listed within the SmPCs for any of the treatments listed	followed-up as per current clinical practice, and no additional monitoring tests are listed within the SmPCs. It is inaccurate to highlight the omission of additional monitoring tests within the CS as a point of critique if there is no evidence to suggest additional monitoring tests are required.	
Page 127, Section 4.2.9.5, Subpoint e) b. states: <i>'However, TA683 reported a RDI of 95.6% based on KEYNOTE-189. The EAG would like to incorporate this into their base-case, although it will not have an impact due to the approach on vial sharing. However, the EAG was not able to find the dose skipping of 4.4% on the TA683 and would like to ask the company to provide more information on this.'</i>	All text within Subpoint b should be removed.	The dose skipping of 4.4% was implemented rather than applying an RDI as dose reductions are not recommended as per the pembrolizumab SmPC. Implementing a 4.4% dose skipping and a 95.6% RDI would lead to an overestimation of the reduced pembrolizumab-chemotherapy costs due to double counting. Therefore, only one of the two (dose skipping or RDI) should be implemented for pembrolizumab, and dose	Not a factual inaccuracy.

This is also related and applicable to matter of judgement 3 (referenced throughout the EAG report).		skipping was implemented in the company model as dose reductions are specifically not recommended for pembrolizumab within the SmPC.	
Page 134, Section 5.3.5 states: 'However, only TA850 was used for comparison, due to the limited number of TAs on patients with EGFR exon 20 insertion mutated advanced NSCLC.'	The statement should be amended as follows: "Only TA850 and TA855 were used for comparison, due to the limited number of TAs on patients with EGFR exon 20 insertion mutated advanced NSCLC.'	This statement should be updated to reflect that multiple TAs were included for comparison.	The statement has been updated.
Page 137, Section 6.1.3, Table 6.1 states: 'Overview of key issues related to the cost effectiveness (conditional on fixing errors highlighted in Section 5.1)'	The statement should be removed or revised as follows: 'Overview of key issues related to the cost effectiveness (conditional on fixing errors highlighted in Section 6.1)'	As no fixing errors were identified, this part of the table caption can be removed. Otherwise, it should be updated to reflect the correct section.	The has been updated.

Issue 2 Minor Typographical and Grammatical Errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 17, Section 1.4, Table 1.4 states: <i>'The company also provided reasons (e.g., not available across databases) for excluding some baselines characterises to estimate the PS.'</i>	Please can ' baselines characterises ' be replaced with baseline characteristics.	This is a spelling error which needs to be amended to ensure clarification of the statement.	This spelling error has been amended.
Page 18, Section 1.4, Table 1.6 states: <i>'Given that the addental ITC analysis for the comparison of amivantamab plus chemotherapy versus immunotherapy alone..'</i>	Please can ' addental ' be replaced with additional.	This is a spelling error which needs to be amended to ensure clarification of the statement.	This spelling error has been amended.
Page 37, Section 3.1.1, Table 3.1 states: <i>'Marchue 2024'</i>	Please can ' Marchue ' be replaced with March.	This is a spelling error which needs to be amended to ensure clarification of the statement.	This spelling error has been amended.
Page 37, Section 3.1.2 states:	Please can the ' to ' be removed from this statement.	This is a grammatical error which needs to be amended to	This grammatical error has been amended.

<i>'The company submission¹ states that an SLR was undertaken to in January 2021..''</i>		ensure clarification of the statement.	
Page 40, Section 3.1.2, Table 3.2 states: <i>'Based on Table 1 of the Appendices Amivantamab.'</i>	Please can the ' Table 1 ' be replaced with ' Table 29 ' to reflect the correct location of this information in the Appendices.	This typographical error must be corrected to ensure the correct location is reported for the information in Table 3.2.	This typographical error has been amended
Page 62, Section 3.2.12.5 states: <i>'In Section B.2.6.2.4 of the CS1 the company reported that, "A substantially higher proportion of patients in the amivantamab-chemotherapy arm had not initiated subsequent systemic therapy compared with the chemotherapy arm at the 3rd May 2023 DCO (62.1% versus 29.7%, respectively)." The further details can be found as below in Table 3.17.</i> <i>The company further added that "A substantially higher proportion of patients in the</i>	Please can the second quote from the CS be reviewed and updated as necessary.	The quote from the CS is repeated and it is not clear what the EAG intended to note here.	Amended.

<i>amivantamab-chemotherapy arm had not initiated subsequent systemic therapy compared with the chemotherapy arm at the 3rd May 2023 DCO (62.1% versus 29.7%, respectively).”</i>			
Page 82, Table 3.29, column ‘Median follow-up (months)’, row ‘PAPILLON’ states: <i>‘14.6 (PFS)^a, 20.9 (OS)^b’</i>	Please can the statement be corrected to: <i>‘14.6 (PFS)^a, 20.9 (OS)^b’</i>	Amending to superscript will ensure that this statement is correctly referenced.	This superscript has been applied to ensure corrected referencing has occurred.
Page 84, Section 3.3.2, Table 3.31, footnotes states: <i>‘Based on Table 27 of CS1’</i>	Please can the statement be corrected to: <i>‘Based on Table 27 of CS1’</i>	Amending to superscript will ensure that this statement is correctly referenced.	Amended.
Page 111, Section 4.2.6.2, Table 4.5 states: <i>‘CP: the Weibull had the best statistical fit while the Gompertz and generalized gamma where within roughly two AIC points (CS Table 57).’</i>	Please can the statement be corrected to: <i>‘CP: the Weibull had the best statistical fit while the Gompertz and generalized gamma where within roughly two AIC points (CS Table 58).’</i>	The incorrect table has been referenced here and this should be corrected.	Thank you for highlighting this. This has been corrected.

Issue 3 Confidentiality Highlighting Errors

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG comment
Page 82, paragraph before Table 3.29, last month reported.	Please can this be reported as: [REDACTED]	Confidentiality highlighting is required to ensure confidential information is not shared publicly.	Appropriate highlighting has been amended to ensure confidential information is not shared publicly.
Page 82, Table 3.29, column 'Period (years)', row 'PAPILLON'.	Please can this be reported as: [REDACTED]	Confidentiality highlighting is required to ensure confidential information is not shared publicly.	Appropriate highlighting has been amended to ensure confidential information is not shared publicly.
Page 82, Table 3.29, column 'Period (years)', row 'ESME'.	Please can this be reported as: [REDACTED]	Confidentiality highlighting is required to ensure confidential information is not shared publicly.	Appropriate highlighting has been amended to ensure confidential information is not shared publicly.
Page 82, Table 3.29, column 'Median follow-up (months)', row 'ESME'.	Please can this be reported as: [REDACTED]	Confidentiality highlighting is required to ensure confidential information is not shared publicly.	Appropriate highlighting has been amended to ensure confidential information is not shared publicly.
Page 82, Table 3.29, column 'Period (years)', row 'COTA'.	Please can this be reported as: [REDACTED]	Confidentiality highlighting is required to ensure confidential information is not shared publicly.	Appropriate highlighting has been amended to ensure confidential information is not shared publicly.

Page 82, Table 3.29, column 'Median follow-up (months)', row 'COTA'.	Please can this be reported as: ■	Confidentiality highlighting is required to ensure confidential information is not shared publicly.	Appropriate highlighting has been amended to ensure confidential information is not shared publicly.
Page 82, Table 3.29, column 'Period (years)', row 'ConcertAI'.	Please can this be reported as: ■■■■■	Confidentiality highlighting is required to ensure confidential information is not shared publicly.	Appropriate highlighting has been amended to ensure confidential information is not shared publicly.
Page 82, Table 3.29, column 'Median follow-up (months)', row 'ConcertAI'.	Please can this be reported as: ■	Confidentiality highlighting is required to ensure confidential information is not shared publicly.	Appropriate highlighting has been amended to ensure confidential information is not shared publicly.
Page 132, Section 5.2 reports the % increase on the ICER from the OS extrapolation of amivantamab-chemotherapy.	Please can this be reported as: ■	Confidentiality highlighting is required to ensure confidential information is not shared publicly.	Thank you for highlighting this. This has been corrected.